Cover page

ID-054-304

Protocol

Official Title:

A Prospective, Multi-center, Double-blind, Randomized, Placebo-controlled, Parallel-group, Phase 3 Study to Assess the Efficacy and Safety of Clazosentan in Preventing Clinical Deterioration Due to Delayed Cerebral Ischemia (DCI), in Adult Subjects With Aneurysmal Subarachnoid Hemorrhage (aSAH)

ClinicalTrials.gov Identifier:

NCT03585270

Date of document:

18 Feb 2022

Clazosentan / ACT-108475

Aneurysmal Subarachnoid Hemorrhage

Protocol ID-054-304

REACT: p**R**evention and tr**E**atment of v**A**sospasm with **C**lazosen**T**an

A prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study to assess the efficacy and safety of clazosentan in preventing clinical deterioration due to delayed cerebral ischemia (DCI), in adult subjects with aneurysmal subarachnoid hemorrhage (aSAH)

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SPONSOR CONTACT DETAILS

Sponsor	Idorsia Pharmaceuticals Ltd Hegenheimermattweg 91 CH-4123 Allschwil Switzerland ☎ +41 58 844 00 00
Clinical Trial Physician	Contact details of the Clinical Trial Physician can be found in the Investigator Site File.
Medical Emergency Hotline telephone number:	The telephone number for the Medical Emergency Hotline can be found in the Investigator Site File.

CONTRACT RESEARCH ORGANIZATIONS' INFORMATION

Some study activities will be delegated to Contract Research Organizations (CROs). A list of site-specific contact details can be found in the Investigator Site File.

SIGNATURE PAGE FOR IDORSIA PHARMACEUTICALS LTD

Hereinafter called Idorsia or sponsor

Treatment name / number

Clazosentan / ACT-108475

Indication

Aneurysmal subarachnoid hemorrhage

Protocol number, study acronym, study title

ID-054-304, REACT (p**R**evention and tr**E**atment of v**A**sospasm with **C**lazosen**T**an)

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I approve the terms and conditions relating to this study as defined in this protocol. I confirm that the information contained in this protocol is consistent with the current risk-benefit evaluation of clazosentan, and with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Title	Name	Date	Signature
Senior Director, Clinical Project Physician	[redacted]	[redacted]	[redacted]

INVESTIGATOR SIGNATURE PAGE

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Clazosentan / ACT-108475

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I agree to the terms and conditions relating to this study as defined in this protocol and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the well-being of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws.

Principal Investigator	Country	Site number	Town	Date	Signature

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AE	Adverse event
ALT	Alanine aminotransferase
aNIHSS	Abbreviated National Institutes of Health Stroke Scale
ARDS	Acute respiratory distress syndrome
aSAH	Aneurysmal subarachnoid hemorrhage
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BP	Blood pressure
CEC	Clinical Event Committee
CFR	Code of Federal Regulations (US)
CI	Confidence interval
CL	Confidence limits
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
CRO	Contract Research Organization
CT	Computed tomography
CTA	Computed tomography angiogram/graphy
CTT	Clinical trial team
CVP	Central venous pressure
DBP	Diastolic blood pressure
DCI	Delayed cerebral ischemia
DICOM	Digital Imaging and Communications in Medicine
DIND	Delayed ischemic neurological deficit
DSA	Digital subtraction angiogram/graphy

ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EEG	Electroencephalogram
EOS	End-of-Study
EOT	End-of-Treatment
ERA	Endothelin receptor antagonist
ET	Endothelin
ETx	Endovascular therapy
EU	European Union
FAS	Full analysis set
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale – Extended
HD	Hemodynamic
HR	Heart rate
i.v.	Intravenous
IAG	Image Acquisition Guidelines
IB	Investigator's Brochure
ICA	Internal carotid artery
ICF	Informed consent form
ICH	International Council for Harmonisation
ICP	Intracranial pressure
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational medicinal product

IRB	Institutional Review Board
IRC	Independent Radiology Committee
IRT	Interactive response technology
ISAC	Independent statistical analysis center
ISF	Investigator Site File
IVC	Inferior vena cava
IVH	Intra-ventricular hemorrhage
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
mGCS	Modified Glasgow Coma Scale
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
OATP	Organic anion transporting polypeptide
OR	Odds ratio
Ox-PAQ	Oxford Participation and Activities Questionnaire
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
PEEP	Positive End Expiratory Pressure
PI	Principal investigator
PPS	Per-protocol analysis set
QoL	Quality of Life
QS	Quality System
RR	Relative risk
RSI	Reference safety information
SAE	Serious adverse event
SAH	Subarachnoid hemorrhage
SaO_2	Arterial oxygen saturation

SAP	Statistical analysis plan
SBP	Systolic blood pressure
SI	Standardized International
SIV	Site initiation visit
SOC	System organ class
SpO_2	Peripheral capillary oxygen saturation
SS-QOL	Stroke Specific Quality of Life
SUSAR	Suspected unexpected serious adverse reaction
SVV	Stroke volume variability
TCD	Transcranial Doppler
TEAE	Treatment-emergent adverse event
US	United States
VAS	Visual analog scale
w/v	Weight/volume
WFNS	World Federation of Neurological Societies
WHO	World Health Organization

SUBSTANTIAL GLOBAL AMENDMENT 6

Amendment rationale

This amendment applies to global protocol ID-054-304 Version 6 dated 29 April 2021. The resulting amended global protocol is Version 7 dated 18 February 2022.

The purpose of this substantial amendment is to modify the definition of the main secondary efficacy endpoint and the hierarchical statistical testing strategy related to the other secondary endpoints.

The main secondary endpoint definition was updated: in addition to the already existing all-cause infarcts ≥ 5 cm^3 at Day 16 post-study drug initiation, clinically relevant infarcts < 5 cm^3 have been added. The latter are defined as those new or worsened infarcts < 5 cm^3 that occur in subjects with CEC-adjudicated clinical deterioration due to DCI.

Routine blinded monitoring of the event rate during the REACT study revealed a lower-than-expected incidence of infarcts ≥ 5 cm^3 resulting in insufficient power to detect a treatment effect. This led to an expansion of the endpoint definition to include smaller but clinically relevant infarcts.

Although the infarcts < 5 cm^3 have a lower association with vasospasm and poor outcome, their vasospastic origin and their contribution to poor outcome cannot be excluded. Further details concerning the rationale for this main secondary endpoint are included in Section 6.6.2.1.

This amendment includes the initial definition of the main secondary endpoint, i.e., all-cause new or worsened infarcts ≥ 5 cm^3 at Day 16 post-study drug initiation, as an exploratory endpoint.

This revised definition of the main secondary endpoint has no impact on the evaluation of the primary efficacy endpoint.

In addition, the modified Rankin Scale has been formally included in the statistical hierarchical testing strategy, just before the GOSE. Results from the Japanese Phase 3 studies (AC-054-305 and 306) show that the mRS can slightly better discriminate the treatment effect of clazosentan on clinical outcome at Week 12 post-aSAH, compared to the GOSE. This suggests a better sensitivity of the mRS, despite the similarity of the two instruments. Indeed, the mRS has recently been recommended over the GOSE as the preferred scale for measuring the long-term clinical outcome in SAH by the international clinical experts of the SAH common data elements working group [Suarez 2019].

Minor editorial changes have been made, including alignment with the latest protocol template, and typographical errors have been corrected.

Changes to the protocol

Two versions of the amended protocol will be prepared: 1) a clean version and 2) a Word comparison document showing deletions and insertions in comparison to the previous protocol version.

Amended protocol sections

The sections of the protocol affected by this amendment are listed below. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis.

2.2	Secondary objectives
3.1.2	Study duration
3.3.3	Clinical Event Committee
6.1.2	Main secondary endpoint
6.1.2.2	Other secondary endpoints
6.1.3.2	Other efficacy endpoints
6.6.2	Rationale for the choice of secondary efficacy endpoints
6.6.2.1	Occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation defined as: all-cause cerebral infarction ≥ 5 cm^3 or cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI
6.6.2.2	Modified Rankin Scale and Glasgow Outcome Scale Extended
7.2.2.1.1	Glasgow Coma Scale
7.2.2.4.4	Day 16 post-study drug initiation
9.1.4	Definition of suspected unexpected serious adverse reactions
10.1.7	Usage of the analysis sets
10.2.2	Secondary efficacy variables
10.2.2.1	Main secondary variables
10.2.2.2	Other secondary efficacy variable
10.3.1	Overall testing strategy
10.3.2.3	Handling of missing data
10.3.3.1	Occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation defined as: all-cause cerebral infarction ≥ 5 cm^3 or cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI

Summary of previous amendments

Amendment	Date	Main reason(s)
1	18 June 2018	Non-substantial amendment to address the applicable comments from those received on 3 May 2018 during the US FDA review for the Clinical Trial Application, and those received on 29 May 2018 during the Voluntary Harmonisation Procedure review for the Clinical Trial Application in the EU: • Extended the duration for the collection of serious adverse events from 30 days post-permanent study drug discontinuation until the End-of-Study visit. • Provided information regarding the potential pulmonary adverse events associated with the concomitant administration of nimodipine and clazosentan. • Clarified the main statistical analysis for the primary endpoint, the overall testing strategy, and the supportive analyses.
2	4 December 2018	Substantial amendment to align the protocol with the Investigator's Brochure (IB) Version 14 which had been amended to address requests received from the US FDA on 30 October 2018, following their review of the IB Version 13: • Restrictions were made concerning the contraception and breastfeeding requirements by extending them from 24 hours to 30 days post-study drug discontinuation. • Clarification was provided on certain study procedures and entry criteria, new/revised

Amendment	Date	Main reason(s)
		exploratory endpoints were added, and other minor modifications were done. • Edits were implemented in the statistical methods section to align with the most recent version of the statistical analysis plan.
3	7 January 2020	Substantial amendment to add a Quality of Life assessment at 24 weeks (6 months) post-aSAH. • The EQ-5D questionnaire was added at Week 24 post-aSAH. • The End-of-Study (EOS) visit at the individual subject level has been rescheduled to Week 24 post-aSAH and the previous EOS visit has been renamed 'Week 12 visit'. • Serious adverse event (SAE) reporting was extended from up to 3 months to up to 6 months. • Clarification on supportive data collection for the primary endpoint has been provided. • The rules for rescue therapy usage have been clarified.
4	2 July 2020	Substantial amendment to describe the follow-up and collection of data until Day 14 post-study drug initiation for subjects who are discharged from the study site prior to Day 14. • A follow-up visit/phone call was introduced for subjects who were discharged from the study site prior to Day 14 post-study drug initiation. The data to be collected and recorded during this follow-up were described. • It was explained how subjects who were discharged prior to Day 14 could meet the primary efficacy endpoint based on data collected between discharge and Day 14. • A separate dedicated section was added to describe the observation period for the primary endpoint.

Amendment	Date	Main reason(s)
		• Information concerning image archiving at the study sites was added.
5	29 April 2021	Substantial amendment to discontinue recruitment into the Early Treatment (ET) group following a recommendation received by the study Independent Data Monitoring Committee (IDMC) on 2 April 2021. The decision to discontinue the recruitment into the ET group was not based on a planned interim efficacy analysis, nor on urgent safety observations but a low rate of recruitment into this cohort since the outset of the study, making the contribution of these subjects to the overall study futile.

PROTOCOL SYNOPSIS ID-054-304

TITLE	A prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study to assess the efficacy and safety of clazosentan in preventing clinical deterioration due to delayed cerebral ischemia (DCI), in adult subjects with aneurysmal subarachnoid hemorrhage (aSAH).
ACRONYM	REACT: p**R**evention and tr**E**ament of v**A**sospasm with **C**lazosen**T**an
OBJECTIVES	**Primary objective** • To determine the efficacy of clazosentan in preventing clinical deterioration due to DCI, in subjects with aSAH. **Secondary objectives** • To evaluate the effect of clazosentan on the occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation. • To evaluate the effect of clazosentan on long-term clinical outcome, cognition, and health-related Quality of Life (QoL) at Week 12 and QoL at Week 24 post-aSAH. • To evaluate the safety and tolerability of clazosentan in the selected population up to 24 hours post-study drug discontinuation. **Other objectives** • To evaluate the effect of clazosentan on healthcare resource utilization.
DESIGN	This is a prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-design, Phase 3 study. Subjects will be randomized 1:1 to clazosentan 15 mg/h or placebo, stratified by their World Federation of Neurological Societies (WFNS) grade at hospital admission (1–2 vs 3–5), patient population (high-risk prevention vs early treatment*), and age at hospital admission (≤ 60 and > 60 years). *Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

	Overall the study will enroll 400 subjects in 2 treatment arms; 200 subjects per arm. The study will be conducted in approximately 100 sites in approximately 15 countries. Once randomized, the subject will enter a double-blind treatment period of variable duration followed by a follow-up period terminating with an End-of-Study (EOS) visit at Week 24 post-aSAH [see Section 3.1 for an overview of the study design]. The study comprises the following consecutive periods: **Screening period:** Starts with the signature of the informed consent form and ends with subject randomization. During the screening period, the subject will be evaluated for suitability for the study based on the inclusion and exclusion criteria. **Treatment period:** Starts immediately with the baseline assessments followed by the initiation of study drug infusion and ends with the permanent discontinuation of study drug. Treatment duration is dependent on the subject's individual clinical course and the investigator's judgment on the perceived need to continue the study drug [see Section 5.1.3.3.4 for further details]. The maximum duration of treatment is 14 days. **Observation period for the primary endpoint:** This period covers the interval over which the subject may qualify for the primary endpoint of the study. It starts with the initiation of study drug infusion and ends on and includes Day 14 post-study drug initiation irrespective of treatment duration. Subjects must not be discharged from the hospital earlier than Day 14 (and not prior to performing the 24-hour safety follow-up period). **24-hour safety follow-up period:** Starts with the permanent discontinuation of study drug and ends 24 hours later. Subjects must not be discharged from the hospital until the end of this period [see Section 7.1.3].

	Extended follow-up period: Starts after the 24-hour safety follow-up period and ends with the EOS visit, occurring 24 weeks after the aSAH [see Section 7.1.4]. **EOS (individual subject):** This is defined as the last visit performed for the study (i.e., the EOS visit, performed 24 weeks after the aSAH), or the date of premature discontinuation from the study, if applicable [see Section 7.1.8]. **EOS (study level):** This time point occurs when the last subject completes his/her EOS visit.
PLANNED DURATION	The study starts with the first subject, first visit and ends with the last subject, last visit. The study is expected to last approximately 47 months. The duration of participation in the study for an individual subject is expected to be approximately 6 months.
SITES/COUNTRIES	Approximately 100 sites in approximately 15 countries.
INCLUSION CRITERIA	1. Written informed consent* to participate in the study must be obtained from the subject or proxy/legal representative at any time from hospital admission to prior to initiation of any study-mandated procedure. *Consent will be obtained by a procedure that is based on local regulations and acceptable to local authorities (including, e.g., deferral of consent). The consent form must also be signed by the investigator or delegate prior to any study-mandated procedure. 2. Males and females aged 18 to 70 years (inclusive, at hospital admission). 3. Subjects with a ruptured saccular aneurysm, angiographically confirmed by digital subtraction angiogram (DSA) or computed tomography angiogram (CTA), which has been successfully secured* within 72 hours of rupture by surgical clipping or endovascular coiling.** *A successfully secured aneurysm (clipping or coiling) is defined as > 80% exclusion by volume with < 50% narrowing of parent vessel or adjacent branches (assessed locally). In addition, 'successful' implies no additional intervention planned on the repaired aneurysm in the 3-month period following the initial procedure.

	**The aneurysm may have been secured by both clipping and coiling. Stent-assisted coiling and other endovascular devices (e.g., Web® device) are not allowed. The temporary use of approved devices during the coiling procedure is allowed, provided their use does not require anti-platelet or other agents affecting clotting mechanisms. Determination of date/time of aneurysm rupture is described in Section 7.2.1.1. 4. WFNS grades 1–4 (based on Glasgow Coma Scale [GCS]) assessed after recovery from the aneurysm-securing procedure and after external ventricular drainage for hydrocephalus, if required. 5. High-risk prevention: Subjects with a "thick and diffuse clot"* on the hospital admission computed tomography (CT) scan, absence of cerebral vasospasm at the time of randomization, and possibility to start study drug in the intensive care unit (ICU; or equivalent environment where all protocol assessments can be performed and the Patient Management Guidelines followed), within 96 hours following the time of the aneurysm rupture. *Thick and diffuse is defined as a thick confluent clot, more than 4 mm in thickness, involving 3 or more basal cisterns. See Appendix 1 for further details. 6. A) Presence of a cerebral CT scan, performed at least 8 hours post-aneurysm-securing procedure and within 24 hours prior to randomization. 6. B) Absence of a significant (e.g., symptomatic or large) new or worsened* cerebral infarct or re-bleeding of the repaired aneurysm on the post-procedure CT scan. *This CT scan will be compared with the admission and any routinely performed post-procedure CT scan(s) to detect new or worsened infarcts and re-bleeding which appear after the aneurysm-securing procedure. 7. A woman of childbearing potential [see definition in Section 4.5] is eligible only if the serum pregnancy test performed during the screening period is negative. Agreement must be obtained to take the necessary precautions to avoid pregnancy from hospital discharge until 30 days post-study drug discontinuation [see Section 4.7].

	If breastfeeding, agreement must be obtained to refrain for the duration of the treatment with study drug and until 30 days post-study drug discontinuation. 8. Males are eligible for study participation only if they agree to take the necessary precautions to avoid pregnancy in a female partner from hospital discharge until 30 days post-study drug discontinuation [see Section 4.8].
EXCLUSION CRITERIA	***aSAH, aneurysm-securing procedure, vasospasm:*** 1. Subjects with subarachnoid hemorrhage (SAH) due to causes other than a saccular aneurysm (e.g., trauma or rupture of fusiform or mycotic aneurysms, SAH associated with arterio-venous malformation, vertebral dissections). 2. Subjects with at least one unruptured aneurysm for whom a subsequent intervention is planned within 3 months of the aSAH. 3. Significant bleeding post aneurysm-securing procedure (e.g., due to intra-ventricular drain, intra-cerebral hemorrhage, epidural hematoma, vessel dissection or rupture, re-bleeding of the repaired aneurysm*), based on investigator judgment. *Re-bleeding prior to the aneurysm-securing procedure is not an exclusion criterion. 4. Intra- or peri-aneurysm securing procedure complication requiring non-routine medical or interventional treatment such as administration of an antithrombotic or anti-platelet agent (e.g., abciximab), which is not completely resolved prior to randomization. 5. Intra-ventricular hemorrhage on the hospital admission CT scan, filling more than 50% of both lateral ventricles and with involvement of the 3rd and 4th ventricles. 6. Intra-cerebral hemorrhage on the hospital admission CT scan, with an approximate volume of > 50 mL.

	7. Presence of cerebral vasospasm at hospital admission (initial admission or transfer from another hospital) believed to be associated with a prior bleed (i.e., occurring before the bleed for which the subject is currently hospitalized). Vasospasm occurring during the aneurysm-securing procedure is not an exclusion criterion. ***Neurological and functional status:*** 8. Subjects with a new major neurological deficit occurring post aneurysm-securing procedure* which is attributable to the procedure and does not improve to pre-procedure status before randomization. *Evaluation for a new major neurological deficit post procedure implies the reversal of sedation (or waiting for the subject to recover from sedation) and the performance of a neurological examination. 9. Subjects who are still under the influence of pharmacological sedation at the time of randomization or who are, for whatever reason, not evaluable for baseline and regular daily neurological assessments. 10. WFNS grade 5 (based on GCS) immediately prior to planned randomization, assessed after external ventricular drainage for hydrocephalus, if required. 11. Subjects with a GCS score of ≤ 9 at the time of randomization and without intracranial pressure (ICP) monitoring. 12. Modified Rankin Scale (mRS) score of 3 or higher, prior to the aSAH (i.e., due to a chronic condition). ***Other clinical considerations:*** 13. Subjects with total bilirubin > 2 × the upper limit of normal, and/or a known diagnosis or clinical suspicion of liver cirrhosis or moderate to severe hepatic impairment. 14. Any concomitant condition or disease (including psychiatric and neurological conditions, drug abuse, severe alcoholism) which, in the opinion of the investigator, would affect the assessment of the safety or efficacy of the study treatment.

	15. Hypotension (systolic blood pressure ≤ 90 mmHg) at time of randomization that is refractory to treatment. 16. Unresolved pulmonary edema or significant pneumonia still present at the time of randomization, or severe hypoxia at the time of randomization in intubated subjects, defined as $PaO_2/FiO_2 \leq 200$. 17. High sustained ICP (> 25 mmHg lasting > 20 minutes) at time of randomization, despite optimal treatment, in subjects with ICP monitoring. 18. Severe cardiac failure requiring inotropic support at the time of randomization. ***Medications and therapies:*** 19. Lumbar and/or cisternal drainage performed specifically to prevent or treat cerebral vasospasm at any time from hospital admission to randomization. 20. Prophylactic or therapeutic administration of intra-arterial vasodilators* or ozagrel, or performance of cerebral angioplasty** at any time from hospital admission to randomization. *Mechanically induced vasospasm occurring during the aneurysm-securing procedure may be treated with local administration of vasodilators (e.g., intra-arterial, topical). **Balloon assisted vascular remodeling during the aneurysm-coiling procedure is permitted. 21. Subjects for whom at the time of randomization administration of urgent rescue therapy (i.e., cerebral angioplasty, intra-arterial/intrathecal/intra-cisternal/ intra-ventricular administration of vasodilators or ozagrel) is anticipated. 22. Use of intrathecal, intra-cisternal, or intra-ventricular* thrombolytics at any time from hospital admission to randomization. *Use of thrombolytics to open an occluded drain is permitted.

	23. Administration of intrathecal, intra-cisternal, and intra-ventricular vasodilators (e.g., nimodipine), intravenous (i.v.) nicardipine (except for blood pressure control), or i.v. milrinone*, within 4 hours prior to randomization. *Administration of i.v. milrinone at any time from hospital admission to randomization is exclusionary if used to prevent or treat cerebral vasospasm. 24. Administration of i.v. fasudil or i.v. ozagrel within 24 hours prior to randomization. 25. Use of intra-aortic balloon counter-pulsation devices at any time from hospital admission to randomization. 26. Use at any time from hospital admission to randomization, of any investigational drugs, procedures or devices, including: • investigational clipping material and investigational coiling material such as liquid embolic material, stents or flow diverting devices, and, • any other medication administered to prevent or treat vasospasm, reduce ischemic complications, or to improve clinical outcome post-aSAH, that has not been approved for these specific indications by local health authorities (e.g., new post-hospital admission prescription of "statins", therapeutic hypothermia). 27. Subjects receiving strong inhibitors of organic anion transporting polypeptide (OATP)1B1 and OATP1B3 transporter proteins (e.g., cyclosporin A, rifampicin, lopinavir/ritonavir), or subjects for whom it is likely at the time of randomization that these medications will be started during the study treatment infusion period. 28. Known hypersensitivity to clazosentan or any excipient in the formulation.

STUDY TREATMENTS	Clazosentan is supplied in clear glass vials as a concentrated solution for continuous i.v. administration, after dilution. Each vial contains 150 mg of clazosentan in a total volume of 6 mL, providing a concentration of 25 mg/mL (2.5% w/v, pH 8.0 ± 0.1). Each vial contains a small volume of overfill. Matching placebo is supplied in identical clear glass vials with the same formulation as described above (excluding clazosentan) and the same volume. Subjects will be administered either clazosentan, as a continuous i.v. infusion at the dose of 15 mg/h, or placebo at the same corresponding infusion rate [see Section 5.1.3.3.2]. For subjects enrolled in the high-risk prevention group, treatment will be administered, where possible, for 14 days. For subjects that require early discharge from the ICU (or equivalent), study drug must be administered for a minimum of 10 days. This duration covers the period when vasospasm is most likely to occur. For subjects randomized in the early treatment group*, treatment will be administered for a minimum of 6 days and a maximum of 14 days. Study treatment must be discontinued if one of the study-treatment stopping criteria is met [see Section 5.1.3.4.1]. *Recruitment into the early treatment group was discontinued from protocol version 6 onwards.
CONCOMITANT THERAPY	**Allowed concomitant therapy** ***Local standard of care*** The usual standard of care for the management of aSAH is allowed until the primary endpoint assessment at 14 days post-study drug initiation, except for those therapies listed in the "forbidden concomitant medication" section and must be documented in the medical charts. Nimodipine (oral or i.v.) may be administered for the usual duration if it is routine standard of care at the site.

	"Statins" (e.g., simvastatin, pravastatin) may only be administered if the subject was receiving them chronically for the treatment of high cholesterol levels. Vaccines (including those for COVID-19) may be administered at any time during the study. ***Rescue therapy*** For the purpose of this study, rescue therapy refers to the escalation of medical therapy beyond standard hemodynamic therapy, for the treatment of refractory vasospasm. Refractory vasospasm is characterized by a minimum of 2-points worsening on either of the neurological scales and no response to HD therapy. The following therapies are considered rescue therapies: • balloon angioplasty, • intra-arterial, intrathecal/intra-cisternal/intra-ventricular administration of vasodilators or ozagrel. The decision to administer the above rescue therapies is based on local standard of care and is allowed at any time during the study for refractory vasospasm. The refractory nature is to be documented in the electronic case report form (eCRF). Intravenous administration of vasodilators (e.g., nicardipine, milrinone) is allowed as rescue therapy only if preceded by intra-arterial administration of a vasodilator. The other medications in the "forbidden concomitant therapy" section below (with their respective routes of administration), are not considered as rescue therapies and their administration is forbidden until Day 14 post-study drug initiation. Study drug must be temporarily interrupted prior to any rescue therapy and must be resumed after the completion of the therapy. **Forbidden concomitant therapy** The following medications/therapies are forbidden until the primary endpoint assessment at Day 14 post-study drug initiation, due to their potential to interfere with the evaluation of efficacy or safety, or due to the potential for a drug-drug

	interaction with study drug (refer to the Investigator's Brochure for more information). Those that are described above under "rescue therapy" are permitted in the treatment of refractory vasospasm, but are forbidden otherwise. • Intra-aortic balloon device. • Lumbar and/or cisternal drainage for the prevention of cerebral vasospasm / DCI. • Milrinone i.v., nicardipine i.v.*, and intrathecal/ intra-cisternal/intra-ventricular vasodilators (e.g., nimodipine), must be discontinued at least 4 hours prior to enrollment. *Administration of i.v. milrinone at any time from hospital admission to randomization is exclusionary if used to prevent or treat cerebral vasospasm. Nicardipine i.v. may be used at any time for blood pressure control. • Magnesium i.v., albumin i.v., or plasma volume expander if administered specifically for the prevention of cerebral vasospasm and/or DCI. • Thrombolytics (including intrathecal, intra-cisternal, and intra-ventricular, administration) and antifibrinolytics (e.g., tranexamic acid). Use of thrombolytics to open an occluded drain is permitted. • Hypertonic saline i.v., if administered in the absence of hyponatremia, brain edema, or high ICP. • Mannitol i.v., if administered in the absence of brain edema or high ICP. • Strong inhibitors of OATP1B1 and OATP1B3 transporter proteins (e.g., cyclosporin A, rifampicin, lopinavir/ritonavir). • Other endothelin receptor antagonists (ERAs). • Any investigational drugs, procedures, or devices, including any other medication administered to treat cerebral vasospasm that has not been approved for this specific indication by local health authorities (e.g., therapeutic hypothermia, "statins").

	• Traditional medicines (i.e., plant-, animal-, or mineral-based medicine, such as traditional Chinese medicine). Study treatment must be permanently discontinued if one of the following is initiated during the treatment period: • Another ERA. • Another investigational product/procedure. • A strong inhibitor of OATP1B1 and OATP1B3 transporter proteins (e.g., cyclosporin A, rifampicin, lopinavir/ritonavir).
ENDPOINTS	**Primary efficacy endpoint** The primary efficacy endpoint is the occurrence of clinical deterioration due to DCI from study drug initiation up to 14 days post-study drug initiation. Clinical deterioration due to DCI is defined as a worsening of at least 2 points compared to the reference score, on the mGCS or the aNIHSS, lasting for at least 2 hours, which cannot be entirely attributed to causes other than cerebral vasospasm. It is centrally adjudicated by the Clinical Event Committee (CEC) based on a written charter and review of clinical data, case narratives, angiograms, and CT scans. **Secondary efficacy endpoints** • **Main secondary endpoint:** The occurrence of clinically relevant cerebral infarction* at Day 16 post-study drug initiation defined as: – all-cause cerebral infarction ≥ 5 cm^3 or – cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI * Cerebral infarction refers to new or worsened infarcts and is determined by central radiology review, comparing the total volume of infarcts on the CT scan performed 16 days after study drug initiation with the total volume on the CT scan performed just prior to randomization. If the CT scan cannot be performed on Day 16, then it is acceptable for the CT to be performed within 7 days following Day 16. If a subject is discharged from the hospital prior to Day 16, the CT scan is performed on the day of hospital discharge. Clinical deterioration due to DCI and cerebral infarctions ≥ 5 cm^3 are

	confirmed by the CEC. Cerebral infarctions < 5 cm^3 in subjects with clinical deterioration due to DCI are derived from both the CEC data (primary endpoint) and the IRC data (for infarct size). **Other secondary endpoints:** • Long-term clinical outcome assessed by the mRS at Week 12 post-aSAH, dichotomized into poor outcome (score ≥ 3) and good outcome (score < 3). • Long-term clinical outcome assessed by the Glasgow Outcome Scale Extended (GOSE) at Week 12 post-aSAH, dichotomized into poor outcome (score ≤ 4) and good outcome (score > 4). **Exploratory efficacy endpoints** Exploratory efficacy endpoints are described in Section 6.1.3. **Safety endpoints** • Occurrence of treatment-emergent adverse events (TEAEs) up to 24 hours after study drug discontinuation. • Occurrence of serious TEAEs up to 24 hours after study drug discontinuation. • Occurrence of TEAEs leading to premature discontinuation of study drug. • Occurrence of death (all causes) up to Week 24 post-aSAH. • Occurrence of TEAEs of specific interest (i.e., lung complications, hypotension, anemia, cerebral hemorrhage, cerebral edema, fluid retention, hepatic disorders, tachyarrhythmia) up to 24 hours after study drug discontinuation. • Occurrence of rescue therapy-specific adverse events up to hospital discharge (or Week 12, whichever is earlier). • Occurrence of treatment-emergent marked laboratory abnormalities up to 24 hours after study drug discontinuation, and changes from baseline to end of study drug administration for selected centrally assessed laboratory parameters.

	Other endpoints Other endpoints are described in Sections 6.1.3, 6.3, 6.4, and 6.5.
ASSESSMENTS	Refer to the schedule of assessments in Table 1 and Table 2.
STATISTICAL METHODOLOGY	**Analysis sets** Screened analysis set The Screened analysis set includes all subjects who have given informed consent to participate in the study and have a subject identification number. Randomized analysis set The Randomized analysis set includes all subjects who have been assigned to a study treatment. Full analysis set The Full analysis set (FAS) includes all subjects from the Randomized analysis set who have started the study treatment. Per-protocol analysis set The Per-protocol analysis set (PPS) comprises all subjects from the FAS who sufficiently complied with the protocol to be likely to exhibit the treatment effects. Safety analysis set The Safety analysis set includes all subjects who started study drug (as recorded in the eCRF). **Statistical hypotheses** Four null hypotheses will be tested according to a fixed-sequence procedure, at the two-sided significance level of 0.05 until first non-rejection. The first null hypothesis is that there is no difference between clazosentan 15 mg/h and placebo in the occurrence of clinical deterioration due to DCI from study drug initiation up to

	14 days post-study drug initiation. This hypothesis will be tested at a two-sided significance level of 0.05. The second null hypothesis is that there is no difference between clazosentan 15 mg/h and placebo in the occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation defined as: • all-cause cerebral infarction ≥ 5 cm^3 or • cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI. This hypothesis will be tested at a two-sided significance level of 0.05. The third null hypothesis is that there is no difference between clazosentan 15 mg/h and placebo in the proportions of subjects with a poor mRS score at Week 12 post-aSAH. This hypothesis will be tested at a two-sided significance level of 0.05. The fourth null hypothesis is that there is no difference between clazosentan 15 mg/h and placebo in the proportions of subjects with a poor GOSE score at Week 12 post-aSAH. This hypothesis will be tested at a two-sided significance level of 0.05. **Analysis of the primary efficacy variable** The primary statistical analysis will be performed on the FAS, according to the intent-to-treat approach. The null hypothesis (H_0) is that the occurrence of clinical deterioration due to DCI in subjects treated with clazosentan 15 mg/h is not different from placebo. The alternative hypothesis (H_A) is that the event rate in the clazosentan 15 mg/h arm differs from the placebo arm. The null hypothesis will be tested using a Cochran-Mantel-Haenszel test, stratified* on WFNS grade (1–2 vs 3–5) and age at hospital admission (≤ 60 and > 60 years), at the two-sided significance level of alpha = 0.05. Sensitivity analyses include repetition of the primary analysis on the PPS.

	Supportive analyses include logistic regression to estimate treatment effect adjusting for hospital admission WFNS grade (1–2 vs 3–5) at time of randomization and age at hospital admission (≤ 60 and > 60 years). The primary efficacy analysis planned in protocols up to version 5 will be performed as a supplementary analysis: i.e., the primary efficacy analysis described in Section 10.3.2.2 will be repeated including the patient population (high-risk prevention vs early treatment) as an additional adjustment factor. *Recruitment into the early treatment group was discontinued from protocol version 6 onwards. Due to the low number of subjects randomized in this stratum this variable will not be used as an adjustment variable and will be excluded from interaction testing and subgroup analyses. **Analysis of the secondary efficacy variables** The proportion of subjects with a clinically relevant cerebral infarction at Day 16 post-study drug initiation and the proportion of subjects with poor clinical outcome (mRS and GOSE) at Week 12 post-aSAH will be analyzed in a similar manner as for the primary efficacy endpoint. **Safety analysis** Summaries of safety will be essentially reflected by descriptive statistics for each treatment arm. **Analysis of other endpoints** Treatment effects on the other endpoints will be evaluated and described in detail in the Statistical Analysis Plan. **Subgroup analysis** Subgroup analyses for the primary and the secondary endpoints will be conducted for WFNS grade and age at hospital admission*, factors identified with a statistically significant treatment × factor interaction, and subgroups described in Section 10.3.2.6. *Recruitment into the early treatment group was discontinued from protocol version 6 onwards. Due to the low number of subjects randomized

	in this stratum this variable will not be used as an adjustment variable and will be excluded from interaction testing and subgroup analyses. **Sample size** Under the assumption that the true incidence of clinical deterioration due to DCI up to Day 14 post-study drug initiation in the placebo arm is 28% and in the clazosentan arm is 14%, a sample size of n = 176 in each treatment arm will have 90% power to show the superiority in response of clazosentan compared to placebo using Pearson's χ^2 test with a 5% two-sided significance level. When taking an approximate 10% drop-out rate into account, 400 subjects have to be enrolled in the study, with n = 200 randomized to each treatment arm.
STUDY COMMITTEES	**Independent Data Monitoring Committee** An Independent Data Monitoring Committee (IDMC) will have overall responsibility for safeguarding the interests of subjects by monitoring unblinded safety and efficacy data obtained in the study at regular intervals during the study, and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted to the highest scientific and ethical standards. The IDMC is empowered to recommend modifications to the protocol or premature study discontinuation, to enhance/preserve subject safety. The composition and operation of the IDMC is described in an IDMC charter. An Independent Statistical Analysis Center, not otherwise involved with study conduct, will perform the analyses and generate unblinded analysis reports for the regular safety analyses, exclusively for review by the IDMC. **Independent Radiology Committee** The Independent Radiology Committee (IRC) is composed of radiologists who are independent from the study/sponsor and blinded to treatment allocation.

	The radiologists will retrospectively review the angiograms and CT scans submitted for each randomized subject to confirm: • the presence of common findings and clot size on the hospital admission CT scan, • the absence of exclusionary CT findings on the pre-randomization CT scan, • the presence and severity of cerebral vasospasm on the baseline angiograms (pre-randomization, for subjects randomized into the early treatment group*) and post-baseline angiograms (for all subjects, after study drug initiation), *Recruitment into the early treatment group was discontinued from protocol version 6 onwards. • the presence, location, and volume of new and worsened cerebral infarcts at Day 16 post-study drug initiation. The composition and operation of the IRC is described in an IRC charter. **Clinical Event Committee** The CEC is composed of clinicians with expertise in aSAH and who are blinded to treatment allocation. The committee will determine whether the primary endpoint and the first component of the main secondary endpoint (infarcts ≥ 5 cm^3) have been met. The clinicians will review clinical and imaging data from all subjects to determine which cases fulfill the definition of the primary efficacy endpoint. They will also adjudicate cases for the presence of a new or worsened cerebral infarct ≥ 5 cm^3, based on the central review of CT scans performed by the IRC or other available data when the Day 16 CT scan is missing. The composition, operation, and adjudication rules of the CEC is described in a CEC charter.

PROTOCOL

1 BACKGROUND

1.1 Subarachnoid hemorrhage

With an estimated overall incidence of 9 in 100,000 people worldwide [Connolly 2012, Stiener 2013] aneurysmal subarachnoid hemorrhage (aSAH) is an orphan disease and has a poor prognosis. Even after successful securing of the aneurysm with surgical clipping or endovascular coiling, patients remain at risk of developing cerebral vasospasm and delayed cerebral ischemia (DCI), which can result in neurological deficits and death [Connolly 2012, Stiener 2013]. Cerebral vasospasm develops in about two-thirds of aSAH patients, occurs most frequently between Days 4 and 10 post-aSAH, and rarely develops beyond 2 weeks after the aneurysm rupture. In 20–40% of aSAH patients, cerebral vasospasm results in clinical deterioration due to DCI [Bauer 2014]. The potential consequences of DCI include cerebral infarction, poor functional outcome, and mortality [Lanzino 1999a, Lanzino 1999b, Nolan 2006, Brilstra 2000, Roos 2000, Fergusen 2007, Rabinstein 2003]. An increasing number of patients survive aSAH today, and functional aspects of the clinical outcome, including neuropsychological deficits, become increasingly important. DCI has recently been identified to be the most important predictor of neuropsychological deficits [Stienen 2014].

1.2 Medical management of aSAH and its vasospastic complications

Initial treatment of aSAH consists of securing the aneurysm with either a surgical clip or an endovascular coil to avoid re-bleeding, followed by a treatment protocol that keeps the patient well hydrated and blood pressure (BP) sufficiently high to ensure cerebral perfusion [Connolly 2012, Stiener 2013].

The only currently approved drug worldwide for the prevention of DCI is the calcium channel blocker nimodipine, which is standard of care in most centers in the US and the EU [Connolly 2012, Stiener 2013]. Nimodipine has been shown to improve neurological outcomes [Neil-Dwyer 1987, Pickard 1989]. Fasudil, a Rho-kinase inhibitor, ozagrel, a thromboxane A_2 antagonist, and alprostadil, a phosphodiesterase inhibitor have been approved for the prevention or treatment of vasospasm in some Asian countries.

As vasospasm is a major complication post-aSAH, the acute period following the aneurysm-securing procedure is accompanied by close monitoring of the patient's neurological status, and routine monitoring may include transcranial Doppler (TCD), computed tomography angiography (CTA), computed tomography (CT) perfusion, or digital subtraction angiography (DSA). Modification in the TCD signal, or the visualization of vasospasm on angiography will trigger an intensification of the patient monitoring and if clinically indicated the start of hemodynamic (HD) therapy to increase the cerebral perfusion pressure.

HD therapy, consisting of the administration of fluids and vasopressors, is the first step in the treatment of symptoms of vasospasm. For aSAH patients who fail to respond to HD therapy, the only remaining treatment option currently available for reversal of cerebral vasospasm is endovascular therapy (ETx), an invasive procedure consisting of balloon angioplasty and/or intra-arterial administration of vasodilators. The use of ETx is recommended by scientific society guidelines, although no prospective randomized trials to prove its effectiveness have been performed [Connolly 2012].

1.3 Unmet medical need in aSAH

Although nimodipine has been approved in the aSAH indication to prevent secondary ischemic complications of aSAH, it has not shown a consistent effect on angiographic cerebral vasospasm [Allen 1983, Petruk 1988].

In uncontrolled studies ETx has shown an immediate effect on angiographic vasospasm. While technical success is achieved in the majority of balloon angioplasty procedures, clinical success rates vary considerably, with reversal of DCI observed in 31–77% of patients. Durability of the effect is relatively poor, and repeated procedures are often required [Abruzzo 2012, Hoh 2005]. ETx is associated with significant risks for the patient (up to 5% serious complications such as thrombosis, vessel rupture or dissection for each intravascular intervention). Furthermore, ETx is not widely available, and mainly limited to expert centers [Kaufmann 2007, Hoh 2005, Hayashi 2014].

Therefore, there is a high medical need for improved treatment options for aSAH following initial surgery or endovascular coiling, as an add-on therapy to nimodipine, to avoid progression to symptomatic vasospasm with its neurological complications and the use of HD or ETx.

1.4 Clazosentan

1.4.1 Mechanism of action

Clazosentan is a highly specific endothelin (ET) receptor antagonist (ERA) with markedly higher binding affinity to the ET_A than to the ET_B subtype of ET receptors. It has vasodilatory properties on brain vessels and moderate systemic vasodilatory effects (refer to the Investigator's Brochure [IB] for further details [Clazosentan IB]). In both nonclinical and clinical settings, it has been demonstrated that clazosentan consistently prevents the occurrence of vasospasm post-aSAH. In a recent exploratory clinical study (REVERSE), clazosentan showed some pharmacological effect on large vasospastic brain vessels as early as 3 hours post-study drug initiation, suggesting that clazosentan may be beneficial in early treatment of vasospasm post-aSAH [Clazosentan IB].

1.4.2 Nonclinical summary

Cerebral vasospasm post-aSAH is principally due to a reaction to extravasated blood from aneurysmal rupture. Increased levels of the potent vasoconstrictor ET are triggered by both oxyhemoglobin-induced ET production [Cosentino 1994] and direct release of ET from lysed red blood cells [Tippler 1994], and increased ET levels correlate with the development of cerebral vasospasm [Seifert 1995]. In nonclinical models of subarachnoid hemorrhage (SAH), ERAs have been shown to prevent or reverse cerebral vasospasm [Clozel 1993, Roux 1995], with minimal effect on the systemic circulation [Roux 1995].

Prevention of cerebral vasospasm following experimental SAH was tested in dog and rabbit models of SAH [Roux 1997]. These studies showed that clazosentan could dose-dependently both prevent and reverse experimental cerebral vasospasm [Roux 1997]. Whereas clazosentan did not significantly affect the mean arterial pressure (MAP) or heart rate (HR) in rabbits, it did moderately decrease MAP in dogs by –17 ± 7% at 2 h after the highest infusion dose of 3 mg/kg/h.

More detailed information can be found in the IB [Clazosentan IB].

1.4.3 Clinical summary

Seven double-blind placebo-controlled clinical trials (three Phase 2, and four Phase 3) and one Phase 2 open-label study have been performed in subjects with aSAH to evaluate the safety and efficacy of clazosentan for prevention or treatment of cerebral vasospasm. These studies, which included over 1800 clazosentan-treated subjects, consistently showed a decreased incidence and severity of cerebral vasospasm in the clazosentan arms. Detailed study results are included in the clazosentan IB and summarized below. The most recent exploratory study investigated the potential of clazosentan to reverse established cerebral vasospasm [Clazosentan IB].

The initial Phase 2a study, AXV-034-2S01, reported a statistically significant reduction in the incidence and severity of angiographic cerebral vasospasm in subjects treated with clazosentan compared to placebo [Vajkoczy 2005]. In addition, this study included an exploratory part, in which the potential for clazosentan to reverse established cerebral vasospasm was shown in a limited number of subjects.

In the subsequent Phase 2b dose-finding study, AC-054-201/CONSCIOUS-1, a statistically significant dose-related decrease in the incidence of moderate or severe cerebral vasospasm post-aSAH was shown at all tested clazosentan doses (1 mg/h, 5 mg/h, and 15 mg/h) vs placebo [Macdonald 2008].

A similar Phase 2b study conducted in Japan and South Korea, AC-054-202, confirmed the decrease in the incidence of moderate or severe angiographic cerebral vasospasm up to 14 days post-aSAH using clazosentan at the doses of 5 mg/h and 10 mg/h [Fujimura 2017].

The results of CONSCIOUS-1 prompted two Phase 3 studies with very similar design, AC-054-301/CONSCIOUS-2 [Macdonald 2011] and AC-054-302/CONSCIOUS-3 [Macdonald 2012]. While CONSCIOUS-2 included aSAH subjects with aneurysm securing by surgical clipping, CONSCIOUS-3 included aSAH subjects post-endovascular coiling of the aneurysm. Both studies compared a 5 mg/h clazosentan dose to placebo and the CONSCIOUS-3 study also included a treatment arm with 15 mg/h clazosentan. The primary endpoint of both studies was the incidence of cerebral vasospasm-related morbidity and all-cause mortality 6 weeks post-aSAH. In CONSCIOUS-2, clazosentan at a dose of 5 mg/h showed a non-significant odds ratio (clazosentan:placebo) of 0.783 (95% confidence limits [CL]: 0.583–1.051; P = 0.1037) for mortality and vasospasm-related morbidity within 6 weeks post-aSAH. The CONSCIOUS-3 study was prematurely terminated due to the inconclusive results from CONSCIOUS-2. Exploratory analysis showed a non-significant odds ratio of 0.786 (95% CL: 0.479–1.289; P = 0.3395) in the 5 mg/h group compared to placebo for mortality and vasospasm-related morbidity within 6 weeks post-aSAH. With the 15 mg/h dose, the treatment effect of clazosentan compared to placebo was nominally statistically significant with an odds ratio of 0.474 (95% CL: 0.275–0.818; P = 0.0073). No significant effect was observed on the 3-month Glasgow Outcome Scale Extended (GOSE) in any of the studies conducted.

The two Phase 3 studies also showed reductions in the use of HD therapy and ETx in clazosentan-treated subjects compared to placebo. In CONSCIOUS-2, clazosentan 5 mg/h reduced the use of rescue therapy, including ETx, by 36% (95% CL: 14–53%). In CONSCIOUS-3, clazosentan at the dose of 15 mg/h reduced the use of rescue therapy, including ETx, by 65% (95% CL: 38–80%), and the incidence of delayed ischemic neurological deficits (DINDs) by 54% (95% CL: 22–72%) compared to placebo.

The REVERSE study (AC-054-203; open-label pilot Phase 2 study), which enrolled a limited number of subjects (n = 14), showed that while clazosentan is able to reverse established vasospasm within 3 hours in some cases, this effect was not pronounced enough in other cases to an extent that ETx could be avoided. However, this study showed a clear pharmacological effect of clazosentan on both large and distal vessels suggesting that when administered early enough, clazosentan could have the potential to reverse established moderate vasospasm.

Two Phase 3 studies with identical designs and endpoints were conducted in Japan. AC-054-305 included aSAH subjects with their aneurysm secured by endovascular coiling and AC-054-306 included aSAH subjects after surgical clipping of the aneurysm. Both studies compared clazosentan at the dose of 10 mg/h vs placebo. The primary endpoint of each study was comprised of 1) the occurrence of vasospasm-related morbidity and all-cause mortality within 6 weeks post-aSAH and 2) the occurrence of all-cause morbidity and mortality within 6 weeks post-aSAH. If it was demonstrated that clazosentan decreased

the occurrence of the former endpoint, the latter would also have been analyzed. Vasospasm-related morbidity and all-cause mortality was defined as death (all-cause), and/or new cerebral infarction due to vasospasm, and/or DIND due to vasospasm. All-cause morbidity and mortality was defined as any of these events, irrespective of underlying cause. In both studies, the primary analysis, performed using a Cochran-Mantel-Haenszel (CMH) test adjusting for pre-procedure World Federation of Neurological Societies (WFNS) grade, showed a statistically significant difference between the two treatment groups in the occurrence of vasospasm-related morbidity and all-cause mortality. In AC-054-305, this endpoint was reached in 28.8% of the subjects in the placebo arm and in 13.6% of the subjects in the clazosentan arm ($p = 0.0055$), corresponding to a relative risk reduction of 53% in the clazosentan-treated subjects. There was no statistically significant difference between treatment groups in the occurrence of all-cause morbidity and mortality. This endpoint was reached in 41.4% of the subjects in the placebo arm and in 33.0% of the subjects in the clazosentan arm (relative risk reduction = 20%, $p = 0.1871$). In AC-054-306, this endpoint was reached in 39.6% of the subjects in the placebo arm and in 16.2% of the subjects in the clazosentan arm ($p = 0.0001$), corresponding to a relative risk reduction of 59% in the clazosentan-treated subjects. There was no statistically significant difference between treatment groups in the occurrence of all-cause morbidity and mortality. This endpoint was reached in 57.5% of the subjects in the placebo arm and in 45.7% of the subjects in the clazosentan arm (relative risk reduction = 21%, $p = 0.0880$).

The safety of clazosentan is addressed in Section 1.6.

More detailed information can be found in the IB [Clazosentan IB].

1.4.4 Clazosentan dose rationale

In the CONSCIOUS-1 study (Phase 2), the dose of 15 mg/h showed a larger effect in the prevention of moderate to severe cerebral vasospasm than lower doses (relative risk reduction 0.65; 95% CL 0.47–0.78) as compared to placebo. In the Phase 3 studies, clazosentan could reduce the use of rescue therapy, including ETx, and at the 15 mg/h dose also showed an effect on reducing DINDs and the overall combined morbidity and mortality endpoint [see Section 1.4.3].

The efficacy of doses lower than 15 mg/h was inconsistent in clinical studies. A dose of 5 mg/h did not show a statistically significant effect on the combined vasospasm-related morbidity/mortality endpoint in the CONSCIOUS-2 and CONSCIOUS-3 studies. In CONSCIOUS-1, a smaller effect on the prevention of angiographic cerebral vasospasm was observed at clazosentan doses of 1 mg/h and 5 mg/h.

The 15 mg/h dose has therefore been chosen for further development. Based on nonclinical and limited clinical data, clazosentan has shown an ability to reverse established cerebral vasospasm at doses similar to those effective in the prevention of vasospasm.

Over 1800 subjects with aSAH have been treated with clazosentan, of whom 314 received the 15 mg/h dose. The safety profile of clazosentan is well known and its potential adverse effects are manageable in an intensive care unit (ICU) setting.

1.5 Rationale of the study

Clazosentan, an anti-vasospastic drug, is expected to provide optimal benefit when initiated early in the pathophysiological sequence aSAH → vasospasm → vasospasm-related ischemic complications.

Nimodipine, a calcium channel blocker, is the only therapy that was widely granted approval for the prevention of ischemic complications of aSAH 30 years ago. Despite improvement in ICU management, clinical deterioration due to DCI remains a serious concern and represents an unmet medical need today. These episodes of deterioration must be avoided because if left untreated they may lead to brain infarcts, aggravate or degrade into further ICU complications (e.g., coma with pulmonary complications), increase the length of stay in ICU, and trigger the performance or administration of invasive ETx (angioplasty or multiple sessions of intra-arterial vasodilators). ETx is a labor intensive and highly specialized procedure, and not all neurosurgical departments have the expertise, facilities and necessary resources to perform it. Particularly in centers/countries which do not have the ability to perform ETx, there is a high unmet medical need for a proven alternative therapy, which could be readily available. The availability of an effective, standardized, minimally invasive treatment of cerebral vasospasm, that reduces the risk of experiencing DCI and the subsequent need for invasive, resource intensive and risky ETx, would therefore constitute a clinically meaningful benefit to patients.

Based on the totality of the data from post-hoc analyses of the CONSCIOUS-2 and CONSCIOUS-3 studies, and data from the REVERSE study, a population at high risk for vasospasm-related ischemic complications has been identified [see Section 4.1]. This enriched population is likely to present more vasospasm-related morbidity than the general aSAH population investigated thus far. The enrichment strategy restricts the use of clazosentan to those subjects who are most likely to benefit from it, thus maximizing the overall benefit-risk profile.

1.6 Summary of known and potential risks and benefits

Clazosentan is expected to prevent the unfavorable consequences of vasospasm, such as neurological deterioration due to DCI, cerebral infarction, and ultimately poor clinical outcome. By preventing vasospasm-related neurological deterioration, it is expected that the administration of clazosentan will also decrease the use of endovascular rescue therapy.

Data from the previous CONSCIOUS studies demonstrate the potential of clazosentan to provide a clinical benefit on these various components of the disease process [see Sections 1.4.3 and 4.2]. Data from these studies, demonstrating the effect of clazosentan on top of standard of care including oral nimodipine, are the basis for the REACT study assumptions; primary endpoint event rates of 28% and 14% are expected in the placebo and clazosentan arms, respectively, representing a 50% relative reduction in the incidence of events in subjects treated with clazosentan. Hence, the totality of the data collected on the use of clazosentan in subjects with aSAH suggests that there is a high probability for an additional benefit when clazosentan is used as an add-on therapy to nimodipine in the treatment of this emergency indication.

The safety profile of clazosentan across the previously conducted studies showed an increased incidence of hypotension, lung complications (primarily due to pleural effusion, pulmonary edema, and pneumonia), anemia, and abnormal liver tests in the clazosentan groups compared with placebo. There was no clear dose relationship for the incidence of most adverse events (AEs), across doses used in the three CONSCIOUS studies. The safety profile of clazosentan was confirmed in the two Japanese Phase 3 studies.

The majority of the lung complication events were related to fluid retention, which is a known effect of ERAs [Stuart 2013]. The safety of clazosentan administered concomitantly with nimodipine has been studied in the clinical program in an aSAH population. The population pharmacokinetic/pharmacodynamic analysis performed in the CONSCIOUS-2 study showed no significant effect of clazosentan on concomitant nimodipine pharmacokinetics. AEs from the CONSCIOUS-2 study showed that lung complications were more frequently reported in the combined clazosentan + nimodipine group (41.1%) compared to the group clazosentan without nimodipine (29.1%). The most frequently reported lung complication was pulmonary edema which was reported more frequently in the combined clazosentan + nimodipine group (10%) compared to clazosentan without nimodipine (3.6%). These results suggest that nimodipine may increase the frequency of lung complications, mainly pulmonary edema, when given concomitantly with clazosentan, due to the known pharmacological effects of both drugs.

In addition, because of the vasodilatory properties of nimodipine, ventilation perfusion mismatch phenomenon may be potentiated when nimodipine is administered together with clazosentan. The Patient Management Guidelines [Appendix 3] provide recommendations on temporary/permanent discontinuation of nimodipine and/or clazosentan.

Hypotension and decrease in BP variables occurred as a result of a systemic vasodilatory effect common to ERAs. Few subjects treated with clazosentan discontinued treatment due to hypotension.

As observed with other ERAs, treatment with clazosentan was associated with a decrease in hemoglobin concentration. This effect is attributed to plasma volume expansion, related to fluid retention as there was no evidence to indicate hemolysis, bleeding, or bone marrow depression.

Clazosentan administration was also associated in some of the studies with a trend for increase in supraventricular arrhythmias.

The following measures are implemented in the protocol to minimize the risks for the subjects participating in the study:

- Exclusion of subjects with unresolved pulmonary edema or significant pneumonia or hypoxia ($PaO_2/FiO_2 < 200$) [see exclusion criterion 16 in Section 4.4];
- Exclusion of subjects with refractory hypotension [see exclusion criterion 15 in Section 4.4];
- Exclusion of subjects with significantly abnormal serum bilirubin and/or known or suspected liver cirrhosis or moderate to severe liver impairment [see exclusion criterion 13 in Section 4.4];
- Requirement to receive study drug in an ICU (or equivalent) environment and strict recommendations regarding fluid management and BP control in the Patient Management Guidelines [see Appendix 3];
- Frequent monitoring of vital signs including BP during the treatment period;
- Regular sampling for protocol-mandated hematology (including hemoglobin) and clinical chemistry (including aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin) assessments during the treatment period;
- Study-specific criteria for interrupting or permanently discontinuing study treatment [see Sections 5.1.3.3.6 and 5.1.3.4.1];
- In addition, safety and efficacy data will be monitored by an Independent Data Monitoring Committee (IDMC) [see Section 3.3.1];

Information concerning the potential effect of clazosentan on spermatogenesis, and potential risks associated with pregnancy and lactation are described in the IB [Clazosentan IB].

2 STUDY OBJECTIVES

The overall objective of this study is to determine the clinical efficacy of clazosentan in a population at high risk for developing ischemic complications post-aSAH and to further evaluate its safety and tolerability in this population.

2.1 Primary objective

To determine the efficacy of clazosentan in preventing clinical deterioration due to DCI, in subjects with aSAH.

Efficacy will primarily be assessed based on a reduction in the occurrence of clinical deterioration due to DCI up to 14 days post-study drug initiation.

2.2 Secondary objectives

- To evaluate the effect of clazosentan on the occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation defined as:
  - all-cause cerebral infarction ≥ 5 cm^3 or
  - cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI
- To evaluate the effect of clazosentan on long-term clinical outcome, cognition, and health-related Quality of Life (QoL) at Week 12 post-aSAH and QoL at Week 24 post-aSAH.
- To evaluate the safety and tolerability of clazosentan in the selected population up to 24 hours post-study drug discontinuation.

2.3 Other objectives

- To evaluate the effect of clazosentan on healthcare resource utilization.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-design, Phase 3 study.

Subjects will be randomized 1:1 to clazosentan 15 mg/h or placebo, stratified by their WFNS grade at hospital admission (1–2 vs 3–5), patient population (high-risk prevention vs early treatment*), and age at hospital admission (≤ 60 and > 60 years).

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

Overall the study will enroll 400 subjects in 2 treatment arms; 200 subjects per arm.

The study will be conducted at approximately 100 sites in approximately 15 countries.

Once randomized, the subject will enter a double-blind treatment period of a maximum duration of 14 days, followed by a safety follow-up period of 24 hours and an extended follow-up period for safety and efficacy assessment that terminates with an End-of-Study (EOS) visit at Week 24 post-aSAH [see Section 3.1.1].

3.1.1 Study periods

An overview of the study periods and "visits" is provided below. Details of each period are described in Section 7.1.

The study comprises the following consecutive periods:

Screening period: Starts with the signature of the informed consent form (ICF) and ends with subject randomization. During the screening period, the subject will be evaluated for eligibility for the study based on the inclusion and exclusion criteria.

Informed consent will be obtained from the subject or proxy, and/or a third party, according to local regulations, and signed by the investigator or delegate, prior to performing any assessment that is considered to be specifically mandated by the study.

The duration of the screening period is short, since subjects must be randomized in a timeframe that allows study drug to be initiated within 96 hours following the time of the aneurysm rupture [see inclusion criterion number 5 in Section 4.3].

Treatment period: Starts immediately with the baseline assessments followed by the initiation of study drug infusion and ends with the permanent discontinuation of study drug.

Treatment duration is dependent on the subject's individual clinical course and the investigator's judgment on the perceived need to continue the study drug [see Section 5.1.3.3.4 for further details].

For subjects in the high-risk prevention group, treatment will start within 96 hours following the time of the aneurysm rupture and be administered where possible for 14 days. For subjects that require early discharge from the ICU (or equivalent environment), study drug must be administered for a minimum of 10 days. This duration of administration covers the period when vasospasm is most likely to occur.

For subjects in the early treatment group*, treatment must begin within 24 hours of the time of the angiogram documenting the cerebral vasospasm necessary for entry into the study. Treatment will be administered for a minimum of 6 days and a maximum of 14 days.

The treatment period includes the baseline assessments performed just prior to study drug start and all assessments during study drug administration.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

Observation period for the primary endpoint: This period covers the interval over which the subject may qualify for the primary endpoint of the study. It starts with the initiation of study drug infusion and ends on and includes Day 14 post-study drug initiation

irrespective of treatment duration. Subjects must not be discharged from the hospital earlier than Day 14 (and not prior to performing the 24-hour safety follow-up period).

24-hour safety follow-up period: Starts with the permanent discontinuation of study drug and ends 24 hours later [see Section 7.1.3].

The End-of-Treatment (EOT) assessments are included in this period. These assessments are performed within 2 hours following permanent discontinuation of study drug.

Subjects must not be discharged from the hospital until the end of this period.

Extended follow-up period: Starts after the 24-hour safety follow-up period and ends with the EOS visit, occurring 24 weeks after the aSAH [see Section 7.1.4].

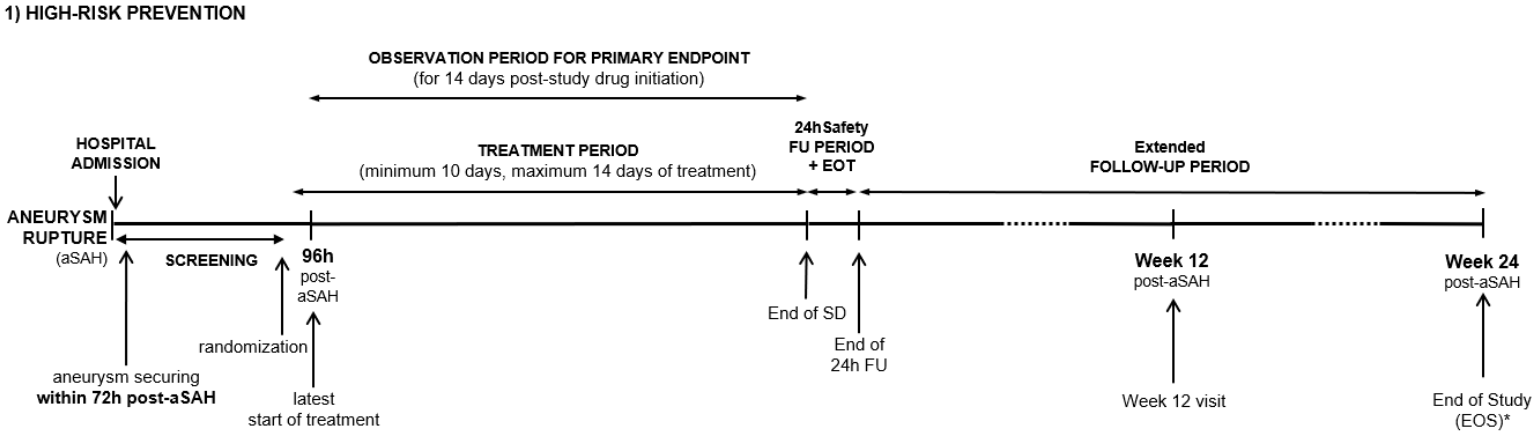
EOS (individual subject): This is defined as the last visit performed for the study (i.e., the EOS visit, performed 24 weeks after the aSAH), or the date of premature discontinuation from the study, if applicable [see Section 7.1.8].

EOS (study level): This time point occurs when the last subject completes his/her EOS visit.

The overall study design is depicted in Figure 1.

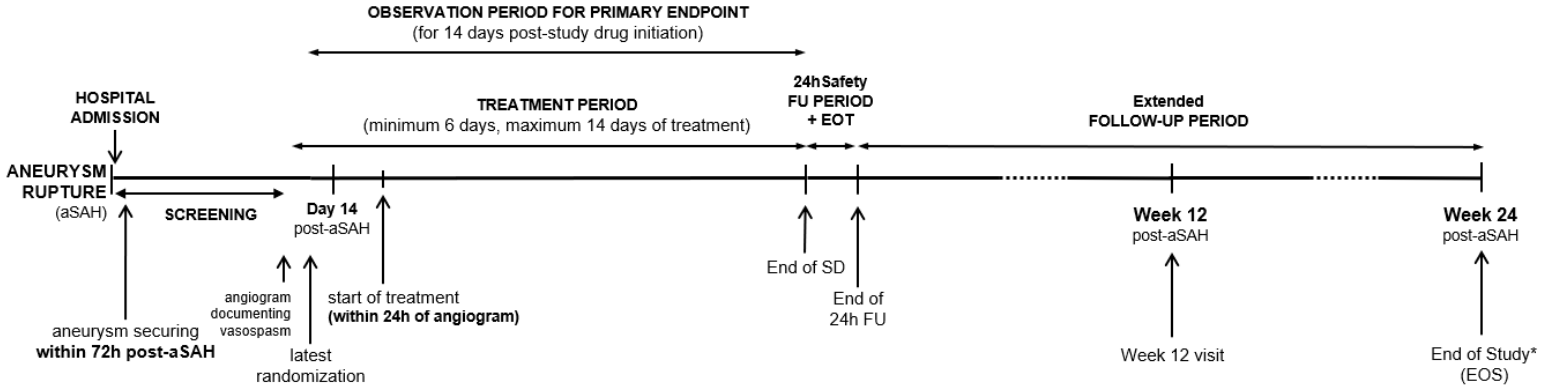
Figure 1 Study design

Note: The study design of the early treatment group is provided below although recruitment into this group was discontinued from protocol version 6 onwards.



* Week 24 post-aSAH: employment status and EQ-5D follow-up telephone call
aSAH = aneurysmal subarachnoid haemorrhage; SD = Study Drug; FU = follow-up, EOT = End of Treatment assessment

2) EARLY TREATMENT GROUP



* Week 24 post-aSAH: employment status and EQ-5D follow-up telephone call
aSAH = aneurysmal subarachnoid haemorrhage; SD = Study Drug; FU = follow-up, EOT = End of Treatment assessment

3.1.2 Study duration

The study starts with the first subject, first visit and ends with the last subject, last visit. The study is expected to last approximately 47 months.

The duration of participation in the study for an individual subject is expected to be approximately 6 months (from informed consent to the EOS visit).

3.2 Overall study design rationale

This is a prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group study designed to assess the efficacy and safety of clazosentan in preventing clinical deterioration due to DCI, in subjects with aSAH treated by endovascular coiling or surgical clipping, and receiving HD therapy with vasopressors and fluids. Study drug will be administered on top of standard aSAH treatment including oral or intravenous (i.v.) nimodipine when this is indicated according to the investigator.

The use of a placebo is justified in the current study design, because all subjects will be permitted to receive nimodipine post-aSAH. Clazosentan will therefore be tested vs placebo on top of existing approved standard therapy, and subjects will be treated according to local medical practice if complications occur.

Subjects will be stratified by potential confounders for clinical outcome such as their hospital admission WFNS grade (1–2 vs 3–5), patient population (high-risk prevention vs early treatment*), as well as their admission age (≤ 60 and > 60 years).

In aSAH, WFNS grade at admission and age are strong predictors of later outcomes [Rabinstein 2004, Macdonald 2017]. Elderly subjects as well as those with poor grade at admission tend to have a less favorable long-term outcome. In addition, data from the CONSCIOUS-2 study of clazosentan indicated a stronger effect of clazosentan on reducing morbidity/mortality events in subjects with a WFNS grade of 3 to 5 at admission than those subjects with WFNS grades 1 and 2 [Macdonald 2011].

Stratification by patient population (high-risk prevention group vs early treatment group*) is based on the fact that these two populations have never been investigated in the same study and may have slightly different outcomes.

The primary endpoint will be assessed during an observation period of 14 days after the day of the start of infusion. This covers the period during which DCI is most likely to occur and the maximum treatment duration for an individual subject.

The follow-up period continues from the end of study drug administration until EOS. At Week 12 post-aSAH, a time point that is clinically meaningful, long-term clinical outcome, QoL, and cognition are to be assessed. QoL will be re-assessed and employment status will be collected at Week 24.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards following a recommendation from the IDMC.

3.3 Study committees

3.3.1 Independent Data Monitoring Committee

An IDMC will have overall responsibility for safeguarding the interests of subjects by monitoring unblinded safety and efficacy data obtained in the study at regular intervals, and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted to the highest scientific and ethical standards. The IDMC is empowered to recommend modifications to the protocol or to prematurely discontinue the study in order to enhance/preserve subject safety. The composition and operation of the IDMC is described in an IDMC charter.

An independent statistical analysis center (ISAC), not otherwise involved with study conduct, will perform the analyses and generate unblinded analysis reports exclusively for review by the IDMC.

3.3.2 Independent Radiology Committee

The Independent Radiology Committee (IRC) is composed of radiologists who are independent from the study/sponsor and blinded to treatment allocation.

The radiologists will retrospectively review the angiograms and CT scans submitted for each randomized subject to confirm:

- the presence of common findings and clot size on the hospital admission CT scan,
- the absence of exclusionary CT findings on the pre-randomization CT scan,
- the presence and severity of cerebral vasospasm on the baseline angiograms (pre-randomization, for subjects randomized into the early treatment group*) and post-baseline angiograms (all subjects, after study drug initiation),

  *Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

- the presence, location, and volume of new and worsened cerebral infarcts at Day 16 post-study drug initiation.

The composition and operation of the IRC is described in an IRC charter.

3.3.3 Clinical Event Committee

The Clinical Event Committee (CEC) is composed of clinicians with expertise in aSAH, who are independent from the study/sponsor, and who are blinded to treatment allocation. The committee will determine, based on a charter, whether the primary endpoint and the first component of the main secondary endpoint (infarcts ≥ 5 cm^3) have been met.

The clinicians will review clinical and imaging data from all subjects on an ongoing basis during the study to determine which cases fulfill the definition of the primary efficacy

endpoint. They will also adjudicate cases for the presence of a new or worsened cerebral infarct ≥ 5 cm^3, based on the central review of CT scans performed by the IRC [Section 3.3.2] or other available data when the Day 16 CT scan is missing.

The composition, operation, and adjudication rules of the CEC is described in a CEC charter.

4 STUDY POPULATION

4.1 Selection of study population

The REACT study will enroll a population of subjects at high risk of developing DCI, including those with either a high risk of developing cerebral vasospasm, and those in whom vasospasm has already developed but is not yet associated with significant neurological deterioration*.

Although these subjects may present initially with different clinical features, their common factor is the high probability they have for developing DCI. If left untreated, the majority of those at high risk of developing vasospasm will indeed go on to develop vasospasm, and a proportion of subjects with asymptomatic vasospasm will transition to a state of vasospasm associated with neurological deterioration.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

4.2 Rationale for the selection of the study population

1) Subjects at high risk of vasospasm (high-risk prevention):

The subjects at the early stage of the disease continuum described above are those who are at high risk of developing cerebral vasospasm. These subjects are characterized by the presence of a large quantity of subarachnoid blood on their hospital admission CT scan, defined as follows:

A “thick and diffuse clot” is defined as a thick confluent clot, more than 4 mm in thickness, involving 3 or more basal cisterns.

The amount of blood on the initial CT scan is known to correlate with the development of symptomatic cerebral vasospasm, cerebral infarction, and poor clinical outcome [Frontera 2009]. A recent review concluded that the amount of blood observed on the admission CT scan was the only consistent risk factor for cerebral vasospasm and delayed ischemic complications after aSAH [Inagawa 2016].

Pre-planned subgroup analyses were performed on the “thick and diffuse clot” high-risk population in the CONSCIOUS-2, and -3 studies. In these studies, it was observed in the placebo groups that subjects with “thick and diffuse clots”, who represented approximately 60% of the overall subject population, developed 2–3 times more clinical deterioration due to DCI (known as DINDs in these studies), and up to 4 times more cerebral infarction compared to subjects with less blood on their initial CT scan. In CONSCIOUS-2, 29% of

placebo-treated subjects with a "thick and diffuse clot" experienced an episode of DIND vs 9% in the "other clot size" group. In CONSCIOUS-3, the incidences of DIND in the same populations were 27% and 11%, respectively. In CONSCIOUS-2, new cerebral infarction due to vasospasm was observed in 22% of the placebo-treated subjects with a "thick and diffuse clot" compared to 6% in the "other clot size" group. In CONSCIOUS-3, the respective incidences of new cerebral infarction were 16% and 10%. In the CONSCIOUS-2 and -3 studies, it was observed that the subjects with "thick and diffuse clots" experienced poor long-term clinical outcome twice as often as the other subjects.

In this subgroup of subjects with severe aSAH in CONSCIOUS-3, a clinically and statistically significant relative risk (RR) reduction of 56% on the "clinical deterioration due to DCI" endpoint (known as DIND in this study) was obtained with the 15 mg/h dose of clazosentan vs placebo. In parallel with this reduction in clinical deterioration, the clazosentan-treated subjects received 65% less rescue therapy for vasospasm than the placebo groups and showed a trend for a reduction in new cerebral infarcts due to vasospasm.

The clinical meaningfulness and known correlation between DCI, cerebral infarction, and poor long-term outcome has been extensively described in the literature [Rosengart 2007, Frontera 2009, Rabinstein 2003]. Data from the CONSCIOUS studies also show a correlation between DIND / new cerebral infarction and poor clinical outcome. The high-risk population is therefore expected to benefit clinically from a prevention strategy. Conversely, in the aSAH population with lower blood load on admission CT scan, subsequent vasospasm was observed less frequently, and the expected smaller benefit of clazosentan may not be sufficient to justify the potential risk associated with clazosentan treatment without demonstration of established vasospasm. Therefore, subjects with less subarachnoid blood on their hospital admission CT scan are excluded from clazosentan treatment unless they develop subsequent vasospasm (see below).

Subjects with large (> 50 mL) intra-cerebral hematoma as well as extensive intra-ventricular hemorrhage (IVH) will also be excluded [see exclusion criteria 5 and 6 in Section 4.4] as these conditions are known to be independent factors for poor prognosis [Meneghelli 2016].

2) Subjects with confirmed vasospasm (early treatment)*:

Some subjects more advanced in their disease process may have confirmed cerebral vasospasm, detected on a routinely performed angiogram, prior to the development of significant neurological deterioration. In the REACT study, these asymptomatic or minimally symptomatic subjects who do not have "thick and diffuse clot" on the hospital admission CT scan, will not be excluded from study participation as they can still potentially benefit from treatment with clazosentan. It is expected that their risk for developing clinical deterioration due to DCI, cerebral infarction, and poor clinical outcome will be as high as that observed in the high-risk prevention subjects. In order to prevent ischemic complications, treatment must be initiated early enough after the confirmation of

vasospasm. Subjects who have already significantly deteriorated will therefore be excluded from the study.

Data from the pilot study REVERSE indicate that clazosentan was associated with a limited effect on large proximal vasospastic vessels 3 hours after the infusion start, but showed a relevant effect on the distal cerebral circulation. This vasospasm-reversing effect may be particularly relevant for patients who are not candidates for intra-arterial intervention, when intra-arterial intervention is not available, or to minimize the use of this invasive intervention. The overall effect of clazosentan on established cerebral vasospasm may be sufficient to prevent vasospasm-related complications such as clinical deterioration due to DCI and cerebral infarction, and therefore explains the inclusion of subjects with early confirmed vasospasm into the REACT study.

In summary, the target population for Phase 3, namely the high-risk vasospasm prevention and early vasospasm treatment population as described above, will be easily identified by physicians using routine imaging assessments post-aSAH, and these subjects will be treated as soon as possible with the objective of preventing clinical deterioration after aSAH. This strategy restricts the use of clazosentan to those subjects who are most likely to benefit from the drug, thus maximizing the overall benefit-risk profile. Furthermore, such an enrichment strategy will allow higher event rates to be achieved and consequently a reasonable sample size in this orphan indication.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards following a recommendation from the IDMC.

4.3 Inclusion criteria

For inclusion in the study, the subject must fulfill all of the following inclusion criteria. It is not permitted to waive any of the criteria for any subject.

1. Written informed consent* to participate in the study must be obtained from the subject or proxy / legal representative at any time from hospital admission to prior to initiation of any study-mandated procedure.

   *Consent will be obtained by a procedure that is based on local regulations and acceptable to local authorities (including, e.g., deferral of consent). The consent form must also be signed by the investigator or delegate prior to any study-mandated procedure. Further details may be found in Section 12.3.

   Information that is available prior to the consent as part of local standard practice can be used to determine subject eligibility for the study, as applicable.

2. Males and females aged 18 to 70 years (inclusive, at hospital admission).
3. Subjects with a ruptured saccular aneurysm, angiographically confirmed by DSA or CTA, which has been successfully secured* within 72 hours of rupture, by surgical clipping or endovascular coiling.**

*A successfully secured aneurysm (clipping or coiling) is defined as > 80% exclusion by volume with < 50% narrowing of parent vessel or adjacent branches (assessed locally). In addition, successful implies no additional intervention planned on the repaired aneurysm in the 3-month period following the initial procedure.

**The aneurysm may have been secured by both clipping and coiling. Stent-assisted coiling and other endovascular devices (e.g., [redacted]® device) are not allowed. The temporary use of approved devices during the coiling procedure is allowed, provided their use does not require anti-platelet or other agents affecting clotting mechanisms. Determination of date/time of aneurysm rupture is described in Section 7.2.1.1.

4. WFNS grades 1–4 (based on Glasgow Coma Scale [GCS]) assessed after recovery from the aneurysm-securing procedure and after external ventricular drainage for hydrocephalus, if required.
5. High-risk prevention: Subjects with a "thick and diffuse clot"* on the hospital admission CT scan, absence of cerebral vasospasm at the time of randomization, and the possibility to start study drug in the ICU (or equivalent environment where all protocol assessments can be performed and the Patient Management Guidelines followed), within 96 hours following the time of the aneurysm rupture.

*Thick and diffuse is defined as a thick confluent clot, more than 4 mm in thickness, involving 3 or more basal cisterns [see Appendix 1 for further details].

6. A) Presence of a cerebral CT scan performed at least 8 hours post aneurysm-securing procedure and within 24 hours prior to randomization.
6. B) Absence of a significant (e.g., symptomatic or large) new or worsened* cerebral infarct or re-bleeding of the repaired aneurysm on the post-procedure CT scan.

*This CT scan will be compared with the admission and any routinely performed post-procedure CT scan(s) to detect new or worsened infarcts and re-bleeding which appear after the aneurysm-securing procedure.

7. A woman of childbearing potential [see definition in Section 4.5] is eligible only if the serum pregnancy test performed during the screening period is negative.

   Agreement must be obtained to take the necessary precautions to avoid pregnancy from hospital discharge until 30 days post-study drug discontinuation [see Section 4.7].

   If breastfeeding, agreement must be obtained to refrain for the duration of the treatment with study drug and until 30 days post-study drug discontinuation.
8. Males are eligible for study participation only if they agree to take the necessary precautions to avoid pregnancy in a female partner from hospital discharge until 30 days post-study drug discontinuation [see Section 4.8].

4.4 Exclusion criteria

Subjects must not fulfill any of the following exclusion criteria. It is not permitted to waive any of the criteria for any subject.

aSAH, aneurysm-securing procedure, vasospasm

1. Subjects with SAH due to causes other than a saccular aneurysm (e.g., trauma or rupture of fusiform or mycotic aneurysms, SAH associated with arterio-venous malformation, vertebral dissections).
2. Subjects with at least one unruptured aneurysm for whom a subsequent intervention is planned within 3 months of the aSAH.
3. Significant bleeding post aneurysm-securing procedure (e.g., due to intra-ventricular drain, intra-cerebral hemorrhage, epidural hematoma, vessel dissection or rupture, re-bleeding of the repaired aneurysm*), based on investigator judgment.

   *Re-bleeding prior to the aneurysm-securing procedure is not an exclusion criterion.

4. Intra- or peri-aneurysm securing procedure complication, requiring non-routine medical or interventional treatment such as administration of an antithrombotic or anti-platelet agent (e.g., abciximab), which is not completely resolved prior to randomization.
5. IVH on the hospital admission CT scan, filling more than 50% of both lateral ventricles and with involvement of the 3rd and 4th ventricles.
6. Intra-cerebral hemorrhage on the hospital admission CT scan, with an approximate volume of > 50 mL.
7. Presence of cerebral vasospasm at hospital admission (initial admission or transfer from another hospital) believed to be associated with a prior bleed (i.e., occurring before the bleed for which the subject is currently hospitalized). Vasospasm occurring during the aneurysm-securing procedure is not an exclusion criterion.

Neurological and functional status

8. Subjects with a new major neurological deficit occurring post aneurysm-securing procedure,* which is attributable to the procedure and does not improve to pre-procedure status before randomization.

   *Evaluation for a new major neurological deficit post procedure implies the reversal of sedation (or waiting for the subject to recover from sedation) and the performance of a neurological examination.

9. Subjects who are still under the influence of pharmacological sedation at the time of randomization or who are, for whatever reason, not evaluable for baseline and regular daily neurological assessments.
10. WFNS grade 5 (based on GCS) immediately prior to planned randomization, assessed after external ventricular drainage for hydrocephalus, if required.
11. Subjects with a GCS score of ≤ 9 at the time of randomization and without intracranial pressure (ICP) monitoring.

12. Modified Rankin Scale (mRS) score of 3 or higher, prior to the aSAH (i.e., due to a chronic condition).

Other clinical considerations

13. Subjects with total bilirubin > 2 × the upper limit of normal, and/or a known diagnosis or clinical suspicion of liver cirrhosis or moderate to severe hepatic impairment.
14. Any concomitant condition or disease (including psychiatric and neurological conditions, drug abuse, severe alcoholism) which, in the opinion of the investigator, would affect the assessment of the safety or efficacy of the study treatment.
15. Hypotension (systolic blood pressure [SBP] ≤ 90 mmHg) at time of randomization that is refractory to treatment.
16. Unresolved pulmonary edema or significant pneumonia still present at the time of randomization, or severe hypoxia at the time of randomization in intubated subjects, defined as $PaO_2/FiO_2 \leq 200$.
17. High sustained ICP (> 25 mmHg lasting > 20 minutes) at time of randomization, despite optimal treatment, in subjects with ICP monitoring.
18. Severe cardiac failure requiring inotropic support at the time of randomization.

Medications and therapies

19. Lumbar and/or cisternal drainage performed specifically to prevent or treat cerebral vasospasm at any time from hospital admission to randomization.
20. Prophylactic or therapeutic administration of intra-arterial vasodilators* or ozagrel, or performance of cerebral angioplasty** at any time from hospital admission to randomization.

    *Mechanically induced vasospasm occurring during the aneurysm-securing procedure may be treated with local administration of vasodilators (e.g., intra-arterial, topical).

    **Balloon assisted vascular remodeling during the aneurysm-coiling procedure is permitted.

21. Subjects for whom at the time of randomization administration of urgent rescue therapy (i.e., cerebral angioplasty, intra-arterial/intrathecal/intra-cisternal/intra-ventricular administration of vasodilators or ozagrel) is anticipated.
22. Use of intrathecal, intra-cisternal, or intra-ventricular* thrombolytics at any time from hospital admission to randomization.

    *Use of thrombolytics to open an occluded drain is permitted.

23. Administration of intrathecal, intra-cisternal, and intra-ventricular vasodilators (e.g., nimodipine), i.v. nicardipine (except for blood pressure control), or i.v. milrinone*, within 4 hours prior to randomization.

    *Administration of i.v. milrinone at any time from hospital admission to randomization is exclusionary if used to prevent or treat cerebral vasospasm.

24. Administration of i.v. fasudil or i.v. ozagrel within 24 hours prior to randomization.
25. Use of intra-aortic balloon counter-pulsation devices at any time from hospital admission to randomization.
26. Use at any time from hospital admission to randomization, of any investigational drugs, procedures or devices, including:
    - investigational clipping material and investigational coiling material such as liquid embolic material, stents or flow diverting devices, and,
    - any other medication administered to prevent or treat vasospasm, reduce ischemic complications, or to improve clinical outcome post-aSAH, that has not been approved for these specific indications by local health authorities (e.g., new post-hospital admission prescription of "statins", therapeutic hypothermia).
27. Subjects receiving strong inhibitors of organic anion transporting polypeptide (OATP)1B1 and OATP1B3 transporter proteins (e.g., cyclosporin A, rifampicin, lopinavir/ritonavir), or subjects for whom it is likely at the time of randomization that these medications will be started during the study treatment infusion period.
28. Known hypersensitivity to clazosentan or any excipient in the formulation.

4.5 Definition of childbearing potential

A woman is considered to be of childbearing potential unless she meets at least 1 of the following criteria:

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy, or hysterectomy;
- Postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause [ICH M3 definition]);
- Premature ovarian failure (confirmed by a specialist), XY genotype, Turner syndrome, uterine agenesis.

The reason for not being of childbearing potential will be recorded in the electronic case report form (eCRF) and hospital charts.

4.6 Breastfeeding women

Women who were breastfeeding at the time of the aSAH must refrain for the duration of the treatment and until 30 days after the discontinuation of study drug. It is unknown whether clazosentan may be excreted into breast milk.

4.7 Contraceptive requirements for women of childbearing potential

Women of childbearing potential [see Section 4.5] must agree to avoid pregnancy during the period from hospital discharge until 30 days post-study drug discontinuation.

One of the following highly effective methods of birth control are allowed for the study:

1. Sexual abstinence
2. Intrauterine device
3. Intrauterine hormone-releasing system
4. Hormonal contraceptives (oral, intra-vaginal, transdermal, injectable or implantable): combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation, **only if** used together with one of the following barrier methods: male or female condom, cervical cap with a spermicide, or diaphragm with a spermicide.
5. Bilateral tubal occlusion/ligation if performed more than 6 weeks prior to hospital discharge
6. Vasectomized partner (medically assessed as successful procedure)

The following methods are **NOT** considered highly effective methods of contraception for the study and should not be **used alone**:

- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- Hormonal contraceptives (oral, intra-vaginal, transdermal, injectable or implantable): combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation.

The following methods are **not allowed** as methods of contraception for the study:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method
- Combination of female condom and male condom

To ensure compliance, the study personnel must remind the subjects of the contraception requirements at hospital discharge and document the reminder in the medical chart.

4.8 Contraceptive requirements for men

Male subjects who are physiologically capable of conceiving a child (based on known information available to the investigator) must agree to take the necessary precautions to avoid pregnancy in a female partner of childbearing potential during the period from hospital discharge until 30 days post-study drug discontinuation.

Sexual abstinence or the use of a condom are considered acceptable methods of birth control for this purpose.

To ensure compliance, the study personnel must remind the subjects of the contraception requirements at hospital discharge and document the reminder in the medical chart.

5 TREATMENTS

5.1 Study treatment

5.1.1 Investigational treatment and matching placebo

Clazosentan is supplied in clear glass vials as a concentrated solution for continuous i.v. administration, after dilution.

Each vial contains 150 mg of clazosentan in a total volume of 6 mL, providing a concentration of 25 mg/mL (2.5% w/v, pH 8.0 ± 0.1). Each vial contains a small volume of overfill.

Matching placebo is supplied in identical clear glass vials with the same formulation as described above (excluding clazosentan) and the same volume.

For instructions on study drug preparation, refer to Section 5.1.3.2 and the study-specific Investigational Medicinal Product (IMP) Handling and Dispensing Guidelines. For a description of study drug packaging and labeling, refer to Section 5.1.6.1.

5.1.2 Treatment assignment

A total of 400 eligible subjects will be randomized in a 1:1 ratio to clazosentan (200 subjects) or placebo (200 subjects), stratified by their WFNS grade at hospital admission (1–2 vs 3–5), patient population (high-risk prevention vs early treatment*), and age at hospital admission (≤ 60 and > 60 years).

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

At the time of enrollment, after having verified that the subject meets all of the inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the interactive response technology (IRT) system to randomize the subject. The IRT system assigns a medication kit number to the subject, matching the treatment arm assigned according to the randomization list. Kit numbers will be entered in the eCRF.

The IRT system is handled by an external independent vendor who will generate the randomization list.

5.1.3 Study treatment dosing, preparation and administration

5.1.3.1 *Study drug dose*

Subjects will be administered either clazosentan, as a continuous i.v. infusion at the dose of 15 mg/h, or placebo at the same corresponding infusion rate [see Section 5.1.3.3.2].

5.1.3.2 *Study drug preparation*

Study drug must be prepared by a qualified person (e.g., pharmacy personnel or study staff) as appropriate, based on the investigative site's organization and local requirements.

The concentrated study drug will be diluted in a 500 mL bag of 0.9% sodium chloride as per the IMP Handling and Dispensing Guidelines.

One study drug infusion bag will be prepared for each 24-hour treatment period. Each prepared infusion bag will theoretically contain enough study drug for up to 30 hours of administration. However, this extra volume takes into consideration the volume of study drug that will be "lost" after flushing and priming the i.v. tubing and indwelling i.v. catheter, which must occur prior to starting the study drug infusion.

In order to adjust the timing of the start of each 24-hour period to a convenient time, it is possible to prepare and administer the second infusion bag prior to the end of the first 24-hour period. However, all subsequent infusion bags will be prepared and administered for a full 24-hour period, and each subsequent bag will be changed at approximately the same time each day, even if not completely empty.

Refer to the IMP Handling and Dispensing Guidelines for further details on preparation and storage of prepared study drug solution.

5.1.3.3 *Study drug administration*

5.1.3.3.1 General administration instructions

The study drug infusion must be administered in an ICU (or equivalent environment where all protocol assessments can be performed and the Patient Management Guidelines followed), as a continuous infusion in parallel to the administration of HD therapy as per the Patient Management Guidelines [see Appendix 3]. Study drug may only be initiated once the subject's BP and fluid status are controlled according to the Patient Management Guidelines.

The study drug will be administered via a dedicated lumen of a central line or a dedicated peripheral line, both used exclusively for the administration of study drug for the entire treatment period. 0.2 µm infusion filters will be used to prevent potential particulate and microbial contamination of the infused solution.

Infusion pumps will be used to administer the study drug infusion and will be calibrated according to local institution standards and practices.

Further details on the technical specifications of the infusion lines/sets/filters and pumps which may be used can be found in the IMP Handling and Dispensing Guidelines.

5.1.3.3.2 Dose and infusion rate

The infusion rate (mL per hour) of the final prepared solution, corresponding to a dose of clazosentan 15 mg/h (or placebo), will depend on the amount of overfill contained in the

500 mL bag, which is to be determined and documented prior to the preparation of study drug for the first subject randomized into the study. Since the volume of overfill may vary from one batch of infusion bags to another, the amount of overfill will need to be determined and documented each time a new batch is used.

The infusion rates (taking into account the amount of overfill in the bags) are indicated in the IMP Handling and Dispensing Guidelines.

The dose will be constant for the entire treatment period. No dosage adjustment is foreseen in this protocol. For situations that may require temporary or permanent study drug discontinuation, refer to Sections 5.1.3.3.4, 5.1.3.3.5, and 5.1.3.4.

5.1.3.3.3 Treatment initiation

For subjects enrolled in the high-risk prevention group, treatment will start as soon as possible, but no later than 96 hours post-aSAH.

For subjects enrolled in the early treatment group*, treatment will start no later than 24 hours after the start time of the angiogram confirming the presence of moderate to severe cerebral vasospasm. This angiographic diagnosis must be made up to and including Day 14 post-aSAH.

Study drug may only be initiated once the subject's BP and fluid status is controlled according to the Patient Management Guidelines, and the baseline assessments have been performed [see Table 1 and Section 7.2].

The i.v. lines (infusion set and indwelling i.v. catheter) must be primed/flushed with the prepared study drug solution prior to starting the infusion to ensure immediate delivery of study drug into the circulation when the infusion pump is activated.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

5.1.3.3.4 Treatment duration

Subjects will remain in the ICU (or equivalent) for the duration of the treatment period. Treatment will be administered where possible for a full 14 days (14 × 24-hour periods).

For subjects in the high-risk prevention group, treatment will be administered where possible, for 14 days. For subjects that require early discharge from the ICU (or equivalent), study drug must be administered for a minimum of 10 days. This treatment duration covers the period when vasospasm is most likely to occur.

For subjects in the early treatment group*, treatment will be administered for a minimum of 6 days and a maximum of 14 days.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

The above described minimum and maximum treatment durations include the time corresponding to temporary treatment interruptions.

The actual duration of treatment will depend on the subject's clinical course, and the investigator's judgment on the perceived need to continue the study drug. Unless permanent study drug discontinuation is believed to be in the best interest of the subject, study drug should be continued until the maximum duration described above, despite the need for escalation of medical therapy for cerebral vasospasm or cerebral ischemia, or the perceived lack of early efficacy.

Study drug must be temporarily interrupted prior to any rescue therapy and must be resumed after the completion of the therapy, unless a decision is made to permanently discontinue its administration at this time. Other potential reasons for temporary interruption of study drug are described in Sections 5.1.3.3.5 and 5.1.3.3.6.

Irrespective of when the study drug was discontinued, all subsequent assessments required during the observation period until Day 14 post-study drug initiation, as described in Section 7.1.4, will be performed according to the protocol.

5.1.3.3.5 Study treatment dose adjustments and interruptions

Study treatment dose adjustments are not permitted by the study protocol.

Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Inability to achieve the target BPs as described in the Patient Management Guidelines may also lead to temporary interruptions. Study-specific criteria for interruption of study treatment are described in the following section.

Interruptions of study treatment should be kept as short as possible.

Any interruption due to an AE is to be recorded in the eCRF.

Interruptions for other reasons (e.g., logistical, administrative), are to be recorded in the eCRF only if their duration is ≥ 15 minutes.

EOT assessments do not need to be performed for temporary interruptions of study treatment. However, if an interruption is initially planned to be temporary, but study treatment is subsequently permanently discontinued, the EOT assessments are to be performed after the permanent discontinuation.

5.1.3.3.6 Study-specific criteria for temporary interruption of study treatment

Study drug must be temporarily interrupted prior to any rescue therapy, and must be resumed after the completion of the therapy, unless a decision is made to permanently discontinue its administration at this time.

The Patient Management Guidelines recommend temporarily interrupting study drug when:

A) the target BP cannot be achieved (after the discontinuation of nimodipine, if applicable)

or

B) pulmonary ventilation/perfusion ratio mismatch is suspected (or is persistent despite discontinuation of nimodipine, if applicable).

5.1.3.4 *Premature discontinuation of study treatment*

The decision to prematurely and permanently discontinue study treatment may be made by the subject (or proxy / legally acceptable representative, if applicable), the investigator, or sponsor personnel. The main reason (e.g., AE, lack of efficacy, study terminated by sponsor) must be documented in the eCRF.

A subject (or proxy / legally acceptable representative, if applicable) has the right to prematurely discontinue study treatment at any time, without any justification, by withdrawing from study treatment only or by withdrawing from any further participation in the study (i.e., premature withdrawal from the study [see Section 8.2]).

Although a subject is not obliged to give his/her reason for prematurely withdrawing from the treatment or the study, it is recommended that the investigator makes a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

The investigator must discontinue study treatment for a given subject if he/she believes that continued administration would be contrary to the best interests of the subject.

Study treatment may be discontinued in response to an AE, lack of efficacy (including disease progression, worsening of subject's condition), a protocol deviation (including eligibility failure, non-compliance with study requirements), a diagnostic or therapeutic procedure, or a laboratory abnormality. Study treatment may also be prematurely discontinued if the target BPs as described in the Patient Management Guidelines [see Appendix 3] cannot be achieved.

Study-specific criteria for premature and permanent discontinuation of study treatment are described in Section 5.1.3.4.1.

A subject who prematurely discontinues study treatment is NOT considered as withdrawn from the study and will be followed up until their EOS visit (i.e., at Week 24 post-aSAH), provided that the subject's consent for this limited participation in the study has not been withdrawn.

At the time of the premature study treatment discontinuation, the EOT assessments will be performed. All subsequent assessments required during the observation period until Day 14 post-study drug initiation, as described in Section 7.1.4, will be performed according to the protocol.

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered as withdrawn from the study. Subjects who die or are lost to follow-up are also considered as withdrawn from the study.

Withdrawal from the study and follow-up medical care of subjects withdrawn from the study are described in Sections 8.2 and 8.4, respectively.

Subjects in the high-risk prevention group, who had their study drug permanently discontinued prior to the 10th calendar day of study drug administration, will be considered as prematurely discontinuing study drug. Subjects in the early treatment group* who had their study drug permanently discontinued prior to the 6th calendar day of study drug administration, will be considered as prematurely discontinuing study drug.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

5.1.3.4.1 Study-specific criteria for premature discontinuation of study treatment

In addition to the general potential reasons for premature study drug discontinuation described above, the study protocol requires the premature and permanent discontinuation of study drug in the following situations:

A) Inability to control or maintain BP as per Patient Management Guidelines, despite discontinuation of nimodipine, if applicable, and temporary study drug interruption.

B) Persistent pulmonary ventilation/perfusion ratio mismatch suspected to be related to study drug administration [see Appendix 3].

C) Presence of generalized brain edema.

D) Presence of severe pulmonary edema.

E) Total bilirubin increases to a level ≥ 3 × the upper limit of normal range or acute liver impairment is suspected.

F) Pregnancy while on study drug; a Pregnancy Form must be completed [see Section 9.4.1].

G) Another ERA, and/or another investigational product/procedure is started during the treatment period.

H) A strong inhibitor of OATP1B1 and OATP1B3 transporter proteins (e.g., cyclosporin A, rifampicin, lopinavir/ritonavir) is started during the treatment period.

5.1.4 Blinding

This study will be performed in a double-blind fashion. The investigator, study personnel, subjects, clinical research associates (CRAs), sponsor personnel, and vendor / Contract Research Organization (CRO) personnel involved in the conduct of the study will remain blinded to the study treatment received by the subjects during the double-blind treatment period until study closure.

To ensure adequate supply of study treatment, the IRT vendor personnel responsible for clinical study supply distribution and the sponsor individuals contributing to clinical supply distribution will need to be unblinded at subject level and depot level, respectively. These persons will be clearly identified, their unblinding will be documented in the trial master file, and they will not take part in any clinical trial team (CTT) meetings after study set-up has been completed.

The IDMC and the ISAC will be unblinded to study treatment allocation.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential, and accessible only to the IRT vendor, sponsor authorized persons (i.e., Pharmaceutical Development group) who are not involved in the conduct of the study, and the IDMC and the ISAC.

All study drug kits will be packaged in the same way, rendering the investigational treatment indistinguishable from its matching placebo.

5.1.5 Unblinding

5.1.5.1 *Unblinding for final analyses*

Full randomization information will be made available for data analysis only after database lock, in accordance with the sponsor's Quality System (QS) documents.

5.1.5.2 *Unblinding for suspected unexpected serious adverse reactions*

If a suspected unexpected serious adverse reaction (SUSAR) [see definition in Section 9.1.4] occurs in a subject participating in the study, the sponsor's Global Drug Safety department will request the unblinding of the treatment assignment in order to meet regulatory reporting requirements.

The treatment assignment will not be communicated to site personnel, subjects, sponsor CTT or any vendor/CRO personnel involved in the conduct of the study.

Unblinded SUSAR information will be reported to respective health authorities and Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) and the IDMC only. SUSARs will be notified to investigators in a blinded fashion.

5.1.5.3 *Emergency procedure for unblinding*

The investigator, study personnel, subjects, CRAs, sponsor personnel, and any CRO personnel involved in the conduct of the study must remain blinded to the subject's treatment assignment.

The identity of the study treatment may be revealed only if the subject experiences an emergency medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the decision to unblind resides solely with the investigator and the investigator can receive the unblinded treatment assignment through

the IRT system. Whenever possible, and provided it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator is invited to discuss the intended unblinding with the sponsor personnel.

The occurrence of any emergency unblinding during the study must be clearly justified and explained by the investigator. In all cases, the sponsor personnel must be informed about the reason for the unblinding as soon as possible before or after the unblinding.

The circumstances leading to unblinding must be documented in the hospital charts, the Investigator Site File (ISF) and in the eCRF.

If unblinding occurs, all assessments as defined in the study protocol must still be performed, unless the subject withdraws consent to participate in the study.

5.1.6 Study treatment supply

Manufacturing, labeling, packaging, and supply of study treatment will be conducted according to Good Manufacturing Practice, GCP, and any local or national regulatory requirements.

All study treatment supplies are to be used only in accordance with this protocol, and not for any other purpose.

5.1.6.1 *Study treatment packaging and labeling*

Study treatment is supplied in kits containing 15 vials of clazosentan or placebo [see Section 5.1.1 for vial descriptions], enough for 5 days of treatment.

Additional kits to cover the entire treatment period can be requested by contacting the IRT system (see the IRT user manual).

Study treatment is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located.

5.1.6.2 *Study treatment distribution and storage*

Study treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the label (store below 30 °C/86 °F, do not freeze).

The study sites will be supplied with study drug according to each center's needs, depending on the rate of subject enrollment. Each center will have an individual supply of study drug, which will be re-supplied automatically as soon as a predefined minimum level of study drug has been reached.

Further instructions regarding the distribution and storage of study drug are provided in the IMP Handling and Dispensing Guidelines.

5.1.6.3 *Study treatment dispensing*

Each kit and each vial will have a label with a tear-off part which must be removed and attached to the IMP Label Log as the study drug is dispensed during the treatment period.

An accurate record of the date and amount of study drug used to prepare the daily infusions for each subject must be available for inspection at any time.

All unused vials are to be stored in the subject kit for inspection by the site monitor at monitoring visits. Used vials should be stored separately from the subject kit.

The study treatment dispensing/return procedures may not be altered without prior written approval from the sponsor (e.g., in the event that a local process requires immediate destruction of vials after preparation and of any unused vials once subject has finished treatment).

Details on how to record the dispensing of study drug are available in the IMP Handling and Dispensing Guidelines.

5.1.6.4 *Study treatment return and destruction*

The protocol-mandated study treatment return procedures may not be altered without prior written approval from the sponsor. On an ongoing basis and/or on termination of the study, the CRA will collect used and unused study drug kits, which will be sent to the warehouse, where the sponsor personnel or a deputy will check treatment reconciliation. In certain circumstances, used and unused study treatment containers may be destroyed at the site once study treatment accountability is finalized and has been checked by the sponsor personnel or the deputy, and written permission for destruction has been obtained from the sponsor.

5.1.7 Study treatment accountability and compliance with study treatment

5.1.7.1 *Study treatment accountability*

The inventory of study treatment dispensed and returned (i.e., study treatment accountability) must be performed by the study staff daily during the treatment period. It is recorded on the IMP dispensing and accountability log and checked by the CRA during site visits and at the end of the study if needed. The log will contain information including the kit and vial numbers, the date/time of study drug preparation, the identity of the person preparing the study drug, and the storage conditions of the prepared infusion bags. The used and unused study medication vials must be retained at the site until they are verified by the CRA. Exceptions may occur e.g., in the event that a local process requests immediate destruction of the study treatment. Local study treatment destruction processes must be provided to, and approved by, the sponsor.

5.1.7.2 *Study treatment compliance*

Study treatment compliance is a measure of how closely the protocol instructions for administering study drug were adhered to.

The start and end date/time of study drug administration and the hourly dose is recorded in the eCRF. As dose adjustments of study drug are not permitted by the study protocol, only the dose of 15 mg/h is expected.

Interruptions of study treatment are allowed by the protocol but should be kept as short as possible. Any interruption due to an AE is to be recorded in the eCRF. Interruptions for other reasons (e.g., logistical, administrative), are to be recorded in the eCRF only if their duration is ≥ 15 minutes.

Over the entire treatment period, compliance is expected to be 100%. Any non-compliance (administration of study drug at a rate other than 15 mg/h), will be considered as a protocol deviation. The investigator must document in the subject's source notes the reasons for this non-compliance and any actions to be taken to avoid future recurrences.

5.2 Previous and concomitant therapy

5.2.1 Definitions

For the purposes of this study, a previous therapy is defined as any treatment for which the end date is prior to the signature of the ICF.

A study-concomitant therapy is defined as any treatment that is ongoing or initiated after the signature of the ICF, or initiated up to 24 hours post-study drug discontinuation.

A therapy that is study treatment-concomitant is any treatment that is either ongoing at the start of study treatment or is initiated during the treatment period until the time of permanent study drug discontinuation.

5.2.2 Concomitant therapy required to control blood pressure and fluid status (mandatory compliance with the Patient Management Guidelines)

Due to the potential for hypotension with clazosentan administration, prior to initiating study drug, BP and fluid status will be controlled, if needed, with i.v. vasopressors and fluid administration as per the study-specific Patient Management Guidelines [see Appendix 3]. Vasopressor and fluid therapy will be administered as required, according to these guidelines, until the permanent discontinuation of study drug.

5.2.3 Allowed concomitant therapy

5.2.3.1 *Local standard of care*

The usual standard of care for the management of aSAH is allowed until the primary endpoint assessment at 14 days post-study drug initiation, except for those therapies listed in the "forbidden concomitant medication" section, and must be documented in the medical charts.

Nimodipine (oral or i.v.) may be administered for the usual duration if it is routine standard of care at the site.

"Statins" (e.g., simvastatin, pravastatin) may only be administered if the subject was receiving them chronically for treatment of high cholesterol.

Vaccines (including those for COVID-19) may be administered at any time during the study. They will be recorded as described in Section 5.2.5.

5.2.3.2 *Rescue therapy*

For the purpose of this study, rescue therapy refers to the escalation of medical therapy beyond standard HD therapy, for the treatment of refractory vasospasm. Refractory vasospasm is characterized by a minimum of 2-points worsening on either of the neurological scales and no response to HD therapy. The following therapies are considered rescue therapies:

- balloon angioplasty,
- intra-arterial/intrathecal/intra-cisternal/intra-ventricular administration of vasodilators or ozagrel.

The decision to administer the above rescue therapies is based on local standard of care and is allowed at any time during the study for refractory vasospasm. The refractory nature is to be documented in the eCRF.

Intravenous administration of vasodilators (e.g., nicardipine, milrinone) are allowed as rescue therapy only if preceded by intra-arterial administration of a vasodilator.

The other medications in the "forbidden concomitant therapy" section below (with their respective routes of administration) are not considered as rescue therapies and their administration is forbidden until Day 14 post-study drug initiation.

Study drug must be temporarily interrupted prior to any rescue therapy, and must be resumed after the completion of the therapy.

5.2.4 Forbidden concomitant therapy

The following medications/therapies are forbidden until the primary endpoint assessment at Day 14 post-study drug initiation, due to their potential to interfere with the evaluation of efficacy or safety, or due to the potential for a drug-drug interaction with study drug (refer to the IB for more information [Clazosentan IB]). Those that are described above under "rescue therapy" are permitted in the treatment of refractory vasospasm, but are forbidden otherwise.

- Intra-aortic balloon device.
- Lumbar and/or cisternal drainage for the prevention of cerebral vasospasm / DCI.
- Milrinone i.v., nicardipine i.v.*, and intrathecal/intra-cisternal/intra-ventricular vasodilators (e.g., nimodipine), must be discontinued at least 4 hours prior to enrollment.

*Administration of i.v. milrinone at any time from hospital admission to randomization is exclusionary if used to prevent or treat cerebral vasospasm. Nicardipine i.v. may be used at any time for blood pressure control.

- Magnesium i.v., albumin i.v., or plasma volume expander if administered specifically for the prevention of cerebral vasospasm and/or DCI.
- Thrombolytics (including intrathecal, intra-cisternal, and intra-ventricular, administration) and antifibrinolytics (e.g., tranexamic acid). Use of thrombolytics to open an occluded drain is permitted.
- Hypertonic saline i.v., if administered in the absence of hyponatremia, brain edema, or high ICP.
- Mannitol i.v., if administered in the absence of brain edema or high ICP.
- Strong inhibitors of OATP1B1 and OATP1B3 transporter proteins (e.g., cyclosporin A, rifampicin, lopinavir/ritonavir).
- Other ERAs.
- Any investigational drugs, procedures, or devices, including any other medication administered to prevent/treat cerebral vasospasm that has not been approved for this specific indication by local health authorities (e.g., therapeutic hypothermia, “statins”).
- Traditional medicines (i.e., plant-, animal-, or mineral-based medicine, such as traditional Chinese medicine).

Study treatment must be permanently discontinued if one of the following is initiated during the treatment period:

- Another ERA.
- Another investigational product/procedure.
- A strong inhibitor of OATP1B1 and OATP1B3 transporter proteins (e.g., cyclosporin A, rifampicin, lopinavir/ritonavir).

5.2.5 Reporting of previous/concomitant therapy in the eCRF

All previous and study-concomitant therapies taken/administered less than or equal to 24 hours prior to randomization into the study will be recorded in the eCRF. Exceptions are made for medications administered for the purpose of the aneurysm-securing procedure, either intra or peri-procedurally (e.g., anesthetics), which do not need to be entered into the eCRF. All medications administered after randomization and up to 24 hours post-study drug discontinuation will also be recorded in the eCRF. Additionally,

- forbidden medication/therapy are to be recorded from hospital admission until Day 14 post-study drug initiation,
- rescue medication must be recorded until Week 12 post-aSAH,

- medications administered for serious AEs (SAEs) are to be recorded from study drug start until EOS.
- medications administered for AEs/SAEs related to a protocol-mandated procedure must be recorded from ICF signature up until EOS.

The generic name, start/end dates and times of administration, route, dose regimen, and indication will be recorded.

The following drug and non-drug therapies should be recorded in the eCRF if they were performed at any time from randomization up to hospital discharge and from hospital discharge up to Week 12:

- ICP monitoring (with start and end dates).
- Ventricular drainage (with start and end dates).
- Shunt (ventriculoperitoneal or ventriculoatrial).
- Sub/epidural hematoma evacuation.
- Lumbar drainage (with start and end dates).
- Mechanical ventilation (with start and end dates).
- Tracheostomy.
- Cerebral angioplasty (with start and end dates/times).
- Other local rescue therapies for cerebral vasospasm (e.g., intrathecal, intra-cisternal, intra-ventricular vasodilators, intra-aortic balloon counter-pulsation) with start and end dates/times.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoint

The primary efficacy endpoint is the occurrence of clinical deterioration due to DCI, from study drug initiation up to 14 days post-study drug initiation.

Clinical deterioration due to DCI is defined as a worsening of at least 2 points compared to the reference score, on the modified GCS (mGCS) or the abbreviated National Institutes of Health Stroke Scale (aNIHSS), lasting for at least 2 hours, which cannot be entirely attributed to causes other than cerebral vasospasm. It is centrally adjudicated by the CEC based on a written charter and review of clinical data, case narratives, angiograms and CT scans.

The initial reference scores to which subsequent scores are compared is assessed within 30 minutes prior to study drug start. Thereafter, the reference scores will depend on the clinical evolution of the subject. After sustained improvements or worsenings in clinical

status, the new reference scores will be recalibrated to reflect the best mGCS and aNIHSS scores attained by the subject immediately prior to an episode of clinical deterioration.

Subjects who die between study drug start up to and including 14 days post-study drug initiation will be considered as presenting with clinical deterioration due to vasospasm. Subjects who cannot be evaluated for neurological status at any time during this same period will be considered as presenting with clinical deterioration due to vasospasm if either rescue therapy was administered for a relevant vasospasm or the reason for not being evaluable is vasospasm-related as confirmed by the CEC. Otherwise, these subjects will not be considered as presenting with clinical deterioration due to vasospasm.

Subjects who are discharged from the study site prior to Day 14 post-study drug initiation will have less than 14 days of neurological scales assessments performed. These subjects will have a follow-up visit or telephone call, covering their clinical status between discharge and Day 14 post-study drug start, as described in Section 7.2.2.2.1. This follow-up data for subjects who were enrolled under earlier protocol versions and discharged prior to Day 14 will also be collected retrospectively. If this follow-up reveals that the subject was re-hospitalized or transferred to another facility, and DCI cannot be ruled out as a primary or contributing cause, the subject will be considered as meeting the primary endpoint.

If a subject has less than 14 days of neurological scales available and there is an absence of follow-up information (including subjects withdrawn from the study during the observation period) the primary endpoint will be assessed based on the totality of available clinical data.

Further details are provided in the CEC charter.

6.1.2 Secondary efficacy endpoints

6.1.2.1 *Main secondary endpoint*

The main secondary endpoint is the occurrence of clinically relevant cerebral infarction* at Day 16 post-study drug initiation defined as:

- all-cause cerebral infarction ≥ 5 cm^3 or
- cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI

*Cerebral infarction refers to new or worsened infarcts and is determined by central radiology review comparing the total volume of infarcts on the CT scan performed 16 days after study drug initiation with the total volume on the CT scan performed just prior to randomization. If the CT scan cannot be performed on Day 16, then it is acceptable for the CT to be performed within the 7 days following Day 16. If a subject is discharged from the hospital prior to Day 16, the CT scan is performed on the day of hospital discharge. Clinical deterioration due to DCI and cerebral infarctions ≥ 5 cm^3 are confirmed by the CEC. Cerebral infarctions < 5 cm^3 in subjects with clinical deterioration due to DCI are derived from both the CEC data (primary endpoint) and IRC data (for infarct size).

6.1.2.2 *Other secondary endpoints*

The other secondary endpoints are:

- the long-term clinical outcome assessed by the mRS at Week 12 post-aSAH, dichotomized into poor outcome (score ≥ 3) and good outcome (score < 3) and
- the long-term clinical outcome assessed by the Glasgow Outcome Scale Extended (GOSE) at Week 12 post-aSAH, dichotomized into poor outcome (score ≤ 4) and good outcome (score > 4).

6.1.3 Exploratory efficacy endpoints

6.1.3.1 *Cognition endpoints*

- Cognitive status, as assessed by the change from baseline to 14 days post-study drug initiation on the Montreal Cognitive Assessment (MoCA), for those subjects that have a MoCA at baseline and at 14 days post-study drug initiation.
- Cognitive status, as assessed by the change from baseline to Week 12 post-aSAH on the MoCA, for those subjects that have a MoCA at baseline and at Week 12 post-aSAH.
- Cognitive status as assessed by the change in MoCA from 14 days post-study drug initiation to Week 12 post-aSAH, for those subjects that have a MoCA at 14 days post-study drug initiation and at Week 12 post-aSAH.
- Cognitive status as assessed by the MoCA at 14 days post-study drug initiation and at Week 12 post-aSAH.

6.1.3.2 *Other efficacy endpoints*

- Number of episodes of clinical deterioration due to DCI from study drug initiation up to 14 days post-study drug initiation, as adjudicated by the CEC.
- Occurrence of all-cause new or worsened cerebral infarction ≥ 5 cm^3 in total volume, as adjudicated by the CEC.

6.2 Safety endpoints

- Occurrence of treatment-emergent AEs (TEAEs) up to 24 hours after study drug discontinuation.
- Occurrence of serious TEAEs up to 24 hours after study drug discontinuation.
- Occurrence of TEAEs leading to premature discontinuation of study drug.
- Occurrence of death (all causes) up to Week 24 post-aSAH.
- Occurrence of TEAEs of specific interest (i.e., lung complications, hypotension, anemia, cerebral hemorrhage, cerebral edema, fluid retention, hepatic disorders, tachyarrhythmia) up to 24 hours after study drug discontinuation.
- Occurrence of rescue therapy-specific AEs up to hospital discharge (or Week 12, whichever is earlier).

- Occurrence of treatment-emergent marked laboratory abnormalities up to 24 hours after study drug discontinuation, and changes from baseline to end of study drug administration for selected centrally assessed laboratory parameters.

6.3 Quality of Life endpoints

- Generic QoL as measured by the EQ-5D at Week 12 and Week 24 post-aSAH and the Oxford Participation and Activities Questionnaire (Ox-PAQ) at Week 12 post-aSAH.
- Generic QoL as measured by the change in EQ-5D index score and visual analog scale from 12 to 24 weeks post-aSAH, for those subjects that have an EQ-5D both at Week 12 and at Week 24 post-aSAH.
- Disease-specific QoL as measured by the Stroke Specific Quality of Life (SS-QOL) at Week 12 post-aSAH.

6.4 Pharmaco-economic endpoints

- Number and type of episodes of rescue therapy, from randomization up to hospital discharge and from hospital discharge up to Week 12 post-aSAH.
- Number and type of specific (pre-specified) medical treatments and therapies from randomization up to hospital discharge and from hospital discharge up to Week 12.
- Length of initial and total ICU stay, length of total hospitalization, and duration in different hospital/institutional care units, from randomization up to hospital discharge and from hospital discharge until Week 12.
- Intensity of rehabilitation care up to Week 12 post-aSAH.
- First post-hospital discharge location.
- Duration of home care support post-initial hospital discharge.
- Employment status at Week 24 post-aSAH.

6.5 Biomarker endpoints

- Area under the plasma concentration-time curve (AUC) of S100b protein from baseline to Day 10 post-study drug initiation.
- AUC of S100b protein from baseline to Day 14 post-study drug initiation.

6.6 Rationale for primary and secondary efficacy endpoints

6.6.1 Rationale for the choice of the primary efficacy endpoint

The primary efficacy endpoint for the proposed Phase 3 study is the occurrence of clinical deterioration due to DCI from study drug initiation up to 14 days post-study drug initiation. It is defined as a sustained worsening in neurological status that cannot be entirely attributed to causes other than cerebral vasospasm as described in Section 6.1.1.

The primary endpoint as defined captures the most relevant clinical manifestations of post-aSAH cerebral ischemia that can be prevented by an anti-vasospastic strategy. The

poor prognosis of patients who develop clinical deterioration due to DCI and its downstream complications are well-established [see Sections 1.1 and 1.5]. Therefore, showing a significant reduction in the incidence of clinical deterioration due to DCI, supported by clinically relevant effects on the secondary and exploratory endpoints, will altogether demonstrate the clinically meaningful benefit of clazosentan in this disease indication.

The assessment period for the primary endpoint extends until 14 days after the initiation of treatment, thus covering the treatment period, and corresponding to the period during which DCI is most likely to occur.

The proposed primary endpoint definition is aligned with the recommendations of an international multi-disciplinary aSAH research group who proposes to standardize the definition of clinical deterioration due to DCI as the occurrence of focal neurological impairment or a decrease of at least 2 points on the GCS lasting for at least 1 hour [Vergouwen 2010]. The extension of the duration of the deterioration to 2 hours in the REACT protocol will exclude transient fluctuations in clinical status and thus increase the robustness of the endpoint definition.

Long-term clinical outcome has not been chosen as the primary efficacy endpoint. At the time the nimodipine trials were conducted, early ischemic complications were largely the first cause of poor outcome and the frequency of brain infarct was in excess of 40–50% post-aSAH [Petruk 1988, Ohman 1991]. Today, the vasospasm-related infarct rate has considerably decreased (13.3 and 13.2% in the placebo groups of the CONSCIOUS-2 and CONSCIOUS-3 studies, respectively), hence reducing the proportion of poor outcome due to vasospasm-related infarcts. It is estimated that today, the direct contribution of vasospasm does not exceed one-third of the overall rate of unfavorable outcome, the remainder of poor outcome being related to the primary injury and iatrogenic and medical complications inherent to the underlying condition. Hence, testing a treatment which only impacts vasospasm would result, with the GOSE as primary endpoint, in a sample size of the study exceeding that which would be feasible given the rarity of the disease [Kreiter 2009].

6.6.2 Rationale for the choice of secondary efficacy endpoints

6.6.2.1 *Occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation defined as: all-cause cerebral infarction ≥ 5 cm^3 or cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI*

Among the known complications of aSAH, the occurrence of cerebral infarction on neuro-imaging has been repeatedly shown to be the strongest predictor of poor long-term clinical outcome [Frontera 2009, Kreiter 2009, Vergouwen 2010]. The clinical relevance of this secondary efficacy endpoint is therefore high, and cerebral infarction was even suggested as a primary endpoint in recent international recommendations for aSAH trials [Vergouwen 2010].

A post-hoc analysis of the data from the CONSCIOUS-2 and CONSCIOUS-3 studies shows that infarcts with a total cumulative volume ≥ 5 cm^3 are mostly related to vasospasm and have a high association with poor clinical outcome at 3 months, as compared to those with a cumulative volume less than 5 cm^3 [Roux 2021]. Therefore, the original secondary endpoint definition (all-cause new or worsened cerebral infarction of a total volume ≥ 5 cm^3) only included those infarcts ≥ 5 cm^3 in order to set a meaningful cut-off for infarct volume when considering all infarcts irrespective of cause. Since the determination of underlying infarct etiology based on CT scan assessment is often challenging, the 5 cm^3 threshold serves as a proxy for vasospasm-relatedness. The endpoint also allowed the identification of ischemic events that are not detectable on clinical examination or that develop in patients who cannot be evaluated neurologically (e.g., due to sedation or very poor clinical status). However, routine blinded monitoring of the event rate during the REACT study revealed a lower-than-expected incidence of infarcts ≥ 5 cm^3, resulting in insufficient power to detect a treatment effect. This led to an expansion of the endpoint definition to include smaller but clinically relevant infarcts.

Although the infarcts < 5 cm^3 have a lower association with vasospasm and poor outcome, their vasospastic origin and their contribution to poor outcome cannot be excluded. The presence of these smaller infarcts may lead to important clinical manifestations [Weidauer 2007, Biesbroek 2017]. It would therefore be desirable to identify, from the smaller infarcts, those that are clinically relevant, rather than including all infarcts < 5 cm^3. Indeed, it has been observed from the CONSCIOUS-1 [Macdonald 2008] and the recently completed clazosentan Japanese Phase 3 studies [in press], that including all infarcts irrespective of size and etiology results in a dilution of the treatment effect. Therefore, the modified endpoint definition includes those smaller infarcts which occur in subjects who deteriorate due to DCI.

Despite being correlated with the primary efficacy endpoint, the main secondary endpoint goes beyond clinical symptoms since deterioration due to DCI does not always result in the development of cerebral infarction. Conversely, cerebral infarction may be observed on a CT scan in the absence of clinical symptoms in up to 20% of aSAH patients [Rabinstein 2005, Schmidt 2008].

The assessment of this endpoint at Day 16 post-study drug initiation will allow for the detection of infarcts that may be the consequence of cerebral ischemia that occur on Day 14 (primary endpoint evaluation is up to Day 14).

6.6.2.2 *Modified Rankin Scale and Glasgow Outcome Scale Extended*

Since the detection of a treatment effect on long-term clinical outcome using an anti-vasospastic drug would require a sample size exceeding several thousand subjects [Kreiter 2009, Rosengart 2007], it is not expected that any beneficial effect of clazosentan on the mRS or the GOSE be demonstrable with the current feasibility-limited sample size. However, the absence of a negative trend on these assessments will be an important part of the overall benefit-risk assessment of clazosentan in subjects post-aSAH. This justifies the

use of mRS and GOSE as other secondary endpoints. The MRS is included in the statistical hierarchical testing strategy, just before the GOSE. Results from the Japanese Phase 3 studies (AC-054-305 and 306) show that the mRS can slightly better discriminate the treatment effect of clazosentan on clinical outcome at Week 12 post-aSAH, compared to the GOSE. This suggests a better sensitivity of the mRS, despite the similarity of the two instruments. The mRS has recently been recommended over the GOSE as the preferred scale for measuring the long-term clinical outcome of SAH by the international clinical experts of the SAH common data elements working group [Suarez 2019].

Prevention of vasospasm and DCI post-aSAH may be demonstrated to have an impact on long-term clinical outcome when confounding factors, on which an anti-vasospastic drug like clazosentan cannot have an effect, have been removed. In CONSCIOUS-3, when subjects with neurological impairment, either due to the initial bleed or the aneurysm-repair procedure are removed, a positive effect of clazosentan on long-term outcome is observed. This observation suggests that in this population, secondary neurological deterioration leading to poor outcome is mainly driven by vasospasm. Hence, an exploratory analysis will assess the effect of clazosentan on the mRS and GOSE at Week 12 post-aSAH, in the subset of subjects who fully recovered neurologically immediately prior to study drug start.

7 STUDY PERIODS, VISITS AND ASSESSMENTS

7.1 Study periods and “visits”

The study periods and “visits” with their respective time windows are listed in the visit and assessment schedules.

Table 1 corresponds to the high-risk prevention group and Table 2 to the early treatment group.

Note: Table 2 is provided for the early treatment group although recruitment into this group was discontinued from protocol version 6 onwards.

Visit and assessment schedules

Table 1 Visit and assessment schedule for subjects in the high-risk prevention group

PERIOD		SCREENING Period		OBSERVATION Period (for 14 days post-study drug initiation irrespective of treatment duration) TREATMENT Period (min. 10, max. 14 days of treatment)				24 h safety FU Period	Extended FU Period (From end of 24 h safety FU Period until EOS)	
Timing / assessment		within 96 hours post-aSAH			for 14 days post-SD start			until 24 h post-SD stop	WEEK 12 VISIT	END OF STUDY (EOS)[19]
	Hospital admission	From ICF to randomization	Prior to study drug (SD) start	SD start	Daily in ICU[8]	During observation period[8]	Worsening of ≥ 2 points on mGCS / aNIHSS[8]	End-of-Treatment (EOT)	84 days post-aSAH (± 7 d)	24 weeks (168 days ± 14 days) post-aSAH
Informed consent		X								
Demographics		X								
Medical history		X	X							
Incl./Excl. criteria		X								
Height, weight		X								
Vital signs (BP, HR, ICP[1], CVP[1])			X (within 60 min)		q6h (± 1 h)	q6h (± 1 h) (every 12 h if not in ICU)				
Body temperature			X (within 60 min)		X (every 12 h ± 1 h)					
Fluid balance (24 h)[16]			X		X					
ECG parameters			X (within 60 min)		X[9]			X (within 2 h post-SD stop)		
Laboratory tests (local [l]/ central [c])		X (l)	X (c) (within 60 min)		X[10] (c) (EOD for 14 days)		X (l) / SpO_2	X[10] (c) (within 2 h post-SD stop)		
Biomarker			X (c) (within 60 min)		X (c) (EOD for 14 days)		X (c) if CNS cause	X (c) (within 2 h post-SD stop)		
Pregnancy test		X (serum, (l))							X (urine)	
Concomitant medications[18]	X				X					
Non-drug treatments / interventions			X		X					
WFNS	X[2]	X, X[3]								

PERIOD		SCREENING Period		OBSERVATION Period (for 14 days post-study drug initiation irrespective of treatment duration) TREATMENT Period (min. 10, max. 14 days of treatment)				24 h safety FU Period	Extended FU Period (From end of 24 h safety FU Period until EOS)	
Timing / assessment		within 96 hours post-aSAH			for 14 days post-SD start			until 24 h post-SD stop	WEEK 12 VISIT	END OF STUDY (EOS)[19]
	Hospital admission	From ICF to randomization	Prior to study drug (SD) start	SD start	Daily in ICU[8]	During observation period[8]	Worsening of ≥ 2 points on mGCS / aNIHSS[8]	End-of-Treatment (EOT)	84 days post-aSAH (± 7 d)	24 weeks (168 days ± 14 days) post-aSAH
Total GCS	X[2]	X, X[3]								
mGCS/aNIHSS			X (within 30 min)		q6h[11] (± 1 h)	X[12] (± 1 h)	X (hourly ± 15 min for first 2 h)			
Angiogram (DSA or CTA)	X[4]	X (local standard of care, not assessed centrally)					X (if CNS cause)			
CT scan	X[4]	X[5]					X (if CNS cause)	X[13] (16 days post-SD start)		
Subject narrative							X (14 days post-SD start)			
MoCA[6]		X[7]				X (14 ± 1 day post-SD start) [17]			X	
GOSE									X	
SS-QOL, Ox-PAQ									X	
EQ-5D									X	X
Study drug administration				X	X					
Adverse events[14]		X			X					
Serious adverse events[15]		X			X					
Pharmaco-economic assessments			X		X					
Employment status										X

1. ICP/CVP will be measured and recorded for those subjects with ICP and/or CVP monitoring in place.
2. If the subject was transferred from another hospital, the GCS score and WFNS grade will correspond to the assessments made at the referral hospital, unless these were not done or not reliable.
3. Two assessments: post aneurysm-securing procedure and prior to randomization.
4. If performed at a referral hospital, is of acceptable quality, and is available in digital format at the investigational site at the time of screening, does not need to be repeated.
5. This CT scan is to be performed at least 8 hours after the aneurysm-securing procedure and within 24 hours prior to randomization.
6. Only performed if subject is GCS ≥ 13 and extubated (if applicable).
7. As soon as possible after recovering from the aneurysm-securing procedure and prior to SD start.
8. If there is a worsening of at least 2 points in the mGCS and/or the aNIHSS the assessments in the "worsening" column must be performed on top of the regularly scheduled assessments. The mGCS and the aNIHSS must be repeated hourly for at least the first 2 hours after a 2-point worsening. If the deterioration is believed to be of CNS origin, a cerebral angiogram and a cerebral CT scan must be performed within 6 hours of the start of the symptoms and submitted for central review and a blood sample for S100b protein must be drawn within 1 hour of the confirmation of the neurological deterioration episode or no later than 3 hours from the initial worsening. Local lab tests should be obtained as close as possible to the time of the clinical worsening (max. 1 hour after time of confirmed worsening) [See Section 7.2.2.2.1 for details].
9. QT, QRS, PR, RR intervals, and HR will be measured and recorded in the eCRF if subject experiences an AE related to cardiac rhythm abnormalities [see Section 7.2.3.7].
10. Any clinically significant laboratory values must be reported as an AE/SAE as appropriate and those still abnormal at the time of the EOS assessment will be followed up based on local routine standard of care. A local laboratory may be requested by the sponsor to document the event and its resolution, and the results recorded in the eCRF [see Section 7.2.4.1].
11. At least once per day for subjects that require uninterrupted continuous sedation.
12. After the end of the study drug infusion, the mGCS and aNIHSS will continue to be assessed every 6 hours if the subject is still in the ICU (or equivalent ward), until 14 days after study drug initiation. They will be assessed at least once per day if the subject requires continuous uninterrupted sedation. If the subject is no longer in the ICU (i.e., has been sent to a regular/general ward), the mGCS and aNIHSS will be assessed at least once every 12 hours (± 1 h) until 14 days after study drug initiation. In the unavoidable situation where the subject is discharged from the study site before completing the observation period, their clinical status must be followed up to cover the period between discharge and Day 14 post-study drug start. The follow-up should be performed on Day 14 post-study drug initiation or as soon as possible after. This follow-up is not required if the subject was discharged on Day 13 and there is at least one set of neurological assessment scales available on this day.
13. If the CT scan cannot be performed on the 16th day post-SD start, then it is acceptable if the CT scan is performed up to 7 days after Day 16. The CT scan will be performed on the day of hospital discharge for those subjects who are discharged from the hospital prior to 16 days after study drug start. If no CT scan is available at hospital discharge, the last CT scan performed prior to discharge may be used for this assessment. For further details see Section 7.2.2.4.4.
14. All AEs that occur after signing the ICF and up to the EOS visit must be recorded if related to a study-mandated procedure. All other AEs are to be reported from SD initiation until 24 hours post-permanent SD discontinuation.
15. All SAEs that occur after signing the ICF and up to the EOS visit must be recorded if related to a study-mandated procedure. All other SAEs are to be reported from SD initiation until EOS. Waived SAEs do not require reporting to the sponsor's Drug Safety department within 24 hours of the knowledge of its occurrence [see Section 9.1.3].
16. Applicable during study drug administration only. Balance is captured if a urine catheter is present. Otherwise, 24-hour fluid intake will be measured and recorded.
17. This MoCA will be performed on the day of hospital discharge for those subjects who are discharged from the hospital prior to 14 days after study drug start.
18. For details on the concomitant medication recording refer to Section 5.2.5.
19. The EOS visit is conducted remotely as a telephone interview.

AE = adverse event; aNIHSS = abbreviated National Institutes of Health Stroke Scale; aSAH = aneurysmal subarachnoid hemorrhage; BP = blood pressure; CNS = central nervous system; CT = computerized tomography; CTA = computerized tomography angiography; CVP = central venous pressure; DSA = digital subtraction angiography; ECG = electrocardiogram; eCRF = electronic case report form; EOD = every other day; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale Extended; HR = heart rate; ICF = informed consent form; ICP = intracranial pressure; ICU = intensive care unit; mGCS = modified Glasgow Coma Scale; MoCA = Montreal Cognitive Assessment; Ox-PAQ = Oxford Participation and Activities Questionnaire; SAE = serious adverse event; SD = study drug; SpO_2 = peripheral capillary oxygen saturation; SS-QOL = Stroke Specific Quality of Life; WFNS = World Federation of Neurological Societies.

Table 2 Visit and assessment schedule for subjects in the early treatment group (recruitment into this group was discontinued from protocol version 6 onwards)

PERIOD		SCREENING Period		OBSERVATION Period (for 14 days post-study drug initiation irrespective of treatment duration)				24 h safety FU Period	Extended FU Period (From end of 24 h safety FU period until EOS)	
			TREATMENT Period (min. 6, max. 14 days of treatment)							
Timing / assessment		until max. Day 14 post-aSAH	within 24 h of pre-randomization angiogram[5]		for 14 days post-SD start			until 24 h post-SD stop	WEEK 12 VISIT	END OF STUDY (EOS) [21]
	Hospital Admission	from ICF to randomization	Prior to study drug (SD) start	SD start	Daily in ICU[9]	During observation period[9]	Worsening of ≥ 2 points on mGCS / aNIHSS[9]	End-of-Treatment (EOT)	84 days post-aSAH (± 7 d)	24 weeks (168 days ± 14 days) post-aSAH
Informed consent		X								
Demographics		X								
Medical history		X	X							
Incl./Excl. criteria		X								
Height, weight		X								
Vital signs (BP, HR, ICP[1], CVP[1])			X (within 60 min)		q6h (± 1 h)	q6h (± 1 h) (every 12 h if not in ICU)				
Body temperature			X (within 60 min)		X (every 12 h ± 1 h)					
Fluid balance (24 h)[18]			X		X					
ECG parameters			X (within 60 min)		X[10]			X (within 2 h post-SD stop)		
Laboratory tests (local [l]/ central [c])		X (l)	X (c) (within 60 min)		X[11] (c) (EOD for 14 days)		X (l) /SpO_2	X[11] (c) (within 2 h post-SD stop)		
Biomarker			X (c) (within 60 min)		X (c) (EOD for 14 days)		X (c) (if CNS cause)	X (c) (within 2 h post-SD stop)		
Pregnancy test		X (serum, (l))							X (urine)	
Concomitant medications[20]		X			X					
Non-drug treatments / interventions			X		X					
WFNS	X[2]	X, X[3]								
Total GCS	X[2]	X, X[3]								

PERIOD		SCREENING Period			OBSERVATION Period (for 14 days post-study drug initiation irrespective of treatment duration)				24 h safety FU Period	Extended FU Period (From end of 24 h safety FU period until EOS)	
				TREATMENT Period (min. 6, max. 14 days of treatment)							
Timing / assessment		**until max. Day 14 post-aSAH**		**within 24 h of pre-randomization angiogram[5]**	**for 14 days post-SD start**			**until 24 h post-SD stop**	**WEEK 12 VISIT**	**END OF STUDY (EOS) [21]**	
	Hospital Admission	**from ICF to randomization**		**Prior to study drug (SD) start**	**SD start**	**Daily in ICU[9]**	**During observation period[9]**	**Worsening of ≥ 2 points on mGCS / aNIHSS[9]**	**End-of-Treatment (EOT)**	**84 days post-aSAH (± 7 d)**	**24 weeks (168 days ± 14 days) post-aSAH**
mGCS/aNIHSS				X (within 30 min)		q6h[12] (± 1 h)	X[13] (± 1 h)	X (hourly ± 15 min for first 2 h)			
Angiogram (DSA or CTA)	X[4]	X[17]	X[5]					X (if CNS cause)			
CT scan	X[4]	X[6]						X (if CNS cause)	X[14] (16 days post-SD start)		
Subject narrative								X (14 days post-SD start)			
MoCA[7]		X[8]					X (14 ± 1 day post-SD start) [19]			X	
GOSE										X	
SS-QOL, Ox-PAQ										X	
EQ-5D										X	X
Study drug administration					X	X					
Adverse events[15]		X				X					
Serious adverse events[16]		X				X					
Pharmaco-economic assessments				X		X					
Employment status											X

1. ICP/CVP will be measured and recorded for those subjects with ICP and/or CVP monitoring in place.
2. If the subject was transferred from another hospital, the GCS score and WFNS grade will correspond to the assessments made at the referral hospital, unless these were not done or unreliable.
3. Two assessments: post aneurysm-securing procedure and prior to randomization.
4. If performed at a referral hospital, is of acceptable quality, and is available in digital format at the investigational site at the time of screening, does not need to be repeated.
5. The DSA or CTA which was performed according to local routine standard of care (preferably between Day 7 and 11 post-aSAH) and used to diagnose and document the vasospasm will be collected.

6. This CT scan is to be performed at least 8 hours after the aneurysm-securing procedure and within 24 hours prior to randomization.
7. Only performed if subject is GCS ≥ 13 and extubated (if applicable).
8. As soon as possible after recovering from the aneurysm-securing procedure and prior to SD start.
9. If there is a worsening of at least 2 points in the mGCS and/or the aNIHSS the assessments in the "worsening" column must be performed on top of the regularly scheduled assessments. The mGCS and the aNIHSS must be repeated hourly for at least the first 2 hours after a 2-point worsening. If the deterioration is believed to be of CNS origin, a cerebral angiogram and a cerebral CT scan must be performed within 6 hours of the start of the symptoms and submitted for central review and a blood sample for S100b protein must be drawn within 1 hour of the confirmation of the neurological deterioration episode or no later than 3 hours from the initial worsening. Local lab tests should be obtained as close as possible to the time of the clinical worsening (max. 1 hour after time of confirmed worsening) [see Section 7.2.2.2.1 for details].
10. QT, QRS, PR, RR intervals, and HR will be measured and recorded in the eCRF if subject experiences an AE related to cardiac rhythm abnormalities [see Section 7.2.3.7].
11. Any clinically significant laboratory values must be reported as an AE/SAE as appropriate and those still abnormal at the time of the EOS assessment will be followed up based on local routine standard of care. A local laboratory may be requested by the sponsor to document the event and its resolution, and the results recorded in the eCRF [see Section 7.2.4.1].
12. At least once per day for subjects that require uninterrupted continuous sedation.
13. After the end of the study drug infusion, the mGCS and aNIHSS will continue to be assessed every 6 hours if the subject is still in the ICU (or equivalent ward), until 14 days after study drug initiation. They will be assessed at least once per day if the subject requires continuous uninterrupted sedation. If the subject is no longer in the ICU (i.e., has been sent to a regular/general ward), the mGCS and aNIHSS will be assessed at least once every 12 hours (± 1 h) until 14 days after study drug initiation. In the unavoidable situation where the subject is discharged from the study site before completing the observation period, their clinical status must be followed up to cover the period between discharge and Day 14 post-study drug start. The follow-up should be performed on Day 14 post-study drug initiation or as soon as possible after. This follow-up is not required if the subject was discharged on Day 13 and there is at least one set of neurological assessment scales available on this day.14. If the CT scan cannot be performed on the 16th day post-SD start, then it is acceptable if the CT scan is performed up to 7 days after Day 16. The CT scan will be performed on the day of hospital discharge for those subjects who are discharged from the hospital prior to 16 days after study drug start. If no CT scan is available at hospital discharge, the last CT scan performed prior to discharge may be used for this assessment. For further details see Section 7.2.2.4.4.
15. All AEs that occur after signing the ICF and up to the EOS visit must be recorded if related to a study-mandated procedure. All other AEs are to be reported from SD initiation until 24 hours post-permanent SD discontinuation.
16. All SAEs that occur after signing the ICF and up to the EOS visit must be recorded if related to a study-mandated procedure. All other SAEs are to be reported from SD initiation until EOS. Waived SAEs do not require reporting to the sponsor's Drug Safety department within 24 hours of the knowledge of its occurrence [see Section 9.1.3].
17. Angiogram performed as per local standard of care to confirm successful aneurysm-securing procedure. Angiogram not assessed centrally.
18. Applicable during study drug administration only. Balance is captured if a urine catheter is present. Otherwise, 24-hour fluid intake will be measured and recorded.
19. This MoCA will be performed on the day of hospital discharge for those subjects who are discharged from the hospital prior to 14 days after study drug start.
20. For details on the concomitant medication recording refer to Section 5.2.5.
21. The EOS visit is conducted remotely as a telephone interview.

AE= adverse event; aNIHSS = abbreviated National Institutes of Health Stroke Scale; aSAH = aneurysmal subarachnoid hemorrhage; BP = blood pressure; CNS = central nervous system; CT = computerized tomography; CTA = computerized tomography angiography; CVP = central venous pressure; DSA = digital subtraction angiography; ECG = electrocardiogram; eCRF = electronic case report form; EOD = every other day; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale Extended; HR = heart rate; ICF = informed consent form; ICP = intracranial pressure; ICU = intensive care unit; mGCS = modified Glasgow Coma Scale; MoCA = Montreal Cognitive Assessment; Ox-PAQ = Oxford Participation and Activities Questionnaire; SAE = serious adverse event; SD = study drug; SpO2 = peripheral capillary oxygen saturation; SS-QOL = Stroke Specific Quality of Life; WFNS = World Federation of Neurological Societies.

7.1.1 Screening/re-screening

7.1.1.1 *Screening period*

The screening period starts with the signature of the ICF [see Section 12.3 for informed consent procedure], and ends when the subject is either randomized into the study or screen-failed.

During this period, the subject is evaluated for suitability for the study based on the inclusion and exclusion criteria. The subjects who agree to participate in the study, and/or their proxy (i.e., a family member, legal representative, third party as applicable depending on local regulations), and the investigator/delegate must sign the ICF prior to any study-related assessment or procedure. These evaluations can take place on different days during the screening period. For a description of all assessments performed during the treatment period, refer to Table 1 and Section 7.2.

If the signing of the ICF and performance of the first study-specific procedures or assessments take place on the same day, it must be clear from the source documents that informed consent was obtained, and the ICF was also signed by the investigator or delegate, prior to any study-specific procedures being performed. If a study-specific procedure or assessment has already been performed as part of local standard practice prior to the consent, this information, provided it fulfills study requirements, may be used for study purposes and does not have to be repeated.

After the ICF has been signed, the investigator/delegate contacts the IRT system to allocate a subject number to the subject. Subjects who have signed the ICF when the enrollment target has been met may still be randomized into the study.

7.1.1.2 *Re-screening*

Subjects who did not meet the criteria for participation in the study (i.e., screen failure) are not allowed to be re-screened.

Since the screening period may extend over more than one day, any potentially transient condition during screening that may exclude a subject from the study (e.g., total bilirubin $> 2 \times$ the upper limit of normal) may be re-assessed at a later time point prior to randomization, to check for resolution or improvement. In this situation, the subject is kept in screening until the re-evaluation and is not immediately screen-failed.

7.1.1.3 *Randomization without subsequent start of study drug*

Subjects who are randomized but for whom study drug is never initiated (e.g., due to a sudden deterioration of the clinical status post-randomization), will be withdrawn from the study for safety or other reasons, by the investigator, and no further assessments will be performed. Imaging (cerebral CT scans and angiograms) that have been performed during

the screening period, and which are required according to the protocol, will be submitted to the imaging CRO for central review.

The EOS page of the eCRF must be completed with the reason for withdrawal from the study documented.

7.1.2 Treatment period

The treatment period starts with the performance of the baseline assessments, after the subject has been randomized into the study, and before the initiation of study drug. The treatment period covers the entire duration of study drug administration, and the corresponding assessments performed during the administration of study drug.

Treatment duration is dependent on the subject's individual clinical course and the investigator's judgment on the perceived need to continue the study drug [see Section 5.1.3.3.4 for further details].

For subjects randomized in the high-risk prevention group, treatment will start within 96 hours following the time of the aneurysm rupture, and be administered where possible, for 14 days. For subjects that require early discharge from the ICU (or equivalent), study drug must be administered for a minimum of 10 days. This treatment duration covers the period when vasospasm is most likely to occur.

For subjects randomized in the early treatment group*, treatment must begin within 24 hours of the time of the angiogram documenting the cerebral vasospasm necessary for entry into the study. Treatment will be administered for a minimum of 6 days and a maximum of 14 days.

For a description of all assessments performed during the treatment period, refer to Table 1 and Section 7.2.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

7.1.3 24-hour safety follow-up period

The 24-hour safety follow-up period starts with the permanent discontinuation of study drug and ends 24 hours later. Subjects must not be discharged from the hospital until the end of this period.

New AEs occurring in the 24-hour period starting from the end of study drug administration are recorded in the eCRF.

The EOT assessments are included in this period. These assessments are performed within 2 hours following the permanent discontinuation of study drug.

7.1.4 Observation period for primary endpoint

The observation period starts with the initiation of study drug infusion and ends on and includes Day 14 post-study drug initiation. This period covers the interval over which the subject may qualify for the primary endpoint of the study. Neurological scales, vital signs, body temperature, and ICP are assessed and central laboratory samples are taken regularly irrespective of study drug administration. Subjects must be kept at the investigational site until at least Day 14 to ensure the assessments required for evaluation of the primary endpoint are performed over the entire observation period.

Exceptional circumstances may occur, resulting in a hospital discharge prior to Day 14 post-study drug initiation. In this situation, a follow-up must be performed to collect relevant clinical information during the period between the discharge and Day 14, as described in Section 7.2.2.2.1. This follow-up also applies to subjects who were enrolled under previous protocol versions and who were discharged prior to Day 14.

7.1.5 Extended follow-up period

The extended follow-up period starts after the 24-hour safety follow-up period and ends with the EOS visit [see Section 7.1.8], occurring 24 weeks after the aSAH.

Safety follow-up information including new AEs related to protocol-mandated procedures and all SAEs and related drug therapies up to EOS will be collected during this period. If the subject has already been discharged from hospital or has been transferred to another hospital, the most appropriate means will be employed to obtain this information. Safety follow-up information includes the follow-up of ongoing AEs.

7.1.6 Unscheduled visits

For the purpose of the study, there will be no unscheduled visits.

7.1.7 Week 12 visit

This visit occurs 12 weeks after the aSAH for both the high-risk prevention and the early treatment* groups. For subjects who prematurely withdraw from the study the pregnancy testing due at this visit may occur earlier.

The Week 12 visit will be conducted face-to-face at the investigational study site at Week 12 (84 days ± 7 days) with the subject and/or a proxy/caregiver, as applicable. In the event that it is impossible for a subject who is already discharged to return to the investigational site for this visit (e.g., due to poor clinical status, distance from hospital), all attempts will be made to conduct the visit and applicable assessments by telephone and complete the remaining assessments by post [see Table 1 and Table 2]. Depending on local regulations, a study staff member from the investigative site may also conduct the Week 12 visit at the subject's place of residence.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

7.1.8 EOS visit (individual subject)

This visit occurs 24 weeks after the aSAH for both the high-risk prevention and the early treatment* groups, and is defined as the last visit performed by an individual subject for the study. This visit may occur earlier for subjects who prematurely withdraw from the study.

The EOS visit will be conducted remotely at Week 24 (Day 168 ± 2 weeks) post-aSAH as a telephone interview with the subject and/or a proxy/caregiver. If the EOS visit cannot be conducted as a telephone interview, the subject and/or a proxy/caregiver will be asked to complete the applicable data collection forms and return them by post.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

7.1.9 EOS (study level)

This time point occurs when the last subject randomized into the study completes his/her EOS visit.

7.2 Study assessments

The study assessments are listed in the visit and assessment schedule [Table 1].

The assessments that are mandatory during a visit are marked with an 'X'.

All study assessments are performed/administered by the investigator/delegate and are recorded in the eCRF, unless otherwise specified.

If a study-specific procedure or assessment has already been performed as part of local standard practice, from hospital admission to the moment informed consent is obtained, it may be used for study purposes and does not have to be repeated.

All QoL questionnaires completed by the subject or proxy, as applicable [see Section 7.2.5], are entered into the corresponding eCRF form by the investigator/delegate. The original paper copies will be filed in the ISF and made available for verification by the site monitor.

During the Week 12 visit, whenever feasible, the following order of assessments is preferred: MoCA, GOSE, SS-QOL, Ox-PAQ, EQ-5D. If the subject is unable to return to the investigative site for the visit, the GOSE will be administered by telephone interview, and the subject will be instructed to complete the paper versions of the QoL questionnaires (which were sent to them via post) in the above order, where possible on the same day as the telephone interview, after the interview has been completed. If it is not possible to complete the questionnaires on the same day as the telephone interview, then they should

be completed as close to the day of the interview as possible (before or after the interview). Depending on local regulations, a study staff member from the investigative site may also conduct the Week 12 visit at the subject's place of residence.

The EOS visit at Week 24 will be conducted remotely by telephone. If a subject cannot be reached following a reasonable number of attempts, the site will attempt to collect the necessary data by post. During the EOS visit, whenever feasible, the following order of data collection is preferred: EQ-5D, employment status.

Calibration certificates / evidence of equipment maintenance for the below-listed equipment used to perform study assessments must be available unless the equipment is provided by the sponsor. Calibration certificates of other equipment must be available as per local requirements.

Equipment for which calibration certificates (or documentation of regular maintenance) are needed:

- Temperature measurement devices for study treatment storage area and laboratory sample storage (e.g., refrigerator, freezer);
- Study drug infusion pump;
- Centrifuges for laboratory samples;
- ECG machine;
- CT (CTA) scanner;
- DSA equipment.

7.2.1 Demographics / baseline disease characteristics

Demographic and baseline disease characteristic data to be collected on all subjects include: age at hospital admission, sex, race, and ethnicity (if allowed in the country), height, weight, total GCS score at hospital admission, and WFNS grade at hospital admission. The individual components of the GCS (i.e., eye opening, verbal, motor) will be recorded in the source documentation. If the subject was transferred from another hospital, the GCS score and WFNS grade will correspond to the assessments made at the referral hospital. However, if the GCS score and WFNS grades from the referral hospital were not done or not evaluable / not reliable (e.g., due to sedation), then the assessments performed at the investigational site will be entered in the eCRF and used for study purposes.

Relevant medical history / current medical conditions other than those related to the aSAH (e.g., chronic and ongoing acute conditions, serious past conditions) present before study-drug initiation will be recorded in the eCRF. Where possible, main diagnoses and not symptoms will be recorded.

Specific baseline conditions/symptoms of interest that are related to the aSAH will be recorded in the eCRF [see Section 7.2.1.1].

7.2.1.1 *aSAH history*

Relevant aSAH-related medical history will be captured in the eCRF and includes:

- Date/time of the aneurysm rupture*
- Total number of aneurysm(s) coiled or clipped
- Location of the ruptured aneurysm
- Location of the repaired aneurysm(s), ruptured and unruptured
- Aneurysm-securing procedure(s) performed
- Start date and end date and time of aneurysm-securing procedure(s)
- Largest diameter of the ruptured aneurysm (mm)
- Complications of the aneurysm-securing procedure which may include, but are not limited to the following:
  - Intracranial hemorrhage (including aneurysm rupture during procedure), intraoperative cerebral artery thrombosis, cardiac arrest, seizure, intracranial hypertension, brain edema or swelling, cerebral infarction/ischemia, cerebral vasospasm, other coiling complications, other surgical complications.
- Previous aSAH (yes/no)

*Date/time of the aneurysm rupture will be estimated based on clinical symptoms experienced by the subject. In general, consider the date/time of the rupture to correspond to the date/time of the major headache which resulted in the hospital admission. Do not consider minor preceding headaches (sentinel headaches, warning leaks). If the subject was found unconscious, then the date/time of the aneurysm rupture corresponds to the date/time when the subject was last seen conscious.

7.2.1.2 *Data to be collected for screening failure subjects*

A minimum set of screening failure information is required to ensure transparent reporting of screening failure subjects.

For subjects who failed screening, the following data will be recorded in the eCRF:

- Age (at hospital admission), sex, race, and ethnicity (if allowed in the country)
- WFNS grade at hospital admission
- Type of aneurysm-securing procedure
- Inclusion criteria not met and/or exclusion criteria met
- Date and time of informed consent

- Whether the subject was subsequently randomized
- AEs and SAEs related to a study-mandated procedure

7.2.2 Efficacy assessments

7.2.2.1 *Neurological assessment scales*

All neurological assessments required for the study, starting from those performed to determine study eligibility just prior to randomization, including the baseline assessments (prior to the start of study drug), and those performed until the end of the observation period for the primary endpoint (i.e., until Day 14 post-study drug initiation), will be performed by study staff specifically trained and certified to perform these assessments for the purpose of the study. The neurological assessments performed at hospital admission and post aneurysm-securing procedure may be performed according to local standard of care, as the subject will, in most cases, not yet be included in the study (i.e., they will be performed prior to signature of the ICF). The GCS assessments for the purpose of assessing the subject's ability to perform the MoCAs may be performed according to routine standard of care.

Certification will be documented by passing a written exam based on content covered in the training materials provided by the sponsor. Each investigational site will train and certify as many site staff as required to ensure the neurological exams can be performed according to the visit and assessment schedule [Table 1 and Table 2] and as described below. Study-specific assessments must not be performed by any study staff until certification has been obtained. Details on the training and certification may be found in the site material provided separately.

7.2.2.1.1 Glasgow Coma Scale

The GCS is a measure of level of consciousness and scores range from 3 (worst score) to 15 (best score). It is composed of three components: the eye-opening response, the verbal response and the motor response. The motor response is assessed in the left and the right arm. If the scores in each arm are not the same, then the **best** score out of the two scores is used to determine the total GCS score. The total GCS score is the sum of the eye-opening response, the verbal response, and the **best** motor response.

Table 3 Glasgow Coma Scale

TEST	RESPONSES	VALUE
Eye-opening	No response	1
Response (1–4)	To pain	2
	To voice	3
	Spontaneously	4
Verbal response (1–5)	No response	1
	Incomprehensible words	2
	Inappropriate words	3
	Disoriented	4
	Oriented	5
Motor response (1–6)	No response	1
Left arm	Abnormal extension (decerebrate)	2
Right arm	Abnormal flexion (decorticate)	3
	Withdrawal	4
	Localizes	5
	Follows commands	6

The assessment is made at hospital admission, post-aneurysm-securing procedure, and pre-randomization for the determination of the GCS scores and the WFNS grades.

Details of the three GCS components (eye opening, verbal, motor) will be recorded in the source documentation but only the total GCS score will be entered into the eCRF.

Intubated subjects

Subjects who are endotracheally intubated will have their verbal score extrapolated from their eye-opening and **best** motor score according to the following table (applicable for GCS and mGCS):

Table 4 Derivation of verbal score for intubated subjects

	Eye score (1–4)			
Best motor score (1–6)	**1**	**2**	**3**	**4**
1	1	1	1	2
2	1	2	2	2
3	2	2	3	3
4	2	3	3	4
5	3	3	4	4
6	3	4	4	5

Derived verbal score = –0.3756 + Motor Score × (0.5713) + Eye-opening Score × (0.4233) [Meredith 1998, Rutledge 1996].

Sedated/paralyzed subjects

Subjects who are sedated or pharmacologically paralyzed should have their sedation/paralysis interrupted/reversed for these assessments. **Assessments that are unreliable due to the influence of sedation or for other reasons are not to be recorded or used to determine subject eligibility for the study.** Subjects who are still under the influence of pharmacological sedation at the time of randomization or who are, for whatever reason, not evaluable for baseline and regular daily neurological assessments are excluded from the study.

Aphasic subjects

The verbal score for aphasic subjects will depend on the severity of the aphasia and what verbal response the subject is actually able to produce. If the subject cannot produce speech at all, then the verbal score is 1, for no response. If the subject can speak but is replacing the expected words with inappropriate ones, then a score of 3, for inappropriate words, may be considered. If the subject does not respond to simple verbal commands, then pantomime or gestures with the body may be required.

7.2.2.1.2 World Federation of Neurological Societies grade

The WFNS grade is a clinical measure of disease severity and is determined from the GCS score and an assessment of motor deficit as follows:

Table 5 WFNS grade

WFNS grade	GCS score	Motor deficit*
I	15	Present or Absent
II	14–13	Absent
III	14–13	Present
IV	12–7	Present or Absent
V	6–3	Present or Absent

*Aphasia is considered equivalent to motor deficit.
GCS = Glasgow Coma Scale; WFNS = World Federation of Neurological Societies.

The GCS score is the sum of the eye-opening response, the verbal response, and the **best** motor response.

The WFNS grade will be determined 3 times in un-sedated subjects at a) hospital admission, b) after recovery from the aneurysm-securing procedure (after external ventricular drainage for hydrocephalus, if required), and c) prior to randomization. The first assessment is used to document the baseline disease characteristics and the latter two are used for evaluation of subject eligibility into the study.

The GCS scores, presence or absence of a motor deficit, and WFNS grades at admission, post aneurysm-securing procedure, and prior to randomization will be recorded in the source documentation and in the eCRF.

7.2.2.1.3 Modified Glasgow Coma Scale

The mGCS is used in conjunction with the aNIHSS [see Section 7.2.2.1.4] to detect episodes of clinical deterioration due to DCI.

It is performed the same way as the GCS [see Section 7.2.2.1.1]. However, the total score is calculated as the sum of the eye-opening response, the verbal response, and the **worst** motor response out of the two arms tested. The worst motor response is used to enable the detection of any new focal deficits from one assessment to the next. The total mGCS score may range from 3 (worst) to 15 (best).

The mGCS is performed as close as possible to the time of study drug initiation (within 30 minutes prior to initiation), then every 6 hours (±1 h) while in the ICU (or equivalent) until Day 14 post-study drug initiation, for the determination of the mGCS score. The first mGCS assessment performed after the start of study drug may be performed earlier than

6 hours (±1 h) after the previous one, in order to ensure all subsequent assessments fall at a convenient time. If study drug is prematurely discontinued prior to Day 14 and the subject is still in the ICU (or equivalent), the mGCS will continue to be performed every 6 hours (±1 h) until Day 14. If the subject has been discharged to a regular ward, the mGCS is performed every 12 hours (±1 h) until Day 14.

The mGCS is used to detect episodes of clinical deterioration due to DCI by comparison with the reference score (initially the one obtained within 30 minutes prior to study drug initiation. If a decrease of at least 2 points in the mGCS score occurs, the assessment must be repeated hourly (±15 min) for at least the first 2 hours. Thereafter, the reference score will depend on the clinical evolution of the subject. After sustained improvements or worsenings in clinical status, the new reference score will be recalibrated to reflect the best mGCS score attained by the subject immediately prior to an episode of clinical deterioration.

The total mGCS scores and the individual components (eye opening, verbal, motor scores) are recorded in the source documentation. The total mGCS scores are collected in the eCRF.

Sedated/paralyzed subjects

Subjects who are sedated or pharmacologically paralyzed should have their sedation/paralysis interrupted/reversed for these assessments (at least once daily). However, if this is deemed unsafe for the subject, then these assessments can be waived for as long as the sedation/paralysis must continue. It is not recommended to administer long-acting sedative agents (e.g., fentanyl by continuous infusion, diazepam, barbiturates). **The mGCS must not be performed in a subject who is still under the influence of sedation/paralysis. Assessments that are unreliable due to the influence of sedation or for other reasons are not to be recorded for study purposes, however the reason for the missing assessments must be documented in the medical chart.**

7.2.2.1.4 Abbreviated National Institutes of Health Stroke Scale

The aNIHSS is used in conjunction with the mGCS to detect episodes of clinical deterioration due to DCI.

It is a measure of limb movement and strength and is comprised of the motor section of the full NIHSS. Four separate scores from 0 (best) to 4 (worst) are determined for each limb (left arm, right arm, left leg, right leg). The total score is the sum of the individual scores corresponding to each limb: Total score = Left arm + Right arm + Left leg + Right leg. The total score may range from 0 (best) to 16 (worst).

The aNIHSS is performed as close as possible to the time of study drug initiation (within 30 minutes prior to initiation), then every 6 hours (±1 h) while in the ICU (or equivalent)

until Day 14 post-study drug initiation. If study drug is prematurely discontinued prior to Day 14 and the subject is still in the ICU (or equivalent), the aNIHSS will continue to be performed every 6 hours (±1 h) until Day 14. If the subject has been discharged to a regular ward, the aNIHSS is performed every 12 hours (±1 h) until Day 14.

The aNIHSS is used to detect episodes of clinical deterioration due to DCI by comparison with the reference score (initially the one obtained within 30 minutes prior to study drug initiation). If an increase of at least 2 points in the aNIHSS score occurs, the assessment must be repeated hourly (±15 min) for at least the first 2 hours. Thereafter, the reference score will depend on the clinical evolution of the subject. After sustained improvements or worsenings in clinical status, the new reference score will be recalibrated to reflect the best aNIHSS score attained by the subject immediately prior to an episode of clinical deterioration.

The total aNIHSS scores and the individual scores for each limb are recorded in the source documentation. The total aNIHSS scores are collected in the eCRF.

Sedated/paralyzed subjects

Subjects who are sedated or pharmacologically paralyzed should have their sedation/paralysis interrupted/reversed for these assessments (at least once daily). However, if this is deemed unsafe for the subject, then these assessments can be waived for as long as the sedation/paralysis must continue. It is not recommended to administer long-acting sedative agents (e.g., fentanyl by continuous infusion, diazepam, barbiturates). **The aNIHSS must not be performed in a subject who is still under the influence of sedation/paralysis. Assessments that are unreliable due to the influence of sedation or for other reasons are not to be recorded for study purposes, however the reason for the missing assessments must be documented in the medical chart.**

Table 6 Abbreviated NIHSS

Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be '9' and the examiner must clearly write the explanation for scoring as a '9'.

0 = No drift, arm holds 90 (or 45) degrees for full 10 seconds.
1 = Drift, arm holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.
2 = Some effort against gravity, arm cannot get to or maintain (if placed in position) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.
3 = No effort against gravity, arm falls.
4 = No movement
9 = Amputation, joint fusion explain: _____
Left Arm: _____
Right Arm: _____

0 = No drift, leg holds 30 degrees position for full 5 seconds.
1 = Drift, leg falls by the end of the 5 second period but does not hit bed.
2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity.
3 = No effort against gravity, leg falls to bed immediately.
4 = No movement
9 = Amputation, joint fusion explain:_____
Left Leg: _____
Right Leg: _____

7.2.2.2 *Primary endpoint assessments*

Clinical deterioration in the context of the primary efficacy endpoint of the study is defined in subjects in whom neurological scales are evaluable, as a worsening of at least 2 points compared to the reference score on the mGCS or the aNIHSS lasting for at least 2 hours. The subject meets the primary endpoint if the deterioration cannot be entirely attributed to causes other than cerebral vasospasm, as adjudicated by the CEC, based on review of clinical data provided by the investigator for the purpose of ruling out other causes. These data are described in Section 7.2.2.2.1.

For any new neurological deterioration episode as defined above, occurring up to Day 14 post-study drug initiation, the primary cause of the clinical deterioration and any potentially contributing causes (based on investigator local assessment) will be recorded in the eCRF. The results of examinations performed to diagnose the cause of the deterioration will also be recorded in the eCRF and a clinical narrative will be written as described below.

The above information will also be collected in the eCRF for subjects who experience an initial worsening of at least 2 points as described above, but are subsequently not evaluable for either the mGCS or the aNIHSS (e.g., due to continuous sedation), and therefore the duration of the worsening cannot be confirmed.

Subjects who are not evaluable for neurological status at any time up to Day 14 post-study drug initiation, will be considered as meeting the primary efficacy endpoint if either rescue therapy was administered for a relevant vasospasm or the reason for not being evaluable is vasospasm-related, as confirmed by the CEC. Therefore, the results of any relevant exams performed which describe the subject's condition during the period in which they were not evaluable, and a clinical narrative will also be collected in the eCRF.

Exceptional circumstances may occur, resulting in a hospital discharge prior to Day 14 post-study drug initiation and an incomplete set of neurological scale assessments. In this situation, a follow-up must be performed to collect relevant clinical information during the period between the discharge and Day 14, as described in Section 7.2.2.2.1. This follow-up will be performed retrospectively for subjects who were enrolled under previous protocol versions and who were discharged prior to Day 14.

If this follow-up reveals that the subject was re-hospitalized or transferred to another facility and DCI cannot be ruled out as a primary or contributing cause, the subject will be considered as meeting the primary endpoint.

A clinical narrative is to be written in English by the investigator/delegate as soon as possible following Day 14 post-study drug initiation. This narrative will describe/summarize the neurological deterioration episode including the nature and evolution of significant clinical findings, treatments initiated in response to the deterioration, and response to treatment. Results of specific tests (e.g., perfusion CT scan, MRI) may be summarized in the narratives. In addition to the above scenarios a subject narrative is also to be written if a subject becomes unevaluable at any time point for neurological scales or has at least one missing neurological assessment for other reasons. For subjects discharged earlier than 14 days post-study drug initiation, the outcome of the follow-up must be described in the narrative including all relevant clinical information that would allow the primary endpoint evaluation to be completed (i.e., to confirm or rule out the occurrence of clinical deterioration due to DCI up to Day 14 post-study drug initiation). Example narratives will be provided in the eCRF completion guideline to standardize the content of the narratives across the participating sites.

7.2.2.2.1 Supportive data for primary endpoint evaluation

Special assessments will be performed and recorded on the "Supportive data" eCRF pages if a subject experiences a worsening of at least 2 points on the mGCS or the aNIHSS within the 14 days following the initiation of study drug. These assessments are required by the

CEC to diagnose the primary and contributing causes of the deterioration and may vary according to the suspected diagnosis and the local routine work-up. However, a minimum set of assessments will be performed for all potential episodes of neurological deterioration, **irrespective of the suspected underlying cause**:

- mGCS and aNIHSS assessments hourly for the following 2 hours after the initial neurological deterioration.
- Blood sample for local laboratory analysis as close as possible to the time of the initial neurological deterioration, but no later than 1 hour after the confirmation of the deterioration, i.e., no later than 3 hours from the initial worsening. Serum sodium, creatinine, and the following arterial blood gases: SaO_2, PaO_2, $PaCO_2$, and pH (if the subject is intubated/ventilated, along with the corresponding ventilator settings), or SpO_2 (oxygen saturation in the blood as measured by pulse oximetry, for those not ventilated, along with the amount of any oxygen administrated) must be included as a minimum. The other laboratory parameters evaluated will be based on investigator judgment according to the specific clinical situation. If the repeated hourly neurological scales assessments cannot be completed because the subject becomes unevaluable the local laboratory tests are still to be performed.

For confirmed episodes of neurological deterioration or when there is an initial worsening of at least 2 points, the duration of which cannot be confirmed because the subject becomes unevaluable due to a **suspected central nervous system (CNS) cause**, the following assessments (in addition to those listed above) are considered to be the minimum:

- Cerebral CT scan within 6 hours of the initial neurological deterioration.
- Cerebral angiogram (DSA or CTA) within 6 hours* of the initial neurological deterioration.

*For subjects randomized into the study in the early treatment group, this angiogram may be waived if the pre-randomization angiogram was performed within 24 h of the initial neurological deterioration. Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

- Blood sample for serum S100b protein concentration (central assessment) drawn within 1 hour of the confirmation of the neurological deterioration episode or within 3 hours from the initial worsening.

Imaging performed as part of the routine work-up is to be centrally provided to support the CEC in their evaluation in the following situations:

- if a subject becomes unevaluable for neurological status and rescue therapy is concurrently administered,

- if the reason for not being evaluable is vasospasm related.

If images had already been submitted for a preceding episode with the same underlying cause, then additional images are not required.

For all episodes of neurological deterioration and periods when a subject is not evaluable for neurological scales, depending on the clinical presentation of the subject and irrespective of the suspected underlying cause, additional assessments may include (but are not limited to):

- Other laboratory parameters (e.g., electrolytes, biochemistry, hematology, coagulation, liver function tests, arterial blood gases, urinary density), analyzed locally.
- Specific examinations (e.g., cerebral CT scan, cerebral angiogram, cerebral perfusion CT scan, EEG, ECG, chest X-ray, chest CT, pulmonary angiogram, TCD, MRI).
- Vital signs (including ICP).
- A hospital discharge summary or autopsy report as applicable, may also be submitted if it is believed to bring additional useful information to the CEC.

For the exceptional cases when subjects are discharged earlier than 14 days post-study drug initiation, a follow-up must be performed on Day 14 post-study drug initiation, or as soon as possible after Day 14 and documented in the source notes. The follow-up is not required if the subject was discharged on Day 13 and there is at least one set of neurological scales assessment available on this day. The information may be collected from the patient or a proxy during a routinely performed or dedicated follow-up visit / telephone call or obtained from another healthcare facility. This follow-up will also be performed retrospectively for subjects who were enrolled under previous protocol versions and who were discharged prior to Day 14.

The outcome of the follow-up must be described in the clinical narrative in the eCRF including all relevant clinical information that would allow the primary endpoint evaluation to be completed (i.e., to confirm or rule out the occurrence of clinical deterioration due to DCI up to Day 14 post-study drug initiation). If a new neurological deterioration event occurred, the appropriate eCRF pages are to be completed. The follow-up information must cover the period from hospital discharge to Day 14 post-study drug initiation and must include, but is not limited to:

- Whether or not the subject was re-hospitalized or transferred to another facility during the above period, the corresponding date and reason for re-hospitalization/transfer, and any relevant subsequent diagnosis made.
- Clinical data describing the presence/absence of symptoms suggestive of clinical deterioration due to DCI, e.g., new focal neurological signs, deterioration in level of

consciousness, stroke and results from any supportive assessments performed (including brain imaging).

- If a new cerebral CT scan was performed at the study site or another hospital (ideally up to Day 16 post-study drug initiation + 7 days), this scan may be used to replace/support a CT scan performed at hospital discharge (or earlier) and submitted to the imaging CRO.

The results of the above additional assessments and the follow-up will be added to / entered in the source documentation and in the eCRF, described in the clinical narrative (as appropriate) and provided to the CEC to perform adjudication. In certain cases, the CEC may request additional clinical information, on top of that which was initially submitted, to ensure sufficient data is available to support their review.

7.2.2.3 *Cerebral angiograms*

All angiograms described in this section will be performed locally, shipped to the central imaging CRO (unless otherwise stated), and reviewed by independent expert readers. All images must be performed according to the Image Acquisition Guidelines (IAG; provided separately), and ideally on the same imaging equipment throughout the entire study. Details regarding the minimum technical requirements for validation of imaging equipment for study purposes are also contained in the IAG. Prior to enrolling subjects into the study, the imaging CRO will verify the ability of each participating site to comply with minimum technical and quality requirements for the cerebral angiograms via the submission of a test image (see IAG).

DSA and CTA are both acceptable imaging modalities for the study. Magnetic resonance angiography is not an acceptable modality for this study. The choice between DSA and CTA is based on local routine standard of care post-aSAH and both modalities may be used throughout the study.

A copy of all imaging (raw and DICOM) must be archived at the site for at least 25 years after study end unless agreed differently within the study agreement with Idorsia.

The site must always keep the original image (unblinded with study subject details included) at the site in order to be able to confirm during audit or inspection that the blinded study images correspond to the correct study subjects.

At study end, the imaging CRO will return copies of images which have been used in the study for IRC and CEC evaluation to each site. These images will not contain any confidential patient health identifiers, only the study-subject number.

A cerebral angiogram is performed at the following time points:

7.2.2.3.1 Hospital admission

An angiogram is performed at hospital admission to document the aneurysmal cause of the SAH and the fulfillment of other angiogram-related entry criteria. If this angiogram was performed at a referral hospital, is of acceptable quality, and is available in digital format at the investigational site at the time of screening, it does not need to be repeated. However, if the angiogram was repeated at the investigational site, the second angiogram will be used for verification of the eligibility criteria and submitted to the imaging CRO.

7.2.2.3.2 Post aneurysm-securing procedure

For subjects who had their aneurysm repaired by endovascular coiling, an angiogram will be performed intra- or post-procedure according to local standard of care, to document the outcome of the aneurysm repair. This angiogram will be used to verify the study eligibility criteria, but will not be submitted to the imaging CRO.

For subjects who had their aneurysm repaired by surgical clipping, a post-procedure angiogram may not always be routinely performed and therefore the outcome of the aneurysm repair may be confirmed by angiogram or by other means and documented in the subject's medical chart.

7.2.2.3.3 Prior to randomization

An angiogram will be performed prior to randomization for those subjects enrolled in the early treatment* population, to document the presence of moderate to severe cerebral vasospasm at the time of randomization.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

7.2.2.3.4 At each episode of neurological deterioration (suspected CNS cause)

An angiogram will be performed at **each** episode of neurological deterioration suspected to be due to a CNS cause, within 6 hours* of the start of the initial deterioration. An angiogram will also be performed when there is an initial worsening of at least 2 points the duration of which cannot be confirmed because the subject subsequently becomes unevaluable. If more than one angiogram was performed for the same episode of neurological deterioration (e.g., after the 6-hour time window), the investigator must submit all relevant angiograms to the imaging CRO, based on his/her clinical judgment.

Routinely performed angiograms, if any, documenting the underlying cause are to be submitted if:

- the subject becomes unevaluable on the neurological scales concurrently with rescue therapy administration or
- the reason for not being evaluable is vasospasm related.

*For subjects randomized into the study in the early treatment group, this angiogram may be waived if the pre-randomization angiogram was performed within 24 h of the initial neurological deterioration. Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

7.2.2.4 *Cerebral CT scans*

All CT scans described in this section will be performed locally, shipped to the central imaging CRO (unless otherwise stated), and reviewed by independent expert readers. All images must be performed according to the IAG (provided separately), and ideally on the same imaging equipment throughout the entire study. Details regarding the minimum technical requirements for validation of imaging equipment for study purposes are also contained in the IAG. Prior to enrolling subjects into the study, the imaging CRO will verify the ability of each participating site to comply with minimum technical and quality requirements for the CT scans via the submission of a test image (see IAG).

Perfusion CT imaging is not an acceptable modality for this study and cannot be used to replace a conventional CT scan. However, if performed to evaluate an episode of neurological deterioration, a description of the results may be submitted to the CEC (e.g., in the clinical narrative [see Section 7.2.2.1]) as complementary information.

A copy of all imaging (raw and DICOM) must be archived at the site for at least 25 years after study end unless agreed differently within the study agreement with Idorsia.

The site must always keep the original image (unblinded with study subject details included) at the site in order to be able to confirm during audit or inspection that the blinded study images correspond to the correct study subjects.

At study end, the imaging CRO will return copies of images which have been used in the study for IRC and CEC evaluation to each site. These images will not contain any confidential patient health identifiers, only the study-subject number.

A cerebral CT scan is performed at the following time points:

7.2.2.4.1 Hospital admission

A CT scan is performed at hospital admission to document the SAH, the baseline disease characteristics including clot size and the presence of IVH, and the fulfillment of other CT scan-related entry criteria. If this CT scan was performed at a referral hospital, is of acceptable quality, and is available in digital format at the investigational site at the time of screening, it does not need to be repeated. However, if the CT scan was repeated at the investigational site, the second scan will be used for verification of the eligibility criteria and submitted to the imaging CRO.

7.2.2.4.2 Post aneurysm-securing procedure

A CT scan is performed at least 8 hours post procedure and within 24 hours prior to randomization to verify the study eligibility criteria.

Any other routinely performed cerebral CT scan performed post aneurysm-securing procedure and prior to the above CT scan, if believed to be relevant by the investigator, will be submitted to the imaging CRO to aid in the detection of new or worsened infarcts and post-procedure complications/re-bleeding.

7.2.2.4.3 At each episode of neurological deterioration (suspected CNS cause)

A CT scan will be performed at **each** episode of neurological deterioration suspected to be due to a CNS cause, within 6 hours of the start of the initial deterioration [see Section 7.2.2.2.1]. A CT scan will also be performed if there is an initial worsening of at least 2 points for which the duration cannot be confirmed because the subject subsequently becomes unevaluable. If more than one CT scan was performed for the same episode of neurological deterioration (e.g., after the 6-hour time window), the investigator must submit all relevant CT scans to the imaging CRO, based on his/her clinical judgment. Routinely performed CT scans, if any, documenting the underlying cause are to be submitted if:

- the subject becomes unevaluable on the neurological scales concurrently with rescue therapy administration or
- the reason for not being evaluable is vasospasm related.

7.2.2.4.4 Day 16 post-study drug initiation

A CT scan will be performed where possible, on Day 16 post-study drug initiation for determination of the main secondary efficacy endpoint. If the CT scan cannot be performed on Day 16, then it is acceptable if the CT scan is performed up to 7 days after Day 16. Only if the subject is discharged from the hospital prior to Day 16, may this CT scan be performed on the day of hospital discharge. If no CT scan was performed on the day of hospital discharge, then the latest CT scan performed prior to discharge will be submitted to the imaging CRO. The subject must not be discharged prior to Day 14 [see Section 7.1.4].

Depending on the specific situation, a CT scan performed later than Day 16 (+7 days) or prior to hospital discharge may be considered acceptable to replace a missing Day 16 scan or to support a scan performed too early. However, the acceptability of these scans will need to be assessed on an individual basis and discussed with the sponsor.

If the subject is re-hospitalized/ transferred to another hospital after an early hospital discharge, and a new cerebral CT scan is performed (ideally up to Day 16 post-study drug

initiation + 7 days), this scan may be used to replace/support the earlier CT scan and submitted to the imaging CRO.

7.2.2.5 *Combined Glasgow Outcome Scale Extended / modified Rankin Scale interview*

The combined GOSE/mRS interview is designed to measure functional outcome and dependency at Week 12 post-aSAH, and is described in detail in Appendix 4. It is conducted as a face-to-face interview by a trained assessor at the Week 12 visit, allowing both the GOSE and mRS scores to be derived from the same interview. Depending on the clinical status of the subject, the interview may be performed with the subject and/or a proxy. If it is impossible for a subject who is already discharged to return to the investigational site for this visit (e.g., due to poor clinical status, distance from hospital), all attempts will be made to conduct the interview by telephone.

The GOSE scores range from 1 (dead) to 8 (upper good recovery) and the mRS scores range from 0 (no symptoms) to 6 (dead) and are calculated by the interviewer based on the algorithm in Appendix 4.

The results of the interview are recorded in the source documents and entered into the eCRF.

Prior to conducting the first interview for the study, the assessor will successfully complete specific training. Further administration instructions can be found in the guidelines for the GOSE and mRS interview (provided separately).

7.2.2.6 *Montreal Cognitive Assessment*

The MoCA is a brief screening assessment for detecting cognitive impairment [see Appendix 5]. The scores range from 0 (worst) to 30 (best). The number of years of education is also collected since the total score may require adjusting based on this information.

It is planned to be conducted face-to-face by a trained assessor up to 3 times during the study; after the aneurysm-securing procedure and prior to study drug initiation, at Day 14 post-study drug start, and at the Week 12 visit. Since the ability to perform this assessment depends on the subject's level of consciousness at the given time points, the MoCA will only be assessed in subjects with a GCS score ≥ 13 (based on routine local assessment) who are extubated (if applicable). The reason for not performing any MoCA will be collected in the source documentation and in the eCRF.

Given the short time interval between the 3 assessments, parallel versions of the MoCA will be used at each of the time points to avoid any learning curve effect that could potentially bias the results. Each version will be identified as version 1, 2 or 3. Each

participating center will have a customized schedule which defines which of the 3 versions should be administered at each time point.

The first MoCA will be performed after the aneurysm-securing procedure and prior to study drug initiation, as soon as the subject has fully recovered from the procedure (including recovery from sedation and anesthesia, with pain adequately controlled), has been extubated if applicable, has cerebrospinal fluid diversion in place (if required), and has provided informed consent to participate in the study. This MoCA can therefore be performed prior to randomization into the study.

The second MoCA will be performed on Day 14 (±1 day) post-study drug initiation. If the subject requires hospital discharge prior to Day 14, the MoCA is performed on the day of discharge.

The third MoCA will be performed at Week 12 (84 days ±7 days) post-aSAH. If it is impossible for a subject who is already discharged to return to the investigational site for the Week 12 visit (e.g., due to poor clinical status, distance from hospital), the MoCA is not performed and the reason for not performing the assessment is recorded in the source documentation and the eCRF.

The results from each MoCA will be filed in the source documents and the scores for each section of the assessment will be entered into the eCRF.

7.2.3 Safety assessments

The definitions, reporting and follow-up of AEs/SAEs and pregnancies are described in Section 9.

7.2.3.1 *Weight and height*

Body weight and height will be measured during screening and recorded in the eCRF.

7.2.3.2 *Vital signs*

SBP will be measured in a supine or sitting position shortly before randomization and recorded in the source documentation. This measurement may be made by arterial line or by sphygmomanometer and will be used to confirm the absence of hypotension as defined in the exclusion criterion.

SBP, diastolic BP (DBP), and HR will be measured via arterial line or sphygmomanometer in a supine or sitting position within 60 minutes prior to the start of the study drug infusion. These measurements will be used as the baseline values to which the values post-study drug initiation will be compared and will be entered into the eCRF. Prior to the initiation of study drug, BP must be controlled as per the Patient Management Guidelines [see Appendix 3].

SBP, DBP, and HR will be measured every 6 hours (±1 h) in the ICU (or equivalent) during study drug administration and the results entered into the eCRF. After permanent study drug discontinuation, these assessments will continue to be performed every 6 hours (±1 h) until Day 14 post-study drug initiation. If the subject is no longer in the ICU (or equivalent), these assessments are performed every 12 hours (±1 h) until Day 14 post-study drug initiation.

It is recommended to use the same position (supine or sitting) and the same method of measurement (arterial line or sphygmomanometer) throughout the study for an individual subject.

7.2.3.3 *Intracranial pressure*

ICP will be measured in subjects with ICP monitoring, before randomization to confirm the absence of high sustained ICP as defined in the exclusion criterion. The measurement will be recorded in the source documentation.

ICP is subsequently measured at approximately the same time as the vital signs, within 60 minutes prior to the start of study drug, then every 6 hours (±1 h) until Day 14 post-study drug initiation, for as long as the ICP monitor is in place.

These measurements are entered into the eCRF. It is recommended that where possible, the same method of ICP monitoring be used throughout the study for an individual subject.

7.2.3.4 *Central venous pressure*

Central venous pressure (CVP) will also be measured and recorded at the same time as ICP, if this monitoring is present. CVP is measured at end expiration without ventilation with the zero reference point (BP transducer) at the level of the left atrium.

7.2.3.5 *Body temperature*

Body temperature will be measured within 60 minutes prior to the start of study drug, then every 12 hours (± 1 h) until Day 14 post-study drug initiation. These measurements are entered into the eCRF.

It is recommended that where possible, the same method of body temperature monitoring be used throughout the study for an individual subject.

7.2.3.6 *24-hour fluid intake and balance*

For subjects with a urine catheter, 24-hour fluid balance will be measured and recorded in the eCRF for as long as the catheter is in place, starting from the day of study drug initiation and ending on the day of permanent study drug discontinuation. On the day of study drug initiation, the first 24-hour period of measurement will include the time of study drug start, unless the available measurement is not representative of a full 24-hour period. In the latter case, the partial 24-hour measurement is not recorded, and the first measurement recorded

in the eCRF will start after the time of study drug initiation. On the day of permanent study drug discontinuation, the last 24-hour period recorded will include the time of study drug discontinuation.

For subjects without a urine catheter, 24-hour fluid intake (including the volume of i.v. drugs and oral liquids administered) will be recorded, according to the periods described above.

The start and end of a 24-hour period is based on local standard of care and does not necessarily correspond to measurements made from midnight to midnight.

7.2.3.7 *Electrocardiogram parameters*

A 12-lead ECG will be performed within 60 minutes prior to the start of study drug, and again at EOT, within 2 hours following permanent study drug discontinuation.

For subjects that experience an AE related to a cardiac rhythm abnormality, an additional ECG will be performed as soon as possible to allow for further investigation of cardiac rhythm and repolarization characteristics.

The following ECG parameters will be assessed and recorded in the eCRF at all time points, along with the date and time of the assessment:

- RR, PR, QT, and QRS intervals
- HR

If the intervals cannot be measured reliably (e.g., subject is in atrial fibrillation), then the measurements are not recorded in the eCRF and the reason for the missing measurements is documented in the source documentation and the eCRF.

7.2.4 Laboratory assessments

7.2.4.1 *Types of laboratory*

Both central and local laboratories will be used in this study. For the purpose of routine medical management of study subjects, the local laboratory results will be used. The results obtained from either the central or the local laboratory may be used by the investigator to report AEs.

A central laboratory (see laboratory manual for contact details) will be used for all regularly scheduled protocol-mandated laboratory tests (with the exception of the screening assessments and the urine [and serum if applicable] pregnancy test at the Week 12 visit).

Local laboratory results for all unscheduled tests performed in the work-up of neurological deterioration episodes will be collected and entered in the eCRF. All relevant local laboratory results will be recorded in the eCRF with the corresponding local normal ranges.

Local laboratory results of the regularly scheduled tests [parameters described in Section 7.2.4.2.1.2] will only be collected in exceptional circumstances (e.g., missing central laboratory results).

Laboratory reports (except for S100b protein concentrations) will be provided by the central laboratory to the investigator/delegate. In the event of specific (pre-defined in the laboratory manual) laboratory abnormalities, the central laboratory will alert the sponsor and the site personnel.

All laboratory reports must be reviewed, signed and dated by the investigator/delegate within 10 working days of receipt and filed with the source documentation.

The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings, as per investigator judgment, that are known at the time of signing of the ICF must be recorded in the medical history form of the eCRF. Any clinically relevant laboratory abnormalities as per investigator judgment detected after signing of the ICF and before randomization must be reported as an AE if they meet the criteria for an AE related to a study-mandated procedure [see Section 9.1.7], and must be followed until the value returns to within the normal range or is considered stable and no longer clinically relevant. Any clinically relevant laboratory abnormalities as per investigator judgment detected after randomization and until the end of the 24-hour safety follow-up period (i.e., up to 24 hours after study drug discontinuation), must be reported as an AE, and must be followed until the values return to within the normal range or are considered stable and no longer clinically relevant. If a clinically relevant laboratory abnormality is not observed on a central laboratory report, the local laboratory result may be requested by the sponsor for documentation purposes. If the abnormality has not yet returned to within normal ranges by the EOS visit, the sponsor may request the reporting of the latest local laboratory value obtained prior to / on the day of the EOS visit.

Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the laboratory manual (provided separately).

7.2.4.2 ***Laboratory tests***

7.2.4.2.1 Blood tests

7.2.4.2.1.1 Screening

A blood sample will be drawn during the screening period for confirmation of the study entry criteria (i.e., serum total bilirubin, PaO_2 in subjects who are intubated/ventilated, serum pregnancy test for women of childbearing potential). This sample will be analyzed by the local laboratory and the results recorded in the source documentation only.

7.2.4.2.1.2 Prior to study treatment start and during observation period for the primary endpoint

Blood for hematology and biochemistry assessments will be drawn within 60 minutes prior to study drug infusion start (baseline assessment), then every second day thereafter until Day 14 post-study drug initiation. The first of the post-baseline samples will be drawn on the second day after the baseline assessment. A sample will be drawn within the 2 hours following permanent study drug discontinuation, if a regularly scheduled sample was not already drawn for analysis on that day. These samples are analyzed centrally.

The laboratory parameters to be analyzed are the following:

Hematology:

- Hemoglobin (g/L)
- Hematocrit (%)
- Leukocyte count (with differential count*) (10^9/L)
- Platelet count (10^9/L)

*The differential leukocyte count is only reported to the site and the sponsor if the total leukocyte count is abnormal.

Blood chemistry:

- Sodium, potassium (mmol/L)
- Creatinine (µmol/L)
- Blood urea nitrogen (mmol/L)
- ALT (U/L), AST (U/L), alkaline phosphatase (U/L)
- Total bilirubin* (µmol/L)
- Gamma glutamyl transferase (IU/L)
- Albumin (g/L)
- C-reactive protein (mg/L)

Biomarker:

- S100b protein (µg/L)

If a routine every other day S100b biomarker assessment falls on the same day as a neurological worsening episode of suspected CNS cause, and an S100b sample has already been drawn for the worsening episode, the regular S100b collection does not need to be repeated.

* If total bilirubin is abnormal, the central laboratory will automatically analyze and report direct bilirubin.

7.2.4.2.1.3 Episodes of neurological deterioration

A blood sample will be drawn and analyzed locally for each episode of confirmed neurological deterioration or when there is an initial neurological worsening the duration of which cannot be confirmed.

The sample will be drawn as close as possible to the time of the initial neurological deterioration, but no later than 1 hour after the confirmation of the deterioration or within 3 hours after the initial worsening. Serum sodium, creatinine, and the following arterial blood gases: SaO_2, PaO_2, $PaCO_2$, and pH (if the subject is intubated/ventilated), must be included as a minimum.

The other laboratory parameters evaluated will be based on investigator judgment according to the specific clinical situation. The results from these locally assessed laboratory samples will be entered into the eCRF. However, if the neurological deterioration episode is suspected to be due to an underlying CNS cause, then the laboratory assessments must include serum S100b protein concentration which will be sent to the central laboratory for analysis.

Local laboratory test result should be entered in the eCRF if available from routine standard of care assessments when the subject becomes unevaluable without an initial neurological worsening.

7.2.4.2.2 Urine tests

A urine pregnancy test will be performed at the Week 12 visit for women of childbearing potential. If pregnancy is suspected at any time, a locally analyzed serum pregnancy test must be performed immediately.

Reporting procedures of pregnancy are described in Section 9.4.1.

7.2.5 Quality of Life assessments

The QoL assessments are to be completed at the Week 12 visit, where possible, after the MoCA and the GOSE/mRS interview and in the following order: SS-QOL, Ox-PAQ, EQ-5D. Additionally, EQ-5D is to be collected at the EOS visit.

7.2.5.1 ***Stroke Specific Quality of Life***

The SS-QOL is a patient-reported outcome measure developed to provide an assessment of health-related QoL specific to patients with stroke. It is comprised of 49 items that cover 12 domains (energy, upper extremity function, work/productivity, mood, self-care, social roles, family roles, vision, language, thinking, and personality) and 13 questions comparing post-aSAH status with pre-aSAH status. It has been validated for use in patients with stroke (including aSAH) [Williams 1999, Boosman 2010].

Subjects are asked to complete the questionnaire at the Week 12 visit by responding to each of the first 49 questions using the appropriate response (modeled on a 5-point Likert scale) and a recall period of 1 week, and the 13 subsequent questions (with one of the 4 potential responses provided). If the subject is unable to complete the questionnaire, a proxy (e.g., family member, caregiver, close friend) is asked to complete the questionnaire. The information on who completed the questionnaire (subject or proxy) will be collected. If the subject is unable to return to the investigational site for the Week 12 visit, all attempts are to be made to have the subject or proxy complete the questionnaire remotely and return it by post to the site. Depending on to local regulations, a study staff member from the investigative site may also conduct the Week 12 visit at the subject's place of residence. It is estimated that 10–15 minutes are required to complete the questionnaire.

The SS-QOL yields both domain scores and an overall SS-QOL summary score. The domain scores are unweighted averages of the associated items while the summary score is an unweighted average of all twelve domain scores [Williams 1999]. The completed questionnaire is filed in the source documents and the answers to the individual questions are entered into the eCRF.

A sample of the SS-QOL (in English) is provided in Appendix 6.

The sponsor has been granted a license agreement for the use of the SS-QOL questionnaire and for performing additional translations as needed.

7.2.5.2 *Oxford Participation and Activities Questionnaire*

The Ox-PAQ is a patient-reported generic health-related QoL instrument developed to assess participation, activities, and level of independence. The instrument assesses the ability of individuals to engage in activities (such as work, hobbies, daily routines) and the level of dependency an individual has on others. It is comprised of 23 questions that cover 3 domains (routine activities, emotional well-being, and social engagement) [Morley 2013, Kelly 2015, Morley 2016].

At the Week 12 visit, subjects are asked to indicate for each question how often they had difficulties with the particular activity or feeling over the past week, using responses modeled on a 5-point Likert scale. If the subject is unable to complete the questionnaire it is not completed by a proxy. If the subject is unable to return to the investigational site for the Week 12 visit, all attempts are to be made to have the subject complete the questionnaire remotely and return it by post to the site. Depending on local regulations, a study staff member from the investigative site may also conduct the Week 12 visit at the subject's place of residence. It is estimated that 8–10 minutes are required to complete the questionnaire. The completed questionnaire is filed in the source documents and the answers to the individual questions are entered into the eCRF.

The Ox-PAQ has not yet been validated in aSAH and testing will be conducted separately and in parallel to the REACT study.

A sample of the Ox-PAQ (in English) is provided in Appendix 8.

The sponsor has been granted a license agreement for the use of the Ox-PAQ and for performing additional translations as needed.

7.2.5.3 *EQ-5D*

The EQ-5D (5L version) is a patient-reported outcome measure developed to assess generic health-related QoL. It is comprised of 5 domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a visual analog scale (VAS) assessing overall health.

For each of the domains, subjects are asked at the Week 12 visit to tick the box corresponding to the statement that best describes their health on the day of the assessment. The subject is also asked to mark an 'X' on the VAS to indicate how their overall health is on the day of the assessment. If the subject is unable to complete the questionnaire, a proxy (e.g., family member, caregiver, close friend) is asked to complete the questionnaire. The information on who completed the questionnaire (subject or proxy) will be collected. If the subject is unable to return to the investigational site for the Week 12 visit, all attempts are to be made to have the subject or proxy complete the questionnaire remotely and return it by post to the site. Depending on local regulations, a study staff member from the investigative site may also conduct the Week 12 visit at the subject's place of residence. It is estimated that 5 minutes are required to complete the questionnaire.

During the EOS visit at 24 weeks post-aSAH the subject will be contacted by telephone to complete the EQ-5D (5L) telephone interview version by the site. The self-complete paper version will be provided in advance to be used as a reference by the responder during the call. If the subject cannot be reached by telephone the self-complete paper version must be completed by the subject/proxy and returned by post to the site.

The completed questionnaires are filed in the source documents and the answers to the individual questions are entered into the eCRF by the site.

A 1-digit number results from the statement that is selected by the subject for each domain. The digits for the five domains can be combined into a 5-digit number that describes the subject's health state. Further details on the instrument and its scoring, and a list of related publications can be found in the EQ-5D-5L user guide, available on the EuroQol website (www.euroqol.org).

A sample of the EQ-5D (5L self-complete version, in English) is provided in Appendix 7.

The sponsor has been granted a license agreement for the use of the EQ-5D questionnaire and for performing additional translations as needed.

7.2.6 Pharmaco-economic assessments

In addition to the interventions described in Section 5.2.5, the following information will be collected from randomization until initial hospital discharge, and from initial hospital discharge until Week 12, for pharmaco-economic purposes:

- Length of stay in the acute care setting including the ICU (or equivalent unit), a specialized care ward (e.g., neurosurgery, neurology), and a general care ward;
- Length of stay in a rehabilitation unit/center and rehabilitation intensity;
- Length of stay in a long-term care facility (e.g., medicalized facility, non-medicalized facility, nursing home, assisted living facility, other);
- Duration of home care support (nurse and physiotherapy visits at home, requirement for a caregiver / healthcare worker at home);
- Location to where the subject was discharged after the initial hospitalization at the investigational study center.

If a subject is discharged from the investigational site prior to the Week 12 visit, he/she will be provided with forms to be completed by the relevant healthcare workers in order to collect the above information, as applicable, for the period from hospital discharge to Week 12.

At EOS 24 weeks post-aSAH (168 days ± 14 days), the pre-aSAH employment/student status, the current employment/student status, and the date of return to work (or to an educational institution, for students, as applicable) will be collected by the study site staff from the subject (or proxy, as applicable) via telephone or postal questionnaire and captured in the clinical database.

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion as per protocol

Subjects who complete the study up to and including the EOS visit are considered to have completed the study as per protocol. This includes subjects who prematurely discontinue study drug, provided the EOS visit has been completed.

8.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die, or are lost to

follow-up. If a subject withdraws consent, no further data will be collected in the eCRF from the date of withdrawal onward. The investigator may withdraw a subject from the study (without regard to the subject's consent) if he/she believes that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by the sponsor for any reason, including premature termination or suspension of the study.

Subjects are considered as lost to follow-up if all repeated attempts by the investigator to communicate with the individual have failed. The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document different potential methods of contact such as telephone number, home address, email address, person to be contacted if the subject cannot be reached). If the subject cannot be reached, the site must make reasonable repeated efforts to contact the subject, document all attempts (date, time and type of contact made), and enter the loss of follow-up information into the eCRF. The following methods must be used: at least 3 contacts (e.g., telephone calls, or e-mails) must be placed to the last available telephone number or email address) and 1 registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., a visit by site personnel to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above he/she will be considered to be lost to follow-up.

The reason for premature withdrawal from the study must be recorded in the eCRF.

If for whatever reason (except death or loss-to-follow-up) a subject is withdrawn from the study, the investigator should make best efforts to schedule a last appointment / telephone call to assess the safety and well-being of the subject. Data obtained during this last appointment / telephone call will be recorded in the subjects' medical records but it will not be collected in the eCRF.

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 8.4.

8.3 Premature termination or suspension of the study

The sponsor reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If the study is prematurely suspended or terminated, the sponsor will promptly inform the investigators, the IECs/IRBs, and health authorities, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated for any reason, the investigator — in agreement with the sponsor — must promptly inform all enrolled subjects who are still in the study and/or their proxies/legal representatives (as applicable), and ensure appropriate treatment and follow-up, as described in Section 8.4. The sponsor may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests. Depending on the reason for premature study termination, the investigator may also inform subjects who are no longer in the study and/or their proxies / legal representatives (as applicable).

In addition, if the investigator suspends or terminates the study without prior agreement from the sponsor, the investigator must promptly inform the sponsor personnel and the IEC/IRB, and provide both with a detailed written explanation of the termination or suspension.

If the IEC/IRB suspends or terminates its approval / favorable opinion of the study, the investigator must promptly notify the sponsor personnel and provide a detailed written explanation of the termination or suspension.

8.4 Medical care of subjects after study completion / withdrawal from study

After the subject's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to subjects what treatment(s) / medical care is necessary and available according to local regulations. Such care may include use of drugs which were forbidden during concomitant study treatment administration.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Safety definitions

9.1.1 Definition of adverse events

An AE is any untoward medical occurrence, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a subject during the course of the study, whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease if considered medically relevant.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.

- Continuous persistent disease or symptoms present at study start that worsen following the signing of the ICF.
- Laboratory test abnormalities if they represent a clinically significant finding (symptomatic or not) which was not present at study start or worsened during the course of the study as per investigator judgment, or led to interruption or permanent discontinuation of study treatment.

For the purposes of this study, certain reported AEs are considered to be of specific interest and will be grouped together and displayed by broader categories (i.e., lung complications, hypotension, anemia, cerebral hemorrhage, cerebral edema, fluid retention, hepatic disorders, tachyarrhythmia).

9.1.2 Definition of serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least 1 of the following criteria:

- Fatal.
- Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring in-patient hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered medically significant based upon appropriate medical judgment, as they may jeopardize the subject, and/or may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing ICF) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (e.g., if a complication prolongs hospitalization).

9.1.3 Definition of waived serious adverse events

The decision to have waived SAEs in a study is appropriate when the safety and tolerability profile of the study drug has been well characterized, allowing a clear understanding of the difference between drug-related and disease-related AEs. In addition, SAEs can only be waived for double-blind studies when an IDMC exists that will ensure the monitoring of these SAEs during the study.

The SAEs listed below are due to the underlying disease, and are therefore expected to occur in this patient population (e.g., cerebral vasospasm). In this study, they will be waived. This means that they will not require reporting to the sponsor's Global Drug Safety department in an expedited way and on an SAE form, and that they will be reported only on the AE pages of the eCRF as serious. Therefore, they will be entered only into the clinical database and not into the drug safety database.

The waived SAEs for this study are the following:

- Any type of cerebral/brain infarction or ischemia (includes all specific sites within the brain), cerebral vascular accident, stroke.
- Cerebral/brain hemorrhage or hematoma (includes all specific sites within the brain).
- DIND, neurological deterioration, clinical deterioration due to DCI, delirium, confusion, disorientation, aphasia, paresis/paralysis (including hemiparesis, limb weakness, limb paralysis).
- Ruptured cerebral aneurysm (re-bleeding of the original cerebral aneurysm).
- Complications related to the initial aneurysm-securing procedure.
- Cerebral vasospasm.
- Brain edema.
- Hydrocephalus.
- Intracranial hypertension.

9.1.4 Definition of suspected unexpected serious adverse reactions

The expectedness of an SAE is determined by the sponsor according to the reference safety information (RSI) section provided in the most recent version of the IB.

Any SAE that is assessed as related and unexpected against the RSI is known as a SUSAR (suspected unexpected serious adverse reaction). Waived SAEs [Section 9.1.3] are considered to be expected due to the underlying disease and are therefore not normally considered as a SUSAR.

Any SUSAR must be reported by the sponsor/CRO to relevant health authorities, and investigators. Submission to central/local IECs/IRBs will be done as per their requirements.

9.1.5 Intensity of adverse events

The intensity of AEs is graded on a three-point scale — mild, moderate, severe — as follows:

- **Mild**

The event may be noticeable to the subject. It does not usually influence daily activities, and normally does not require intervention.

- **Moderate**

The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

The event may cause noticeable discomfort and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 9.1.2]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than intensity assessment, determines the regulatory reporting obligations [see Section 9.3.2].

9.1.6 Relationship to study treatment

Each AE/SAE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated.

9.1.7 Relationship to protocol-mandated procedure

An AE/SAE is defined as related to protocol-mandated procedure if it appears to have a reasonable possibility of a causal relationship to either the study design or to a protocol-mandated procedure.

The determination of the likelihood that a protocol-mandated procedure caused the AE/SAE will be provided by the investigator.

9.2 Time period and frequency for adverse event / serious adverse event assessment and follow-up

The occurrence of an AE/SAE may come to the attention of study personnel during study visits, telephone calls or interviews of study participants presenting for medical care.

At the Week 12 and at the EOS visit, the investigator will inquire about the occurrence of AE/SAEs since hospital discharge and since the Week 12 visit, respectively or since the last contact with the subject.

9.2.1 Follow-up of adverse events

AEs still ongoing at the EOS visit must be followed up until resolution, until no longer considered clinically relevant or until stabilization.

9.2.2 Follow-up of serious adverse events

SAEs still ongoing at the EOS visit must be followed up until resolution, stabilization, or until the event outcome is provided.

9.3 Reporting procedures

9.3.1 Reporting of adverse events

All AEs with an onset date and time from study drug initiation up to 24 hours after study treatment discontinuation (i.e., the 24-hour safety follow-up period) must be recorded on AE forms of the eCRF. Those AEs occurring from signature of the ICF until EOS will also be recorded on an AE form in the eCRF, if they are believed to be related to a protocol-mandated procedure [see Section 9.1.7].

Information to be collected in an AE form in the eCRF includes date and time of onset, action taken with the study treatment, outcome of AE, date of resolution (if applicable) and principal investigator's (PI's) assessment of seriousness and intensity, and relationship to study treatment, study design or protocol-mandated procedures. For AEs related to cardiac rhythm abnormalities, additional ECG parameters may be collected [see Section 7.2.3.7].

If the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE form. If the AE lessens in intensity, no change in the severity is required to be reported.

For AEs ongoing at the start of study treatment, worsening of the AE after the start of study treatment will be recorded as a separate AE with the new intensity.

Follow-up information on any ongoing AEs obtained after the subject's EOS visit will not be collected in the eCRF.

9.3.1.1 *Reporting of acute respiratory distress syndrome*

To standardize the reporting of acute respiratory distress syndrome (ARDS), it is recommended to consider the following definitions [ARDS Definition Taskforce 2012].

- Mild ARDS: $300 \geq PaO_2/FiO_2 > 200$ with Positive End Expiratory Pressure (PEEP) or Continuous Positive Airway Pressure (CPAP) > 5 cm H_2O

- Moderate ARDS: 200 ≥ PaO_2/FiO_2 > 100 with PEEP > 5 cm H_2O
- Severe ARDS: 100 ≥ PaO_2/FiO_2 with PEEP > 5 cm H_2O

In addition, the following criteria should be met:

- Acute onset (within 1 week of known clinical insult).
- Bilateral opacities on chest X-ray (not explained by effusions, collapse, or nodules).
- Respiratory failure not fully explained by heart failure or fluid overload (objective assessment such as echocardiogram recommended if no risk factor).

9.3.2 Additional reporting procedure for serious adverse events

All SAEs (except those that are waived) with an onset date and time from study drug initiation up to EOS must be recorded on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures. Those SAEs occurring from signature of the ICF until EOS will also be recorded on an SAE form, if they are believed to be related to a protocol-mandated procedure [see Section 9.1.7].

These SAEs must be reported by the investigator to the sponsor's Global Drug Safety department (see contact details on the SAE form) within 24 hours of the investigator's first knowledge of the event. The investigator must complete the SAE form in English and must assess the event's causal relationship to the study treatment.

Any relevant information from source documents regarding the SAE, e.g., hospital notes or discharge summaries, etc., must be summarized on the SAE form.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The sponsor's Global Drug Safety personnel may contact the investigator to obtain further information.

If the subject is hospitalized in a hospital other than that of the study site or has already been discharged home, it is the investigator's responsibility to contact the hospital or the subject to obtain all SAE-relevant information and documentation.

New SAEs occurring after the EOS visit must be reported to the sponsor's Global Drug Safety department within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

9.4 Pregnancy

If despite the negative serum pregnancy test at screening a woman becomes pregnant while on study treatment, study treatment must be permanently discontinued [see Section 5.1.3.4.1].

The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

9.4.1 Reporting of pregnancy

Any pregnancy occurring in a female subject after signing of the ICF and up to the Week 12 visit must be reported to the sponsor's Global Drug Safety department within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the sponsor Pregnancy form, which is faxed to the sponsor's Global Drug Safety department (see contact details provided on the Pregnancy form). Pregnancies are not considered to be an AE and therefore are not recorded as such in the eCRF.

The investigator must complete the pregnancy form in English.

9.4.2 Follow-up of pregnancy

Any pregnancies as described in Section 9.4.1 must be followed up to their conclusion and the outcome must be reported to the sponsor's Global Drug Safety department.

9.5 Breastfeeding women

Women who were breastfeeding at the time of the aSAH must agree to refrain from breastfeeding for the duration of the treatment and until 30 days after the discontinuation of study drug. It is unknown whether clazosentan may be excreted into breast milk.

9.6 Reporting of study treatment overdose, misuse, abuse and medication errors

Study treatment overdose (defined as higher than the dose of study treatment prescribed), and study treatment errors will be reported as an AE when associated with signs or symptoms.

In addition, study treatment errors must be documented in the study drug log of the eCRF.

Misuse (e.g., medication error) and abuse of the study treatment will be reported as an AE/SAE.

9.7 Study safety monitoring

Study safety information (AEs, SAEs, laboratory results, vital signs, and study-specific examinations as required) is monitored and reviewed on a continuous basis by the sponsor (who has the responsibility of ensuring subjects' safety as well as data quality).

The sponsor may request additional data pertaining to the diagnostic work-up of an AE or SAE (e.g., medical imaging, local laboratory values) for the purpose of monitoring safety. Such additional data may be shared with external experts.

10 STATISTICAL METHODS

10.1 Analysis sets

10.1.1 Screened analysis set

The Screened analysis set includes all subjects who have given informed consent to participate in the study and have a subject identification number.

10.1.2 Randomized analysis set

The Randomized analysis set includes all subjects who have been assigned to a study treatment.

10.1.3 Full analysis set

The Full analysis set (FAS) includes all subjects from the Randomized analysis set who have started the study treatment. The rationale for this choice of the FAS is that, per study design, due to the emergency setting, the investigator has the possibility to withdraw randomized subjects from the study before study drug initiation for safety or other reasons (e.g., due to a sudden deterioration of the clinical status post-randomization). Defining the FAS as all subjects who have started study treatment is expected to preserve the intent-to-treat principle, because: a) randomized but untreated subjects will be rare (in previous Phase 3 studies, i.e., CONSCIOUS-2 and -3, less than 1% of the randomized subjects were not treated), and b) the decision whether or not to begin treatment cannot be influenced by knowledge of the assigned treatment.

Nevertheless, the reasons for not treating these subjects and the potential bias arising from this specific exclusion will be carefully examined.

To adhere to the intent-to-treat principle as much as possible, subjects will be evaluated according to their assigned study treatment (not actual treatment received) and stratum information as recorded in the IRT system.

Unless otherwise stated, all available efficacy data for the primary and secondary endpoints will be included in the analyses up to the planned analysis time point, regardless of study treatment discontinuation and/or use of rescue therapies.

10.1.4 Per-protocol analysis set

The Per-protocol analysis set (PPS) comprises all subjects from the FAS who complied with the protocol sufficiently to be likely to exhibit the treatment effects.

Criteria for sufficient compliance include adequate exposure to treatment, availability of key endpoint measurements and absence of major protocol deviations that have an impact on the treatment effect assessment for the primary endpoint.

The precise reasons for excluding subjects from the PPS will be detailed in the statistical analysis plan (SAP) before making the full randomization information available.

10.1.5 Safety analysis set

The Safety analysis set includes all subjects who started study drug (as recorded in the eCRF).

Subjects will be evaluated according to the actual treatment they received, which may differ from the randomly assigned treatment.

10.1.6 Other analysis sets

Other analysis datasets will be defined in the SAP (or corresponding SAPs), e.g., QoL, pharmaco-economics and subgroups of interest.

10.1.7 Usage of the analysis sets

Table 7 describes the analysis sets used for the analysis of each data set.

Subject listings will be produced on the Screened analysis set, unless otherwise specified.

Table 7 Analysis datasets usage

	Analysis sets				
Analyses	**SCR**	**RND**	**FAS**	**PPS**	**SAF**
Subject disposition	X				
Protocol deviations, Analysis sets		[X]	X	(x)	
Demographics characteristics		[X]	X	(x)	
Baseline disease characteristics		[X]	X	(x)	
Medical history and current medical conditions		[X]	X	(x)	
Previous and concomitant therapies		[X]	X	(x)	
Study treatment exposure				(x)	X
Primary efficacy endpoint		(x)	X	(x)	
Secondary efficacy endpoints		(x)	X	(x)	
Exploratory efficacy endpoints			X		
Quality of Life endpoints			X		
Pharmaco-economic endpoints			X		
Safety endpoints					X

Note: X: main analysis, [X]: if RND and FAS differ by more than 5%, some tables may be replicated on the RND; (x): Sensitivity analysis to be conducted only if > 5% difference of set size with set used for main analysis.
FAS = Full analysis set; PPS = Per-protocol analysis set, RND = Randomized analysis set; SAF = Safety analysis set; SCR = Screened analysis set

10.2 Variables

In this section, variables are defined in detail for the primary and secondary efficacy endpoints and for the safety endpoints. Variables for all other endpoints will be defined in detail in the SAP.

10.2.1 Primary efficacy variable

The primary endpoint is the occurrence of clinical deterioration due to DCI from study drug initiation up to 14 days post-study drug initiation [see Section 6.1.1].

According to the rules specified in the CEC charter, the CEC will define the occurrence as a binary variable (yes/ no) for each subject submitted.

It is assumed that the death status (within 14 days post-study drug initiation) and the primary endpoint assessment from the CEC will be available at the time of the final analysis.

10.2.2 Secondary efficacy variables

10.2.2.1 *Main secondary variable*

The main secondary endpoint is the occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation defined as:

- all- cerebral infarction ≥ 5 cm^3 or
- cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI [see Section 6.1.2.1].

According to the rules specified in the CEC charter, the CEC will define the occurrence as a binary variable (yes/ no) for each subject.

It is assumed that the assessment from the CEC is available at the time of the final analysis.

10.2.2.2 ***Other secondary efficacy variable***

The other secondary endpoints are:

- the long-term clinical outcome assessed by the mRS at Week 12 post-aSAH, dichotomized into poor outcome (score ≥ 3) and good outcome (score < 3) and
- the long-term clinical outcome assessed by the GOSE at Week 12 post-aSAH, dichotomized into poor outcome (score ≤ 4) and good outcome (score > 4).

The mRS scores range from 0 (no symptoms) to 6 (dead) and the GOSE scores range from 1 (dead) to 8 (upper good recovery) and are calculated by the interviewer based on the algorithm in Appendix 4.

The mRS will be dichotomized into poor (a score of 3 to 6) vs good (a score of 0 to 2) and the GOSE score into poor (a score of 1 to 4) vs good (a score of 5 to 8).

10.2.3 Safety variables

The variables described in this section are to be used for the derivation of the safety endpoints described in Section 6.2.

10.2.3.1 ***Adverse events***

An AE is defined as any event that is recorded on the AE eCRF module with an onset date/time ≥ date/time of informed consent and ≤ EOS.

TEAEs are those with an onset date/time ≥ start date/time of study treatment up to 24 hours after study treatment discontinuation. For SAEs, this period is extended to EOS.

The handling of missing or incomplete date/time of AEs will be described in the SAP.

10.2.3.2 ***Laboratory data***

Laboratory analyses are based on both central and local laboratories [see Section 7.2.4].

For regularly scheduled protocol-mandated laboratory tests, the results obtained from the central laboratory will be considered first.

Baseline laboratory test refers to the latest laboratory test performed prior to the start of study treatment.

No imputation for missing laboratory values will be performed unless necessary, in which case this will be described in detail in the SAP.

EOT laboratory test refers to the laboratory test performed at EOT. If no laboratory data are available at EOT, the results of the latest available post-baseline laboratory tests performed prior to EOT date/time are used for the analysis.

For each continuous laboratory parameter, the following variables will be summarized:

- Absolute value at each scheduled assessment,
- Absolute change from baseline to each scheduled assessment,
- Treatment-emergent marked laboratory abnormalities (i.e., from study drug initiation and up to 24 hours after EOT).

For categorical laboratory parameters, the following variables will be summarized:

- Proportion of subjects by categories at each time point.

Treatment-emergent marked laboratory abnormalities are those which are not present at baseline (e.g., change from no marked abnormality to any marked abnormality) or if a worsening occurred, as compared to the corresponding value at baseline (e.g., change from a pre-existing abnormality at baseline to a worse category of abnormality). Abnormality thresholds for laboratory data will be defined in the SAP.

For all unscheduled tests performed in the work-up of neurological deterioration episodes, results obtained from local laboratories, no normalization of result and references ranges will be performed unless necessary, in which case this will be described in detail in the SAP.

Data listings with individual subject data will be provided for the Safety analysis set including all laboratory parameters assayed during the study, centrally and locally.

10.3 Description of statistical analyses

All available data for each subject will be used in all statistical analyses unless otherwise specified.

Unless otherwise stated, all available efficacy data for the primary and secondary endpoints will be included in the analyses up to the planned analysis time point, regardless of study treatment discontinuation and/or use of rescue therapies.

All analyses will be presented by treatment arms, i.e., clazosentan 15 mg/h and placebo, and also, when relevant, by population group (early treatment* vs high-risk prevention).

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards

10.3.1 Overall testing strategy

Four null hypotheses will be tested according to a fixed-sequence procedure, at the two-sided significance level of 0.05 until first non-rejection.

The first null hypothesis is that there is no difference between clazosentan 15 mg/h and placebo in the occurrence of clinical deterioration due to DCI from study drug initiation up to 14 days post-study drug initiation.

The alternative hypothesis H_{1a} is that there is a difference between these arms:

$$H_{10}: p_{11} = p_{10} \quad \text{vs} \quad H_{1a}: p_{11} \neq p_{10}$$

Here p_{10} and p_{11} denote the incidence of clinical deterioration due to DCI in the placebo and clazosentan arms, respectively. This hypothesis will be tested at a two-sided significance level of 0.05.

Superiority will be concluded if the upper limit of the two-sided 95% confidence interval (CI) for the relative risk of clazosentan compared to placebo is lower than 1.

The second null hypothesis H_{20}, which will be tested if H_{10} is rejected, assumes no difference between clazosentan and placebo in the occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation defined as: all-cause cerebral infarction ≥ 5 cm^3 or cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI. The alternative hypothesis H_{2a} is that there is a difference between these arms:

$$H_{20}: p_{21} = p_{20} \quad \text{vs} \quad H_{2a}: p_{21} \neq p_{20}$$

Here p_{20} and p_{21} denote the incidence of occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation defined as: all-cause cerebral infarction ≥ 5 cm^3 or cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI in the placebo and clazosentan arms, respectively. This hypothesis will be tested at a two-sided significance level of 0.05.

Superiority will be concluded if the upper limit of the two-sided 95% CI for the relative risk of clazosentan compared to placebo is lower than 1.

The third null hypothesis H_{30}, which will be tested if H_{20} is rejected, assumes no difference between clazosentan and placebo in the proportion of subjects with a poor mRS score at Week 12 post-aSAH.

The alternative hypothesis H_{3a} is that there is a difference between these arms:

$$H_{30}: p_{31} = p_{30} \quad \text{vs} \quad H_{3a}: p_{31} \neq p_{30}$$

Here p_{30} and p_{31} denote the proportion of subjects with a poor mRS at Week 12 post-aSAH in the placebo and clazosentan arms, respectively. This hypothesis will be tested at a two-sided significance level of 0.05.

Superiority will be concluded if the upper limit of the two-sided 95% CI for the relative risk of clazosentan compared to placebo is lower than 1.

The fourth null hypothesis H_{40}, which will be tested if H_{30} is rejected, assumes no difference between clazosentan and placebo in the proportion of subjects with a poor GOSE score at Week 12 post-aSAH.

The alternative hypothesis H_{4a} is that there is a difference between these arms:

$$H_{40}: p_{41} = p_{40} \quad \text{vs} \quad H_{4a}: p_{41} \neq p_{40}$$

Here p_{40} and p_{41} denote the proportion of subjects with a poor GOSE at Week 12 post-aSAH in the placebo and clazosentan arms, respectively. This hypothesis will be tested at a two-sided significance level of 0.05.

The study will be considered successful if the first null hypothesis (H10) is rejected.

10.3.2 Analysis of the primary efficacy variable

10.3.2.1 *Hypotheses*

The null hypothesis (H_0) is that the occurrence of clinical deterioration due to DCI in subjects treated with clazosentan is not different from placebo. The alternative hypothesis (H_A) is that the event rate in the clazosentan arm differs from the placebo arm.

10.3.2.2 *Primary statistical analysis*

The primary statistical analysis will be performed on the FAS, according to the intent-to-treat approach.

The null hypothesis will be tested using a CMH test stratified* on WFNS grade (1–2 vs 3–5) and age (≤ 60 and > 60 years) at hospital admission at the two-sided significance level of alpha = 0.05.

The treatment effect (clazosentan vs placebo) will be expressed in terms of odds ratios (ORs) and also in terms of relative risk reduction of the active arm compared to placebo with corresponding 95% CL. A relative risk lower than 1 will indicate a response to treatment in favor of clazosentan over placebo. The relative risk reduction, representing the difference in event rates relative to (or proportional to) the placebo event rate, expressed

as a percentage, will be calculated. A value lower than 100% will indicate a response in favor of clazosentan over placebo.

Homogeneity of the treatment effect across strata* will be investigated using the Breslow-Day test.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards. Due to the low number of subjects randomized in this stratum this variable will not be used as an adjustment variable and will be excluded from interaction testing and subgroup analyses.

The incidence rates will be displayed together with the exact 95% CL (Clopper-Pearson). The treatment effect will be described, each with its 95% CL, with:

- The absolute difference in the rates,
- The odds ratio,
- The relative risk and relative risk reduction.

10.3.2.3 *Handling of missing data*

Subjects randomized and treated

The CEC will provide a final assessment (yes or no) on the primary endpoint, indicating for each subject whether it has been met, therefore it is assumed that there will not be any missing data for the primary endpoint. In addition, the CEC will distinguish between the cases of clinical deterioration due to DCI and the cases imputed according to the substitution rules described in Section 6.1.1.

There will be no missing data for the variables included in the model since these variables are collected as stratification factors for the randomization.

Subjects randomized but not treated

No further data will be collected for these subjects. They will not be reviewed by the CEC and will be considered as having met the primary endpoint, i.e., the worst possible outcome is assumed in a sensitivity analysis.

10.3.2.4 *Supportive analyses*

This analysis uses a logistic regression model instead of the CMH test on the FAS.

The primary endpoint follows a binomial distribution and the assessment of clazosentan 15 mg/h treatment effect relative to placebo will be done using a logistic regression adjusting* for hospital admission WFNS grade (1–2 vs 3–5), and age (≤ 60 and > 60 years) at hospital admission.

The linear model used for testing the treatment effect is described by:

$$\log (p/(1-p)) = \alpha + \beta_1 * \text{treatment} + \beta_2 * \text{WFNS} + \beta_3 * \text{age},$$

where:

- p refers to the probability of the event,
- treatment refers to clazosentan 15 mg/h and placebo (reference is placebo),
- WFNS refers to hospital admission WFNS grade (1–2 vs 3–5),
- age (years) refers to that at hospital admission (continuous).

The coefficients α, β_1, β_2 and β_3 will be estimated by the method of maximum likelihood.

Results of the logistic regression will be presented by the odds ratios, the corresponding 95% Wald CL and the p-value derived from the Wald statistic (Type III analysis of effects).

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards. Due to the low number of subjects randomized in this stratum this variable will not be used as an adjustment variable and will be excluded from interaction testing and subgroup analyses.

The primary efficacy analysis planned in protocols up to version 5 will be performed as a supplementary analysis: i.e., the primary efficacy analysis described in Section 10.3.2.2 will be repeated including the patient population (high-risk prevention vs early treatment) as an additional adjustment factor.

10.3.2.5 *Sensitivity analysis*

The CMH analysis will be repeated on the PPS in order to assess the impact of important protocol deviations on the assessment of the primary endpoint. This analysis will, in particular, address the issue of the lack of adherence to important protocol requirements or compliance with study treatment.

The CMH analysis may also be repeated on the FAS, on the subset of subjects for which the primary endpoint was met based on the occurrence of clinical deterioration due to DCI in order to address the possible issue of unclear cases potentially linked to missing data.

The CMH analysis may also be repeated on the Randomized analysis set. This analysis will only be conducted if the number of subjects randomized but not treated is greater than 5%.

Additional sensitivity analyses will be specified in the SAP.

10.3.2.6 *Subgroup analyses*

The aim of these exploratory subgroup analyses, classifying subjects according to important baseline characteristics, is to explore the consistency of treatment effect in a variety of relevant subject subgroups to support the efficacy evaluation of clazosentan in this indication.

The study is stratified by the following subgroup variables:

- WFNS grade at hospital admission (1–2 vs 3–5).
- Patient population (high-risk prevention vs early treatment*).
- Age (≤ 60 and > 60 years) at hospital admission.

The following pre-specified subgroups may also be considered for the analyses (details will be provided in the SAP):

- Geographical location.
- Gender.
- Type of aneurysm-securing procedure.

Additional subgroup analyses for the primary endpoint may also be conducted for factors that would be identified with a statistically significant treatment × factor interaction*.

Results of the subgroup analyses will be displayed in a forest plot and will include:

1. An estimate of the treatment effect (OR for clazosentan vs placebo) with its 95% CL for each level of each subgroup. It will be calculated using the CMH estimator of the common OR obtained separately in each subgroup level as described for the main analysis.
2. A vertical reference line displayed at the level of the overall treatment effect.

The subgroup analyses will also be performed using a logistic regression model stratified* by WFNS grade and age at hospital admission and including terms for "subgroup", "treatment" and "treatment by subgroup" interaction*. Results will be summarized in a table and will include:

1. An estimate of the treatment effect (OR for clazosentan vs placebo) with its 95% CL for each level of each subgroup.
2. A p-value for the interaction tests.

The study is not designed or powered to detect interactions but an arbitrary two-sided significance level of alpha = 0.10 will be used for the interpretation of the interaction test. No multiplicity adjustment is introduced as the subgroup analyses are exploratory in nature.

If there are issues due to very small sample sizes (e.g., interaction test failing due to presence of observed zero cells), the use of other methods may be considered.

*Recruitment into the early treatment group was discontinued from protocol version 6 onwards. Due to the low number of subjects randomized in this stratum this variable will not be used as an adjustment variable and will be excluded from interaction testing and subgroup analyses.

10.3.3 Analysis of the secondary efficacy variables

10.3.3.1 *Occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation defined as: all-cause cerebral infarction ≥ 5 cm³ or cerebral infarction < 5 cm³ in subjects with clinical deterioration due to DCI*

Hypotheses

The null hypothesis (H_0) is that the occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation defined as: all-cause cerebral infarction ≥ 5 cm^3 or cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI in subjects treated with clazosentan is not different from placebo. The alternative hypothesis (H_A) is that the event rate in the clazosentan arm differs from the placebo arm.

Primary statistical analysis

The proportion of subjects with the main secondary endpoint will be analyzed in a similar manner as for the primary efficacy endpoint.

The primary statistical analysis will be performed on the FAS, according to the intent-to-treat approach.

Handling of missing data

Subjects randomized and treated

The CEC will provide a final assessment (yes or no) on the first component of the main secondary endpoint (infarcts ≥ 5 cm^3), indicating for each subject whether it has been met and distinguishing between the true cases of cerebral infarction ≥ 5 cm^3 and imputed cases (as per CEC charter). Regarding the second component, subjects who met the primary endpoint as per CEC but with missing CT scan at Day 16 will be considered to have met the secondary endpoint (i.e., the worst possible outcome is assumed).

There will be no missing data for the variables included in the model since these variables are collected as stratification factors for the randomization.

Subjects randomized and not treated

No further data will be collected for these subjects. They will not be reviewed by the CEC and will be considered to have met the secondary endpoint, i.e., the worst possible outcome is assumed in a sensitivity analysis.

Supportive analyses

This analysis uses a logistic regression model instead of the CMH test on the FAS. It will be conducted in a similar manner as for the primary efficacy endpoint.

Sensitivity analyses

The CMH analysis will be repeated on the PPS performed in order to assess the impact of important protocol deviations on the assessment of the primary endpoint. This analysis will in particular, address the issue about the lack of adherence to important protocol requirements or compliance to study treatment.

In order to address possible issues of unclear cases that are potentially linked to missing data, the CMH analysis may also be repeated on a subset of subjects from the FAS for whom the secondary endpoint was met based on the occurrence of all-cause new or worsened cerebral infarction ≥ 5 cm^3.

The CMH analysis may also be repeated on the Randomized analysis set. This analysis will only be conducted if the number of subjects randomized but not treated is greater than 5%.

Subgroup analyses

Exploratory subgroup analyses may be conducted in the subgroups defined for the primary endpoint.

10.3.3.2 ***Clinical outcome as assessed by the mRS at Week 12 post-aSAH***

Primary statistical analysis

The proportion of subjects with a poor (score of 3 to 6) clinical outcome (mRS) at Week 12 post-aSAH will be analyzed in a similar manner as for the primary efficacy endpoint.

Handling of missing data

Subjects randomized and treated

If the mRS score from the Week 12 interview is missing, and the subject did not die prior to Week 12, the missing mRS score is replaced by the score 4 (moderately severe disability), with the following exception:

- If the subject had their mGCS score reported at least once per day, from study drug initiation up to 14 days post-study drug initiation, and all reported scores regardless of day and time point are ≥ 14, and the location the subject was discharged to after the initial hospitalization at the investigational study center is home, then the missing mRS is substituted with 2 (slight disability).

Subjects randomized but not treated

These subjects will not be observed up to Week 12 post-aSAH, therefore the worst possible outcome is assumed in a sensitivity analysis. If the subject is still alive at the time they withdraw from study, a missing mRS score will be replaced by the score 4 (moderately severe disability).

10.3.3.3 *Clinical outcome as assessed by the GOSE at Week 12 post-aSAH*

Hypotheses

The null hypothesis (H_0) is that the proportion of subjects with poor clinical outcome treated with clazosentan is not different from placebo. The alternative hypothesis (H_A) is that the event rate in the clazosentan arm differs from the placebo arm.

Primary statistical analysis

The proportion of subjects with a poor (score of 1 to 4) clinical outcome (GOSE) at Week 12 post-aSAH will be analyzed in a similar manner as for the primary efficacy endpoint.

Handling of missing data

Subjects randomized and treated

If the GOSE score from the Week 12 interview is missing, and the subject did not die prior to Week 12, the missing GOSE score is replaced by the score 3 (lower severe disability), with the following exception:

- If the subject had their mGCS score reported at least once per day, from study drug initiation up to 14 days post-study drug initiation, and all reported scores regardless of day and time point are ≥ 14, and the location the subject was discharged to after the initial hospitalization at the investigational study center is home, then the missing GOSE is substituted with 5 (lower moderate disability).

Subjects randomized but not treated

These subjects will not be observed up to Week 12 post-aSAH, therefore the worst possible outcome is assumed in a sensitivity analysis. If the subject is still alive at the time they withdraw from study, a missing GOSE score will be replaced by the score 3 (lower severe disability).

Supportive analyses

Logistic regression

This analysis uses a logistic regression model instead of the CMH test on the FAS. It will be conducted in a similar manner as for the primary efficacy endpoint.

Proportional odds regression model

As ordinal analysis of outcome substantially increases statistical power, the proportional odds model will be used as a supportive analysis to assess treatment effect on GOSE data under the assumption that the OR for the treatment variable is the same for all possible ways of collapsing the ordinal outcome scale (i.e., GOSE) into a better and a worse category. The likelihood ratio test evaluates whether this odds ratio differs from 1.

Sensitivity analyses

The CMH analysis will be repeated on the PPS performed in order to assess the impact of important protocol deviations on the assessment of this secondary endpoint.

The CMH analysis may also be repeated on the Randomized analysis set. This analysis will only be conducted if the number of subjects randomized but not treated is greater than 5%.

Subgroup analyses

Exploratory subgroup analyses may be conducted in the subgroups defined for the primary endpoint. Additional analyses may also be conducted on predefined subsets such as subjects who had mGCS ≥ 14 and aNIHSS = 0 prior to study drug start.

10.3.4 Analysis of other efficacy variables

The analysis of all other efficacy variables will be described in detail in the SAP.

The analysis of the effect of clazosentan on long-term clinical outcome, cognition, and health-related QoL at Week 12 post-aSAH will be, in particular, described through an integrated approach as subject-relevant outcomes.

Other variables may also be analyzed by subgroups. Additional analyses, especially for the exploratory efficacy endpoints, may also be conducted on predefined subsets such as subjects who had mGCS ≥ 14 and aNIHSS = 0 prior to study drug start.

Other efficacy endpoints will be analyzed at each relevant time point listed in the visit and assessment schedule [see Table 1 and Table 2].

10.3.5 Analysis of the safety variables

The Safety analysis set will be used to perform all safety analyses.

If not otherwise stated, only treatment-emergent safety data will be considered in tables and figures. All safety data will be included in listings, with flags for safety data considered to be treatment-emergent.

Summaries of safety will be essentially reflected by descriptive statistics for each treatment arm.

No statistical comparisons among the treatment arms with respect to any of the safety parameters will be performed.

10.3.5.1 *Adverse events*

TEAEs and serious adverse events

TEAEs and SAEs will be tabulated by study treatment, system organ class (SOC) and preferred terms within each SOC: the number and percentage of subjects who experienced

at least one (S)AE, at least one (S)AE within each SOC and at least 1 (S)AE within each preferred term will be displayed. (S)AEs will also be summarized by decreasing frequency of preferred term and tabulated by maximum intensity and relationship to clazosentan or placebo.

AEs leading to premature discontinuation of study drug

(S)AEs leading to premature discontinuation of study drug will be summarized in a similar manner as that described above.

TEAEs of specific interest

They will be tabulated by study treatment, category (e.g., lung complications, hypotension, anemia) and preferred term within each category: the number and percentage of subjects who experienced at least one AE of specific interest within each preferred term will be displayed.

Occurrence of rescue therapy-specific AEs up to hospital discharge

They will be summarized in a similar manner as that described above.

10.3.5.2 ***Laboratory data***

Changes from baseline in laboratory variables

Descriptive summary statistics by visit and study treatment will be provided for observed values and absolute changes from baseline for laboratory tests (e.g., hematology, blood chemistry).

Data will be displayed in SI units whenever possible and graphical approaches will be applied for certain variables.

Treatment-emergent marked laboratory abnormalities

Treatment-emergent marked laboratory abnormalities will be summarized descriptively by study treatment as categorical variables.

10.3.6 Analysis of other variables

A full description of all other analyses will be described in the SAP.

10.4 Interim analyses

No interim analyses are planned in this study.

10.5 Sample size

A total of approximately 400 subjects are planned for enrollment into this study and will be randomized according to a 1:1 ratio. Assuming a 10% drop-out rate, this should provide approximately 360 evaluable subjects.

10.5.1 Primary efficacy objective

Data observed in previous studies in similar sets (placebo arm, high-risk population) showed an incidence rate of clinical deterioration due to DCI of 28%

Under the assumption that the true incidence of events in placebo arm is 28% and in clazosentan arm is 14%, a sample size of n = 176 in each treatment arm will have 90% power to show the superiority in response of clazosentan compared to placebo using Pearson's χ^2 test with a 5% two-sided significance level. When taking an approximate 10% drop-out rate into account, 400 subjects have to be enrolled in the study, with n = 200 randomized to each treatment arm. If the true incidence rate in the placebo arm is as low as 22% this sample size (N = 352) will still provide a power of 80% at alpha level of 5% to demonstrate a treatment effect of 50%.

10.5.2 Secondary efficacy objective (main)

This study includes an important endpoint that is the occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation defined as: all-cause cerebral infarction ≥ 5 cm^3 or cerebral infarction < 5 cm^3 in subjects with clinical deterioration due to DCI. With this sample size (N = 352) and under the following assumptions, this study has 75% power to demonstrate a statistically significant reduction at alpha level of 5% two-sided between placebo and clazosentan arms from 20–10%.

11 DATA HANDLING

11.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness and timely reporting of subject data. All source documents should be completed in a neat, legible manner to ensure accurate interpretation and traceability of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

eCRF data will be captured via Electronic Data Capture. The investigator and site personnel will be trained to enter and edit the data via a secure network, with secure access features (username, password, and identification — an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (ref. to US 21 CFR Part 11).

Entries recorded by the subject or the proxy, and/or the assessor (where applicable), on the paper copies of the MoCA, the GOSE, the SS-QOL, the Ox-PAC, and the EQ-5D are considered source data. Site personnel will review and ensure completeness of the subjects' entries.

For each subject screened, regardless of subsequent randomization and study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study.

11.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On eCRFs or other documents (e.g., documents submitted to the CEC or those attached to SAE forms / Pregnancy forms) submitted to the sponsor or any vendors or CROs, subjects must be identified only by number and never by their name or initials, date of birth, hospital numbers, or any other personal identifier. The investigator/delegate must keep a subject identification code list at the site, showing the subject number, the subject's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICFs) must not be sent to the sponsor, any vendor or CROs, and must be kept in strict confidence by the investigator/delegate.

11.3 Database management

eCRFs will be used for all subjects. The investigators will have access to the site eCRF data until the database is locked. The eCRF must be kept current to reflect subject status at any time point during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by the sponsor personnel on an ongoing basis to look for unexpected patterns in data and for study monitoring. Should discrepant data be detected, a query specifying the matter and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, supply the sponsor with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of health authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database lock.

Laboratory samples will be processed through a central laboratory and the results of the randomized subjects will be electronically sent to the sponsor.

AEs and medical history are coded according to the latest MedDRA™ version used by the sponsor or its delegate. Medications are coded according to the latest WHO Drug Dictionary version used by the sponsor or its delegate.

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time may only be made as described in the appropriate sponsor QS docs. After database lock, the investigator will have read-only access to the site eCRF subject data, until receipt of an electronic copy of the site eCRFs (including the audit trail) on electronic media.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Ethics and Good Clinical Practice

The sponsor personnel and the investigators will ensure that the study is conducted in full compliance with ICH-GCP Guidelines, the principles of the Declaration of Helsinki, and with the laws and regulations of the country in which the study is conducted.

12.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document(s) provided to the subject (such as the ICF) to an IEC/IRB. Approval from the committee/board must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator to the IEC/IRB in accordance with local procedures and regulations [see Section 12.6].

A list of members participating in the IEC/IRB meetings must be provided, including the names, qualifications, and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation.

If a member of the site study personnel was present during an IEC/IRB meeting, it must be clear that this person did not vote.

12.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP and Declaration of Helsinki guidelines and local regulations from each individual subject participating in this study and/or his/her legally designated representative/proxy. If the subject is not able to provide personal consent at the time the consent is obtained, then he/she must provide this consent as soon as possible once his/her clinical condition has improved to the extent that providing personal consent is possible, unless local regulations state otherwise.

The investigator/delegate must explain to subjects/representatives/proxies that they are completely free to refuse to enter the study, or to voluntarily withdraw from the study at

any time for any reason without having to provide any justification. Special attention shall be paid to the information needs of specific subject populations and of individual subjects, as well as to the methods used to give the information. Adequate time shall be given for the subject/representative/proxy to consider his or her decision to participate in the study and it shall be verified that the subject/representative/proxy has understood the information (e.g., by asking the subject/representative to explain what is going to happen). The ICF will be provided in the country's local language(s).

Site personnel authorized (according to local regulation and sponsor requirements) to participate in the consent process and/or to obtain consent from the subject will be listed on the Delegation of Authority form.

The subject/representative/proxy and authorized site personnel listed on the Delegation of Authority form must sign, personally date, and time (if the first study-mandated procedure is to be performed on the same day informed consent is obtained) the ICF before any study-related procedures (i.e., any procedures required by the protocol and are not part of routine standard of care) begin.

12.4 Compensation to subjects and investigators

The sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject in the event of study-related injuries will comply with applicable regulations.

12.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the IEC/IRB and/or the regulatory authority-approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the subject.

If a protocol deviation occurs, the investigator/delegate will inform the sponsor or its representative in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. Deviations considered to be a violation of ICH-GCP must be reported to the IEC/IRB and regulatory authorities according to the sponsor or (overruling) local requirements.

All protocol deviations will be reported in the clinical study report. IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

12.6 Protocol amendments

Any change to the protocol can only be made through a written protocol amendment. An amended protocol must be submitted to the IEC/IRB and regulatory authorities, according to their requirements.

12.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring, and available when needed.

These records are to be classified into 2 different categories of documents: ISF and subjects' source documents.

These records must be kept by the investigator for as long as is necessary to comply with the sponsor's requirements (i.e., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and the sponsor to store these documents outside the site, so that they can be retrieved in the event of a regulatory inspection. No study document should be destroyed without prior written approval from the sponsor. Should the investigator wish to assign the study records to another party, or move them to another location, the sponsor must be notified in advance.

If the site is using an electronic/computerized system to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the CRA has been provided personal and restricted access to the data for study subjects, to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the CRA could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by the CRA. The printouts must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies having the same information as the original source data. The printouts will be considered as the official clinical study records and must be filed either with the subject's medical records or with the subject's eCRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The CRA does not need to verify this process for all data of all subjects but at least for some of them (e.g., first subject; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per the sponsor instructions. If it were not possible for the CRA to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study.

12.8 Monitoring

Prior to study start at a site, all required approvals must be obtained. A site initiation visit (SIV) will be performed after the required essential study documents are approved by the sponsor. The study treatment will be shipped to the site upon approval of the required essential documents.

The PI must ensure that all site personnel involved in the study are present during the SIV and will dedicate enough time to it. Site Information Technology support should also be available during the SIV to assess the use of the eCRF.

The SIV must be completed before the site can start the screening of study subjects. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the PI and filed in the ISF.

During the study, the CRA will contact and visit the site regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the eCRFs and other protocol-related documents. The sponsor monitoring standards require full verification that informed consent has been provided, verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety, and tolerability endpoints. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring guidelines. The frequency of the monitoring visits will be based on subject recruitment rate and critical data collection times.

The PI must ensure that the eCRF is completed as soon as possible after each of the study periods, and after each visit / telephone call / other contact, and that all requested subject files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the CRA. The required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

The investigator agrees to cooperate with the CRA(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site when there are no more active subjects and all follow-up issues have been resolved. If a site does not enroll any subjects, the close-out visit may be performed prior to study closure at the discretion of the sponsor.

12.9 Investigator Site File

Each site will be provided with an ISF prior to the SIV. It will contain all the essential documents that are required to be up-to-date and filed at site as per ICH-GCP section 8.

The ISF will include a table of content listing the essential documents. All study-related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the CRA regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. The ISF must be kept by the site for as long as is necessary to comply with the sponsor's requirements (i.e., as specified in the clinical study agreement), ICH-GCP and national and/or international regulations, whichever would be the longest period. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the PI must immediately inform the sponsor.

If the PI changes, or if the site relocates, the CRA must be notified as soon as possible.

12.10 Audit

The sponsor representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to the sponsor requirements (e.g., standard operating procedures) will also be verified. Prior to initiating this audit, the investigator will be contacted by the sponsor to arrange a time for the audit.

The investigator and site personnel must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

12.11 Inspections

Health authorities and/or IEC/IRB may also conduct an inspection of this study (during the study or after its completion) at the site.

Should an inspection be announced by a health authority and/or IEC/IRB, the investigator must immediately inform the sponsor (usually via the CRA) that such a request has been made.

The investigator and site personnel must cooperate with inspector(s) and allow access to all study documentation (e.g., subject records) and study facilities.

12.12 Reporting of study results and publication

The sponsor will post the key elements of this protocol and the summary of results within the required timelines on publicly accessible databases (e.g., clinicaltrials.gov, EU database), as required by law and regulation.

Study results will be documented in a clinical study report that will be signed by the sponsor's representatives and the coordinating investigator.

In accordance with the Good Publication Practices and ethical practice as outlined in internationally recognized guidance documents (e.g., European Medical Writers Association, American Medical Writers Association, international Society for Medical Publication Professionals), the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before submission to a peer-reviewed journal.

All involved persons (including the coordinating investigator, if applicable), will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with the sponsor personnel prior to submission to a peer-reviewed journal or presentation at a congress.

Authorship will be determined in accordance with the International Committee of Journal Editors criteria, and be based on:

- substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data; and
- drafting of the publication or critical review for important intellectual content; and
- providing final approval of the version to be published; and
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The list of authors of any publication of study results may include representatives of the sponsor and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to the sponsor for review at least 30 days prior to submission for publication or presentation

at a congress. Upon review, the sponsor may provide comments, and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

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14 APPENDICES

Appendix 1 Definition of "thick and diffuse clot" on hospital admission CT scan

A "thick and diffuse clot" is defined as a thick confluent clot, more than 4 mm in thickness, involving 3 or more basal cisterns.

A basal cistern contains a thick clot, if SAH completely fills the cistern or a part of a larger cistern (e.g. Sylvian fissure) and is at least 4 mm in thickness measured along the shortest dimension. Care should be taken to not assess the clot thickness where the cistern is primarily in the axial plane as it will artificially increase the apparent thickness of the clot. A single isolated spot with 4 mm thick SAH is not sufficient to designate a cistern as "thick clot". The clot should occupy a significant portion of the cistern. At least 3 cisterns must contain a thick clot.

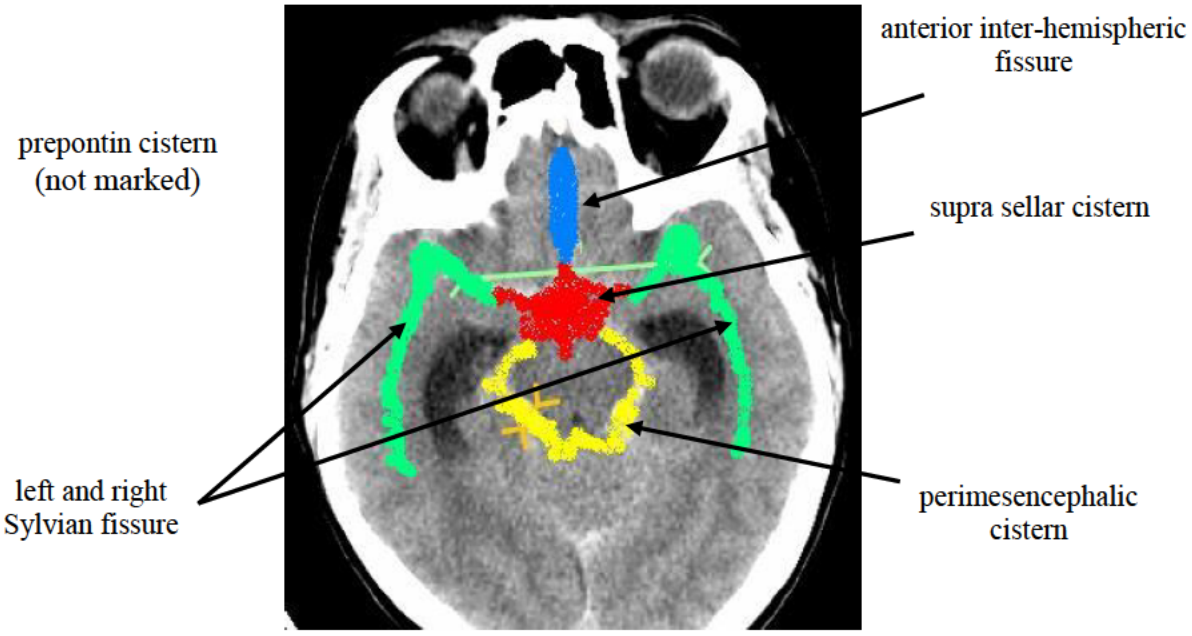
The following guidelines should be used to confirm that the subarachnoid blood in a basal cistern is thick:

- SAH maintains a thickness of 4 mm or more over at least a 20 mm extent of the cistern.
- The cistern appears expanded because of SAH.
- There is a "negative" contrast with hyper-dense subarachnoid blood outlining subarachnoid structures.

In order to determine the overall extent of the hemorrhage, the following basal cisterns (see below figure) must to be assessed at different levels (i.e., all contiguous slices from the inferior aspect of the brain stem to the most superior aspect of the Sylvian fissures), and at least 3 of the cisterns must contain a thick clot in order to be eligible for the study.

- left Sylvian fissure (green)
- right Sylvian fissure (green)
- supra sellar cistern (red)
- perimesencephalic cistern (yellow)
- anterior inter-hemispheric fissure (blue)
- prepontin cistern (not marked on the figure below)

COLLAPSED VIEW OF BASAL CISTERNS



Appendix 2 Global vasospasm assessment

Note: This appendix is only applicable to subjects recruited into the early treatment group. Recruitment into the early treatment group was discontinued from protocol version 6 onwards.

The presence/absence of vasospasm will be determined at the level of the proximal (vertebro basilar, intradural internal carotid artery [ICA], A1, M1 and P1) and distal (A2, P2 and M2) brain vessels. If vasospasm is present, its location and severity will be indicated. For distal vessels, vasospasm is only considered to be present if at least two branches are affected. If only one branch shows vasospasm, the segment is NOT considered to be affected by vasospasm.

The severity of the vasospasm in each predefined vessel segment will be indicated based on the following 4 categories:

1. None = No vasospasm
2. Mild = up to 1/3 of vessel narrowing
3. Moderate = more than 1/3 and up to 2/3 of vessel narrowing
4. Severe = more than 2/3 of the vessel narrowing

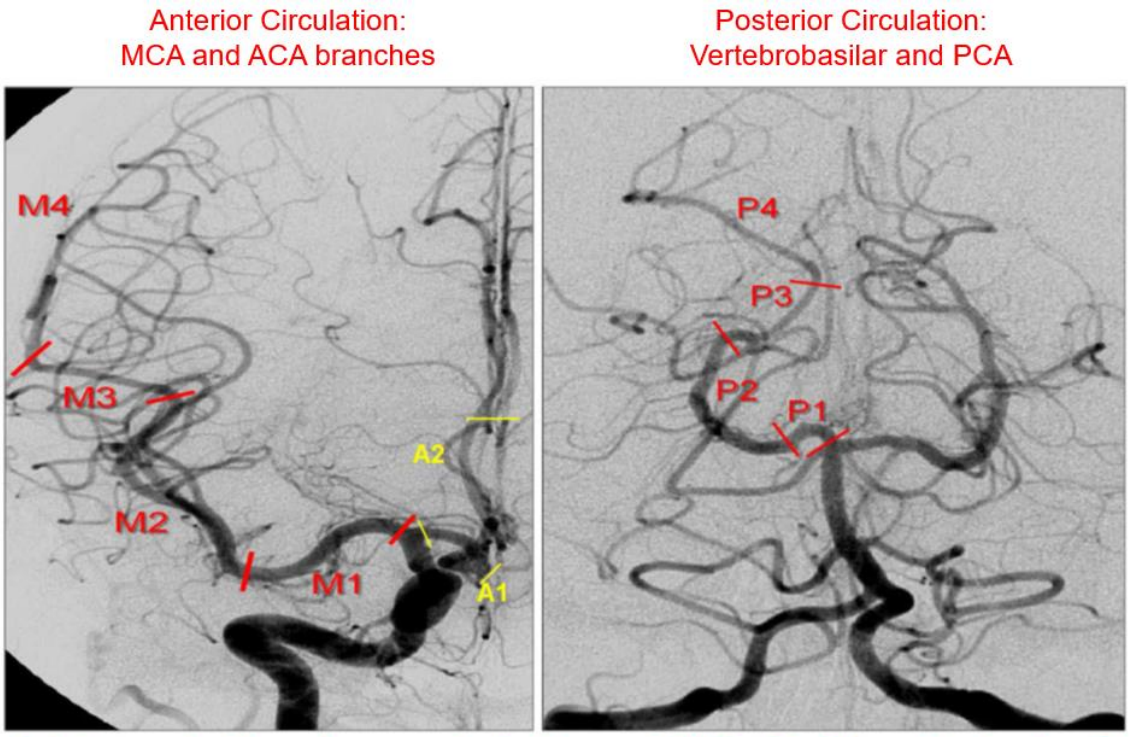
The location of the vasospasm will be indicated from among the following:

- vertebro basilar
- intradural ICA (Left/Right)
- A1 (Left/Right)
- A2 (Left/Right)
- M1 (Left/Right)
- M2 (Left/Right)
- P1 (Left/Right)
- P2 (Left/Right)

For the assessment of global vasospasm, only the predefined vessels mentioned above are considered. Vasospasm that is present exclusively in the most distal parts (e.g., A3, A4, P3) should not be taken into account.

The severity of global vasospasm will be indicated using the using the following definitions:

- **Moderate vasospasm**: at least two segments with moderate vasospasm and/or one segment with severe vasospasm
- **Severe vasospasm**: at least two segments with severe vasospasm



Only the proximal branches, namely, the intracranial ICAs, A1, M1, vertebrobasilar, P1, and the distal branches A2, M2, and P2 will be graded for the degree of vasospasm.

Anterior and Posterior Circulation Nomenclature

Anterior Circulation	Posterior Circulation

Middle Cerebral Artery (MCA) M1: Pars sphenoidalis M2: Pars insularis M3: Pars horizontalis M4: Pars terminalis Anterior Cerebral Artery (ACA) A1: Carotid terminus to Anterior Communicating artery (ACOM) A2: ACOM to next bifurcation	Posterior Cerebral Artery (PCA) P1: Precommunicating segment P2: Ambiens (circular) segment P3: Quadrigeminal segment P1 – P3: Pars circularis P4: Pars corticalis

Appendix 3 Patient Management Guidelines

It is expected that, wherever possible, the rules in the guidelines are followed. However, during the treatment period, individual subject characteristics and specific clinical situations may not always allow the strict adherence to these guidelines. Any deviation is to be documented in the subject's source notes along with medical justification. Key measures of compliance with the Patient Management Guidelines will be checked by the sponsor or representative.

1. Main objectives

- To reduce the incidence of predictable and preventable AEs via information and proactive management.
- To increase consistency and standardization in the level of care across all study sites for certain key clinical parameters.

2. Background and rationale

The safety profile of clazosentan has been well characterized based on the data accumulated from previously conducted Phase 2 and 3 clinical trials in which over 1800 subjects with aSAH were treated with active drug, including over 300 subjects at the currently tested 15 mg/h dose. Certain AEs are associated with the administration of clazosentan, notably hypotension, lung complications (in particular pulmonary edema, pleural effusion, and respiratory failure) and anemia.

When objective BP measurements were analyzed, the magnitude of the BP decrease was seen to be modest, in the order of 10%. Clazosentan has a systemic vasodilatory effect, common to ERAs.

Anemia is a class effect of ERAs, is believed to be related to hemodilution, and is typically reversible after discontinuation of clazosentan.

Fluid retention is also a common finding with ERAs. An association between a positive cumulative fluid balance and the occurrence of lung complications has been observed previously in aSAH subjects, suggesting an important role of fluid management in the occurrence of these events.

The above described events are either preventable or manageable in a typical ICU setting. Patient Management Guidelines that emphasize the maintenance of euvolemia and target BP goals, are expected to decrease the incidence of lung complications related to fluid retention and hypotension and to facilitate their management in the event they should occur.

Study drug must therefore be administered in parallel to vasopressors and fluids, as needed, and must not be initiated until BP is adequately controlled according to the below guidelines. Similarly, vasopressor and fluid therapy should not be discontinued until after the discontinuation of study drug.

During the study treatment period, all subjects must be in an ICU (or equivalent environment where all protocol assessments can be performed and these Patient Management Guidelines followed) with strict BP monitoring.

Prior to enrolling a subject into the study, BP and fluid status must be controlled, as needed, with i.v. vasopressors and fluid administration according to these guidelines. Conditions contraindicating increased doses of vasopressors are described in these guidelines (see General BP Control) and if present at the time of enrollment, investigator judgment is required regarding the suitability of the subject for the study.

3. Fluid management

3.1 General fluid monitoring and control

The goal of the following recommendations is to emphasize euvolemia to avoid fluid overload.

Central venous monitoring is highly recommended in all subjects, for enabling administration of vasopressors, fluids, and CVP measurement.

Maintenance of i.v. fluid administration

- Administer saline, Ringer's Lactate, or a balanced crystalloid solution (e.g., Isofundine®, Plasma-Lyte®, Stereofundin®) starting at 1.0 to 1.5 mL/kg/h. This hourly infusion rate should include the volume of fluid administered with the study drug and be adjusted based on other i.v. administered products.

- Evaluate for the presence or absence of euvolemia.

Indicators of **euvolemia** include:

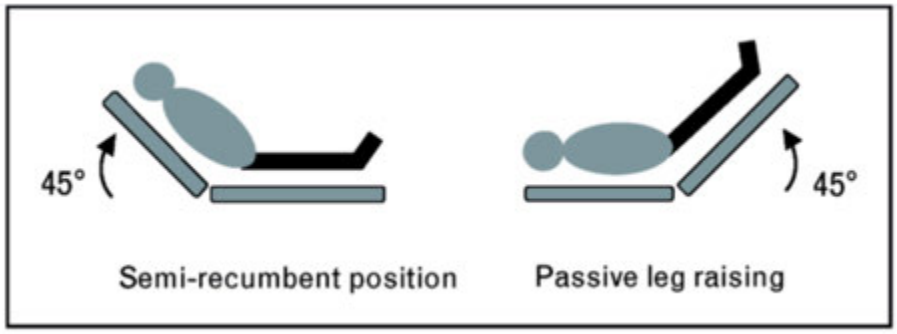
1. Total 24-hour fluid output is well matched to fluid input (i.e., within 500 mL/day)

2. Inferior vena cava (IVC) is non-collapsible with spontaneous respirations (< 40% fluctuation in diameter as observed on echocardiography) off the ventilator circuit

3. A 15% or less increase in IVC diameter (as observed on echocardiography) with inspiration in mechanically-ventilated subjects given a tidal volume of 10 mL/kg with a PEEP of 0 cm H_20

4. Stroke volume variability (SVV) is < 10% (using Cheetah NICOM®, Edwards FloTrac®, PiCCO®, or another advanced circulatory monitoring device)

5. Increase in stroke volume to passive leg raising is < 10% (measured with a hemodynamic monitoring device)



The passive leg-raising test consists of measuring the hemodynamic effects of a leg elevation up to 45°. A simple way to perform the postural maneuver is to transfer the subject from the semi-recumbent posture to the passive leg-raising position by using the automatic motion of the bed.

Conversely, the potential for **hypovolemia** is assessed by **fluid-responsiveness indicators** which are the following:

1. IVC collapses > 40% with respiratory cycle off ventilator circuit

2. CVP ≤ 5 mmHg off ventilator circuit

3. SVV is > 10% with respiratory cycle (measured with Cheetah NICOM®, Edwards FloTrac®, PiCCO®, or a similar hemodynamic monitoring device)

4. Passive leg raising to 45° results in a > 10% increase in left ventricular stroke volume (measured with a hemodynamic monitoring device), a > 10% increase in arterial pulse pressure (measured via arterial line), or a 5% increase in $ETCO_2$ (end-tidal CO_2).

Of note, a positive fluid responsiveness does not necessarily mean extra fluids are required. The absence of fluid responsiveness usually indicates that extra fluids are not required.

Administer a crystalloid or colloid fluid bolus if, and only if, there is evidence of potential fluid-responsive hypotension.

Warning: Administration of large fluid boluses (≥ 1 liter cumulatively over 24 hours) to subjects not documented to be fluid-responsive must be avoided. The reason for administering fluid boluses with a cumulative volume of > 1 liter over 24 hours or any total 24-hour fluid input of > 4 liters (or > 60 mL/kg/day, if greater) must be documented in the source notes. For subjects with a urine catheter, a positive fluid balance of more than 1000 mL over at least two consecutive days is to be justified in the subject's medical chart.

3.2 Permanent study drug discontinuation due to fluid retention

Due to the potential for clazosentan to induce fluid retention, the occurrence of generalized brain edema as well as severe pulmonary edema should result in the permanent discontinuation of study drug.

4. Blood pressure management

4.1 General BP control

The goal of the following recommendations is to optimize BP by the preferential administration of vasopressors to avoid excessive administration of fluids. Fluid administration should not exceed that which is described in the Fluid Management section of these guidelines.

1. BP measurements obtained in the supine position by arterial line or noninvasive cuff (sphygmomanometer) are both acceptable. However, the same modality should be used consistently for each BP measurement for a given subject.

2. In the absence of vasospasm or in the presence of asymptomatic vasospasm (i.e., angiographic vasospasm without obvious clinical symptoms of vasospasm), the minimum target SBP should be 120 mmHg or higher. This guideline applies for most of the cases. However, it is acknowledged that in some instances, the subject's known normal BP may be lower than this. If this is the case, then the target SBP should be the subject's usual SBP.

3. In the presence of symptomatic cerebral vasospasm, the minimum target SBP is 150 mmHg, or higher as needed, with the target SBP titrated against clinical response. If

the target SBP cannot be met because the subject's baseline (normal) BP is low, then the target SBP should be a 30% increase from the baseline SBP.

If the target SBP is not already achieved spontaneously, BP should be raised by administering vasopressors unless specifically contraindicated. If BP is below the defined targets with more than 10% for more than 3 consecutive hours, the underlying reason is to be documented in the subject's source notes.

Contraindications to increasing the dose of vasopressors include heart failure (due to pre-existing cardiac disease or myocardial injury in the context of aSAH) in which case the increase in BP should be balanced against the decrease in cardiac output due to increased cardiac afterload, significant cardiac arrhythmias, pulmonary edema, and clinical or biological evidence of hypoperfusion (e.g., increase in serum lactate and creatinine).

The dosing of oral or i.v. nimodipine (if applicable) should be adjusted according to local standard practice if the above target BPs cannot be met or maintained adequately. Consider temporarily interrupting or permanently discontinuing nimodipine as appropriate.

If the target BP is already achieved spontaneously without requiring medical intervention, the potential need for vasopressors should be anticipated and the appropriate measures put into place to ensure their rapid initiation should the need arise.

4.2 Hypotension management

Automatic administration of bolus i.v. fluids in this scenario is discouraged unless there is compelling evidence that the subject is *fluid responsive*.

Bedside clinical assessment should occur and intervention should be implemented in the following order:

1. Ensure that lines administering vasopressors are patent and flowing.

2. Adjust the dose of nimodipine (if applicable) and titrate the dose of vasopressor(s) upward until maximum dose is achieved.

3. If SBP does not reach the target pressure despite maximal vasopressor therapy and adjustment/discontinuation of nimodipine, study drug should be discontinued temporarily. Study drug may be restarted when the SBP stabilizes above the target. If the hypotension is refractory and suspected to be related to study drug, the study drug should be permanently discontinued.

4. Recommended vasopressors: phenylephrine or norepinephrine (noradrenaline). Epinephrine (adrenaline) and dopamine use is discouraged (due to the unpredictable effect on BP with dopamine and its potential to cause severe tachycardia, and the potential for severe arrhythmias with epinephrine).

5. In the event that the SBP goals are not reached or maintained, **"**fluid responsiveness" should be checked (see above under fluid management section).

5. Mechanical ventilation considerations

With low response to increased O_2 administration and/or PEEP, be aware of the possibility of pulmonary ventilation/perfusion ratio mismatch:

- If suspicion of this phenomenon is present, standard approaches to countering hypoxia should be applied. However, PEEP and FiO_2 should not be continuously increased beyond the usual ranges.
- If the condition does not improve, nimodipine should be stopped to check for signs of improvement. If the condition improves, then nimodipine should be discontinued permanently. If no improvement is seen after a couple of hours, it is left to the appreciation of the investigator to restart nimodipine or not. Study drug should then be temporarily interrupted to check for any potential relationship. If the condition is suspected to be related to study drug, then study drug should be permanently discontinued.

6. General patient management

Continuous ECG monitoring in the ICU is mandatory for the period of study drug administration. It is expected that each site will have a standard protocol in place, which will be adhered to for the following:

- Fever management (i.e., temperature > 38 °C/100 °F)
- Gastro-intestinal bleeding prophylaxis (e.g., ranitidine)
- Deep vein thrombosis prophylaxis (e.g., heparin 5000 units subcutaneously q12h or enoxaparin 40 mg subcutaneously once daily)
- Serum glucose monitoring and control

Appendix 4 Glasgow Outcome Scale (extended version) and Modified Rankin Scale

Glasgow Outcome Scale – Extended (GOSE)

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Modified Rankin Scale (mRS)

[redacted]

Structured Interview for the Extended Glasgow Outcome Scale and the Modified Rankin Scale

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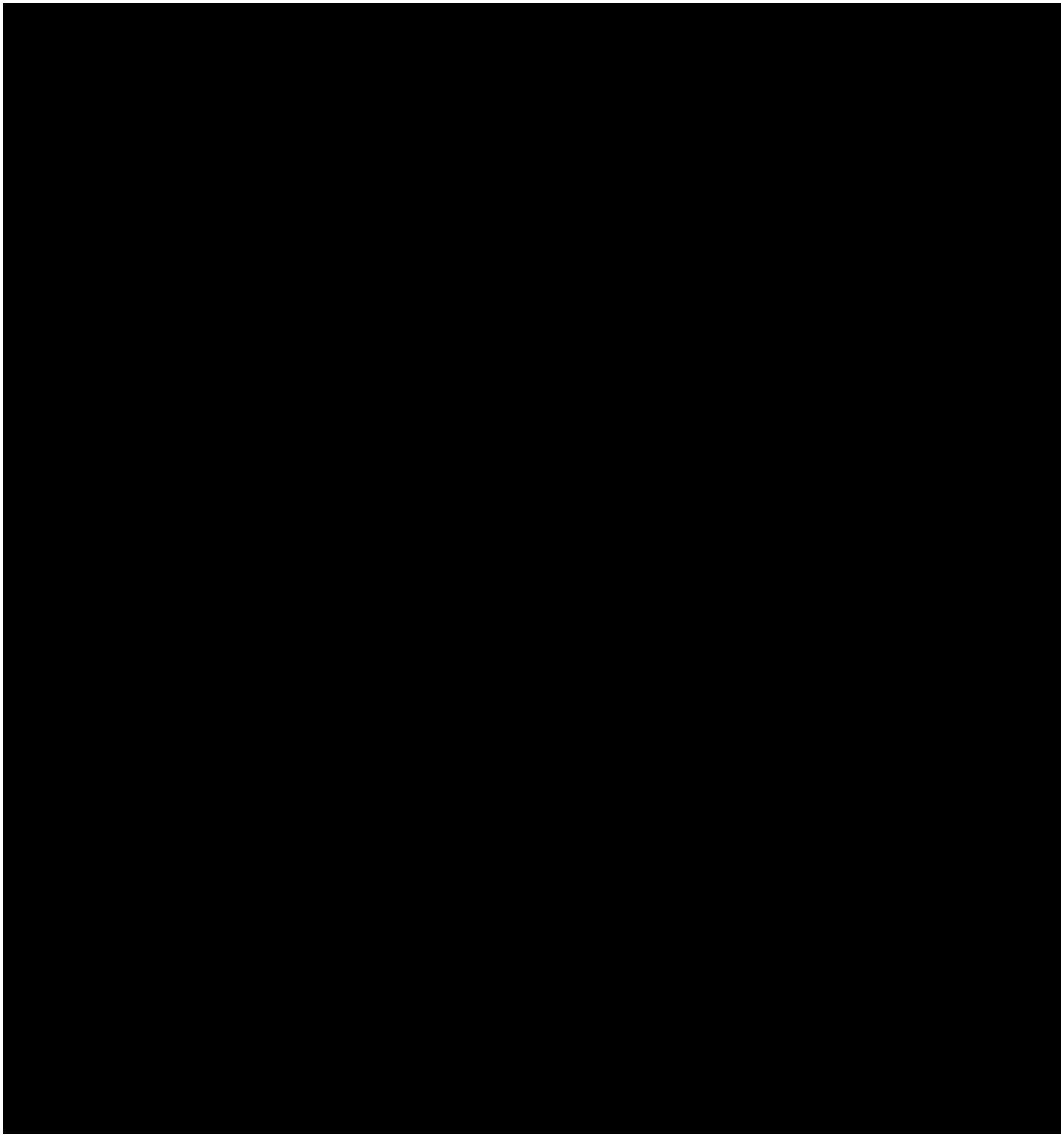

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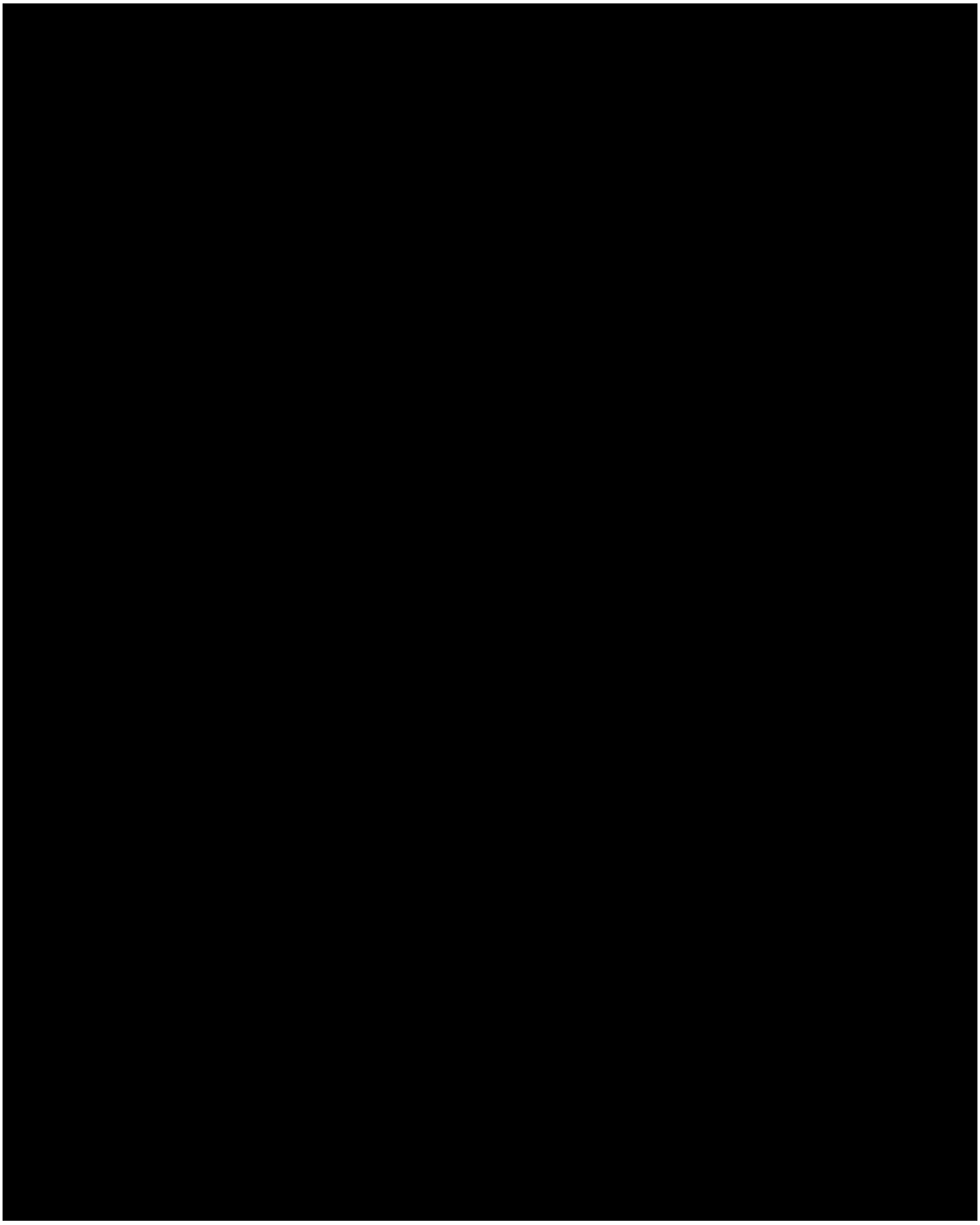
Calculation of Glasgow Outcome Scale (extended) and Modified Rankin Scale scores

GOSE and mRS scores will be derived by the interviewer from the responses to the individual interview questions following the rules detailed below:

Appendix 5 Montreal Cognitive Assessment



Appendix 6 Stroke Specific Quality of Life

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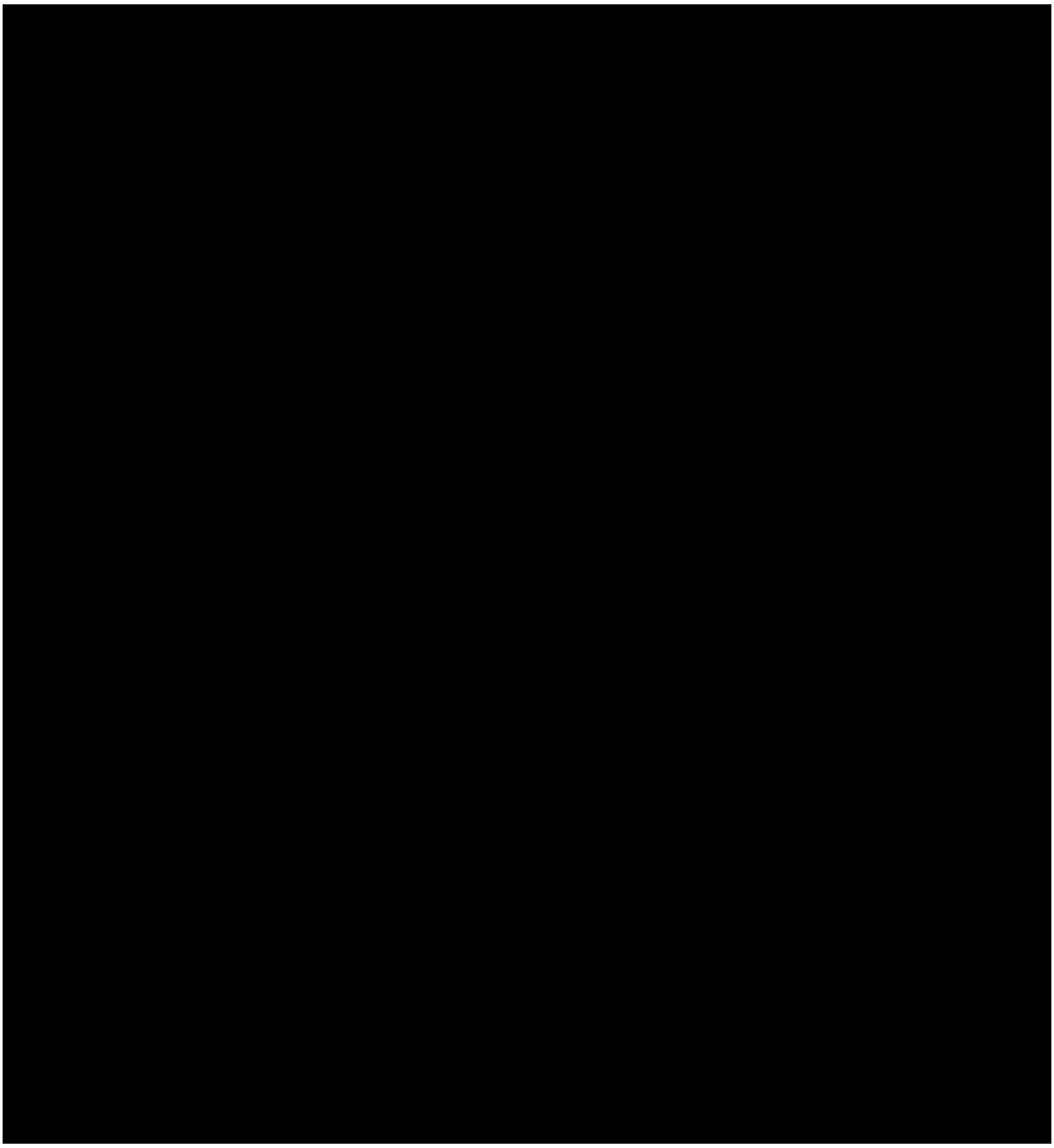
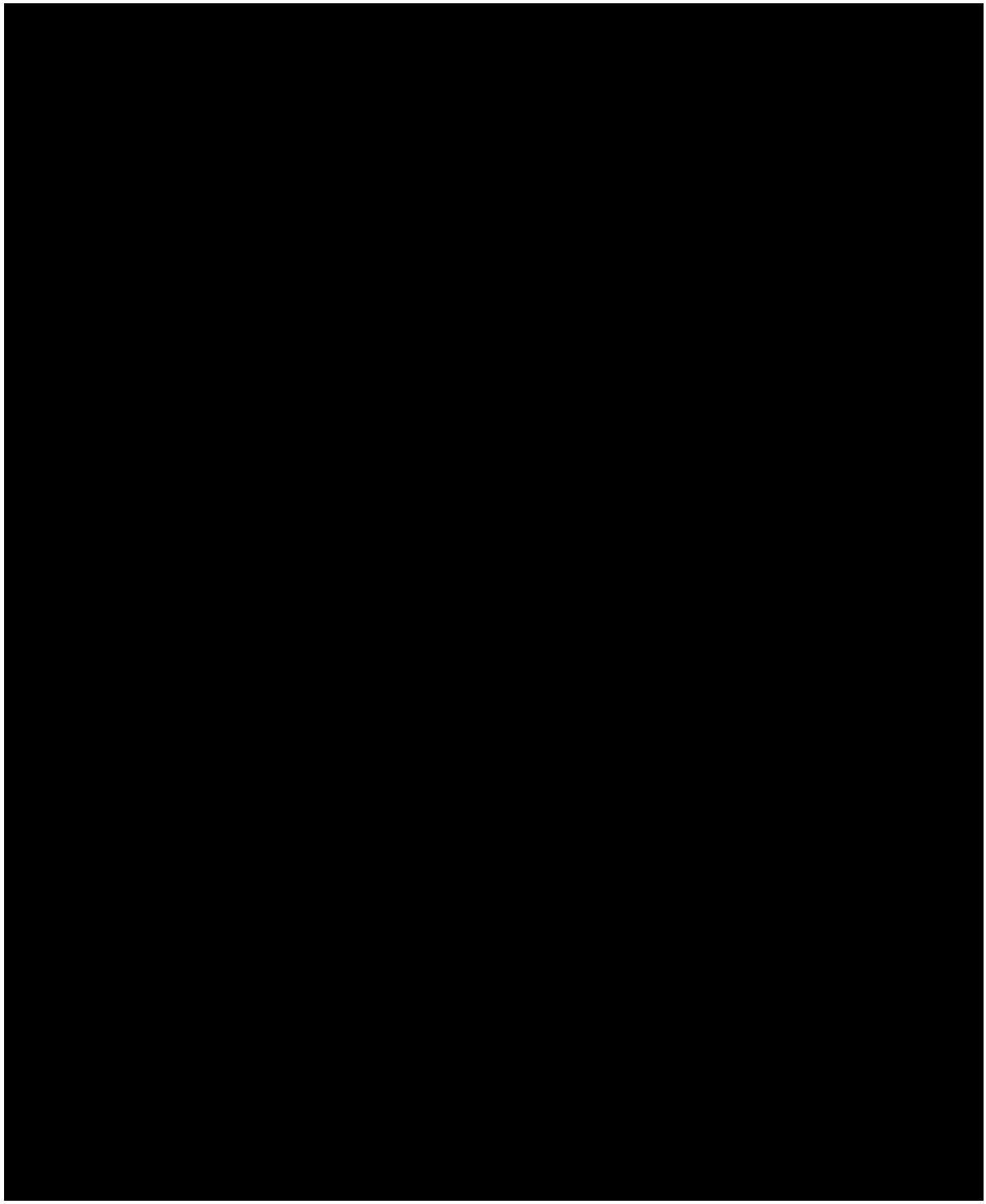
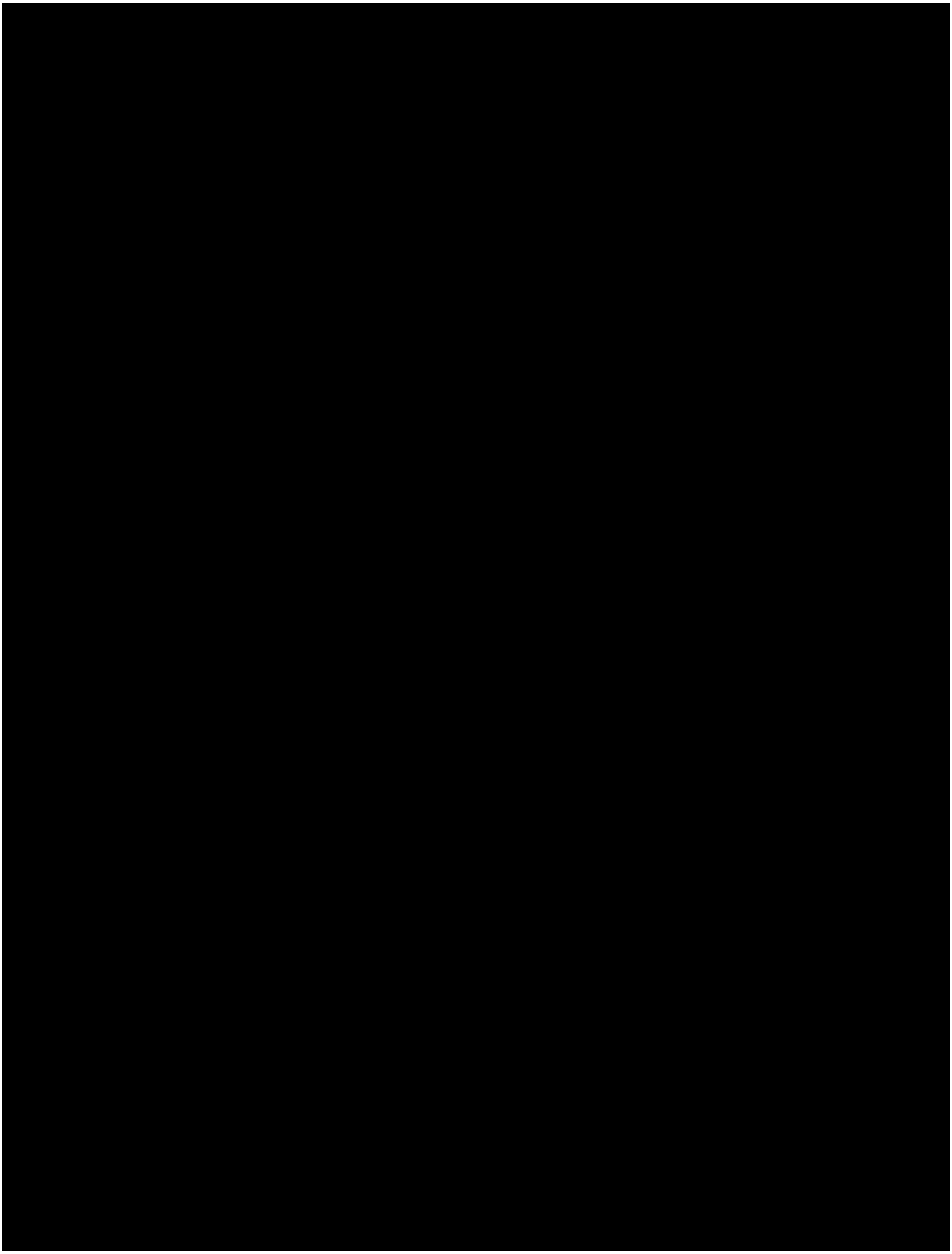
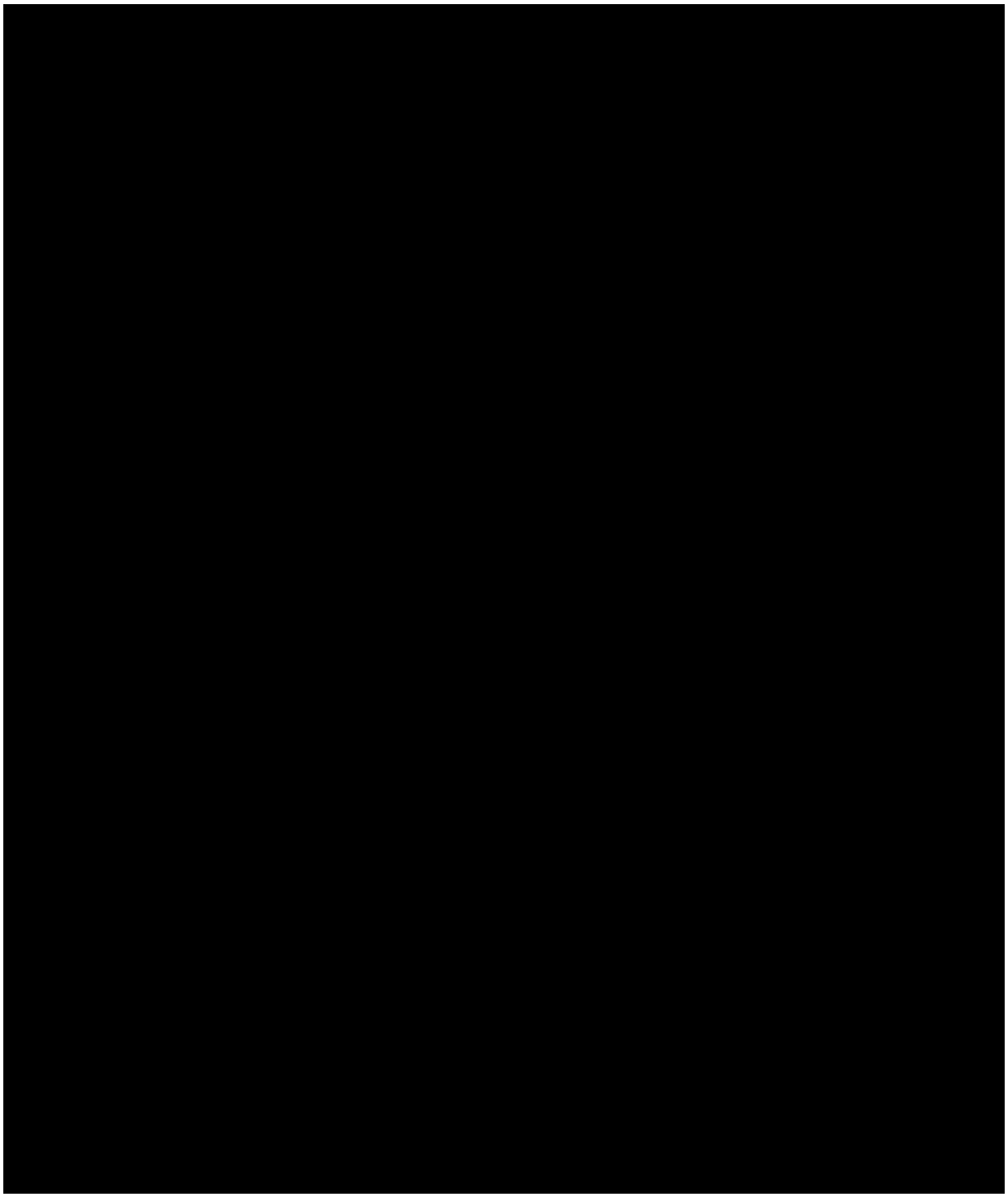
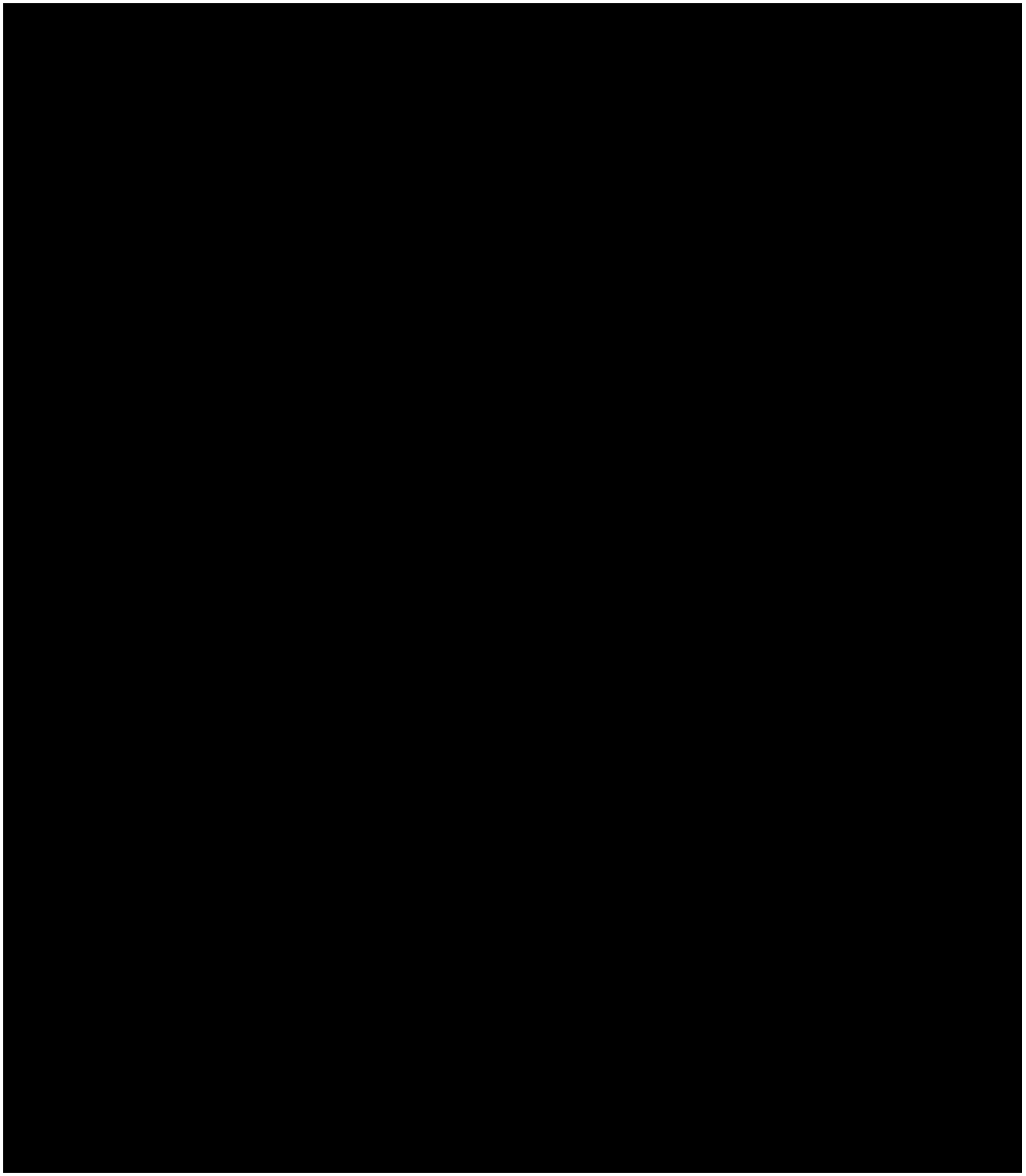


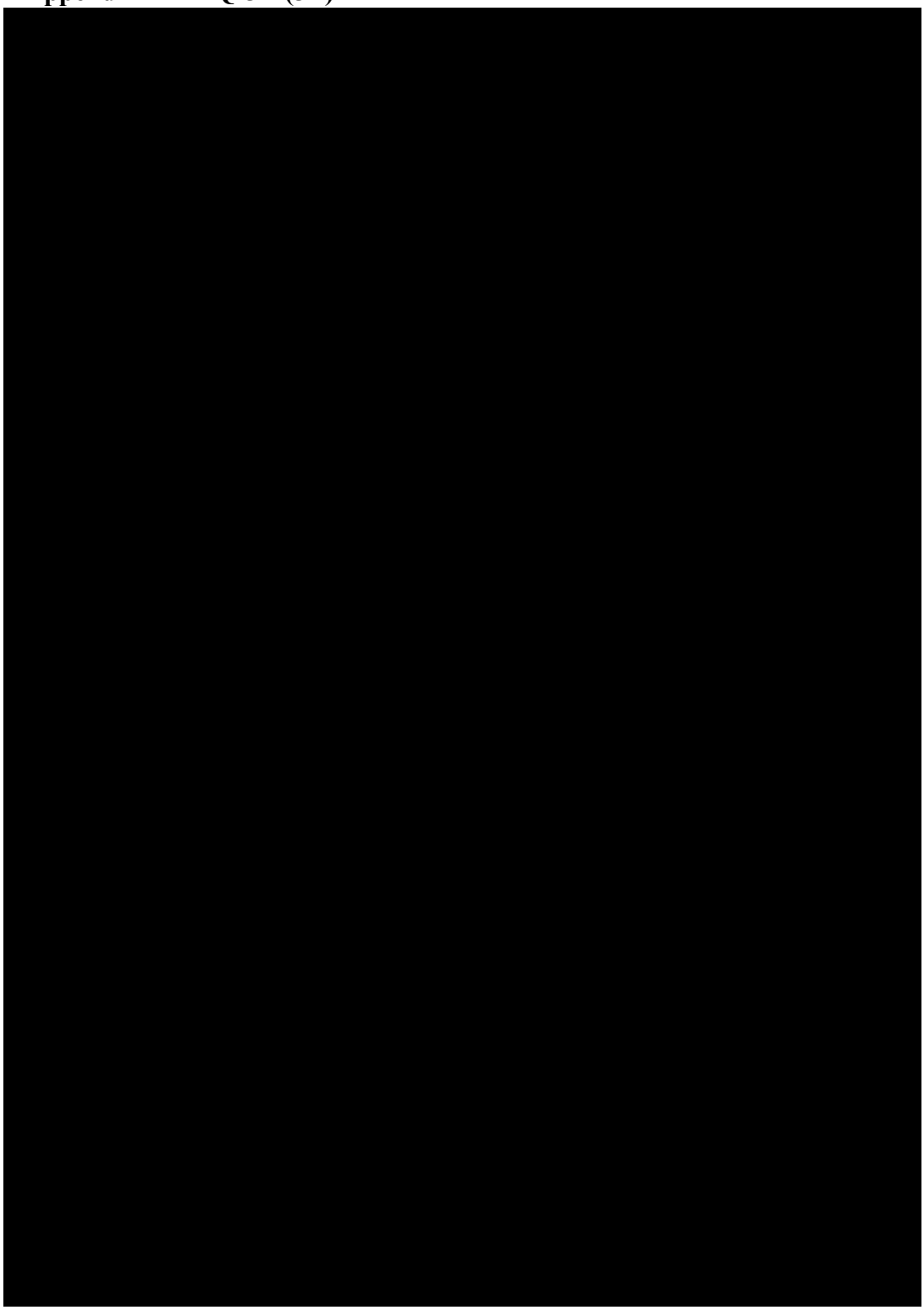


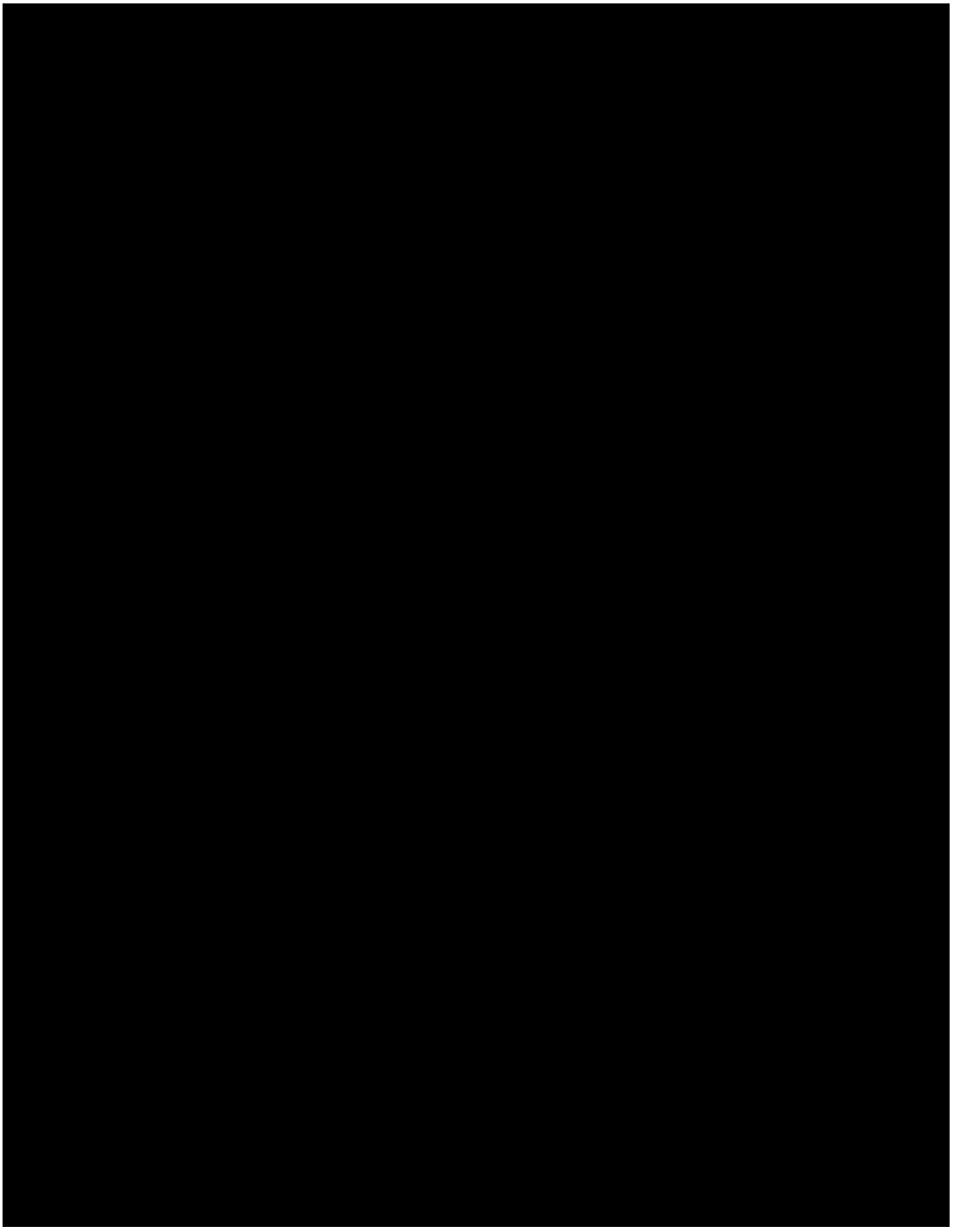






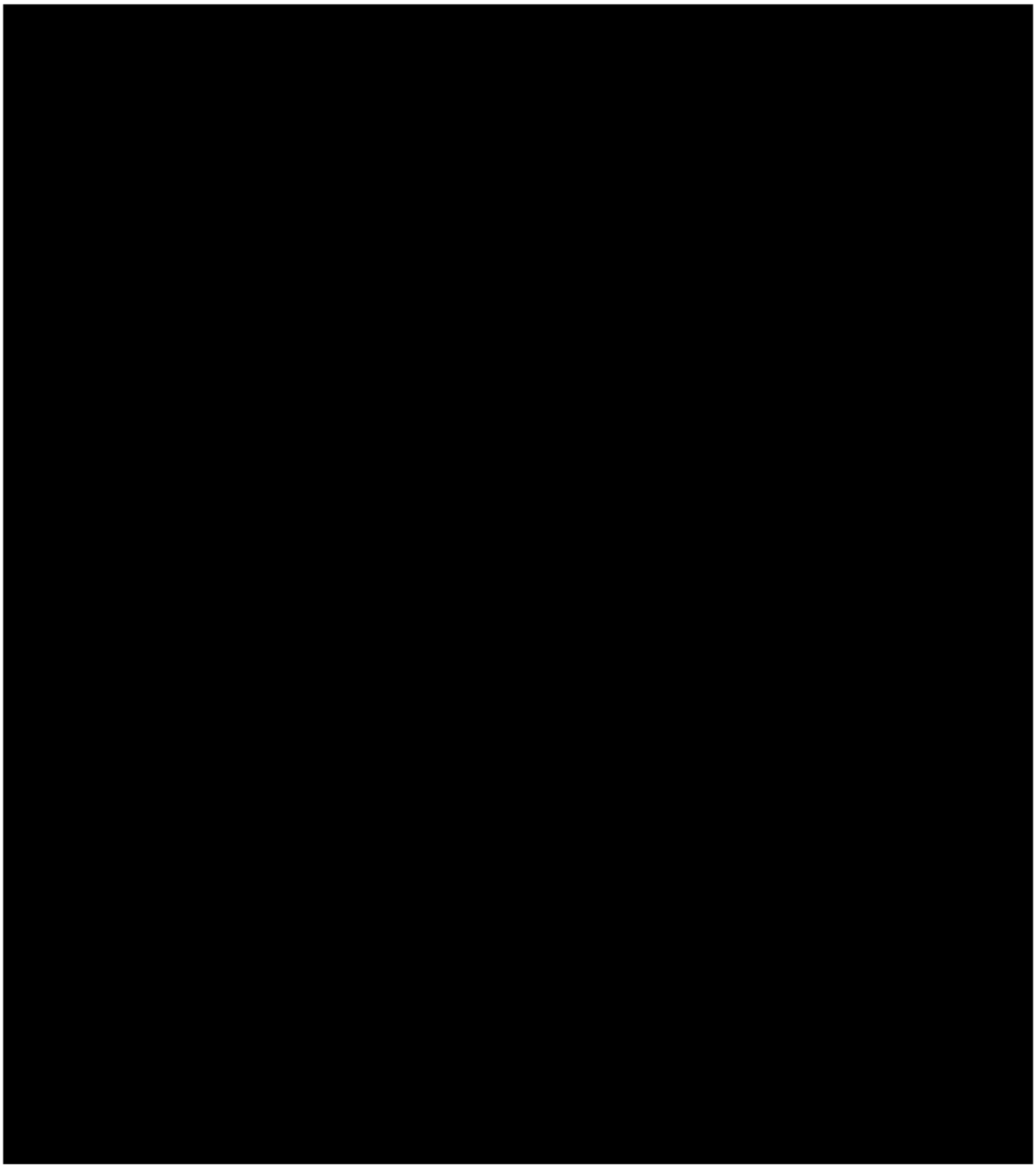
Appendix 7 EQ-5D (5L)





Appendix 8 Oxford Participation and Activities Questionnaire

Oxford Participation and Activities Questionnaire (Ox-PAQ)



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