Cover page

ID-054-304

Statistical Analysis Plan

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:

26 January 2023

CLAZOSENTAN (ACT-108475)

STATISTICAL ANALYSIS PLAN

FOR CLINICAL STUDY REPORT

ID-054-304

REACT

pREvention and trEatment of vAsospasm with ClazosenTan

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)

Version 4

Document Number: D-23.039

26 January 2023

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
ALT	Alanine aminotransferase
aNIHSS	Abbreviated National Institutes of Health Stroke Scale
ANOVA	Analysis of variance
aSAH	Aneurysmal subarachnoid hemorrhage
AST	Aspartate aminotransferase
CEC	Clinical Event Committee
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
CT	Computed tomography
DCI	Delayed cerebral ischemia
eCRF	Electronic case report form
EOS	End-of-Study
FAS	Full analysis set
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale – Extended
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IE	Intercurrent event
IRC	Independent Radiology Committee
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
mGCS	Modified Glasgow Coma Scale
MLA	Marked laboratory abnormality
MoCA	Montreal Cognitive Assessment
mRS	Modified Rankin Scale
OR	Odds ratio
Ox-PAQ	Oxford Participation and Activities Questionnaire
PCA	Principal Component Analysis

POM	Proportional odds model
PT	Preferred Term
QoL	Quality of life
RND	Randomized analysis set
RR	Relative risk
RRR	Relative risk reduction
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SCR	Screened analysis set
SI	Standard International
SOC	System Organ Class
SS-QoL	Stroke-Specific Quality of Life
TEAE	Treatment-emergent adverse event
VAS	Visual analog scale
WFNS	World Federation of Neurological Societies
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the analyses and data presentation for the final clinical study report (CSR) for study ID-054-304 (REACT). Version 4 of the SAP is based on protocol version 7, dated 18 February 2022 [D-22.069] and replaces the previous SAP version 3, dated 27 September 2022. A revision history of the SAP is provided in Appendix 14.1.

Obvious corrections to address minor formatting errors or spelling mistakes may be performed at the time of analysis without amending this and related documentation (e.g., mock shells).

The study includes the study committees displayed in Table 1, each having a specific role.

Table 1 Study committees

Committee	Responsibility
Independent Data Monitoring Committee	Reviewing unblinded safety and efficacy data obtained in the study at regular intervals, and making appropriate recommendations based on the reported data.
Independent Radiology Committee	Reviewing retrospectively (during the course of the study) the angiograms and CT scans submitted for each randomized subject to determine the presence of pre-defined radiological features and to perform required measurements.
Clinical Event Committee	Determining, based on a charter, whether the primary and main secondary endpoint (first component, see Section 6.3.1 for details) have been met.

CT = computed tomography.

2 STUDY DESIGN AND FLOW

2.1 Study design

This is a prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group, 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 (I–II vs III–V), patient population (high-risk prevention vs early treatment), and age at hospital admission (≤ 60 and > 60 years). Recruitment into the early treatment stratum was discontinued from protocol version 6 (29 April 2021) onwards.

Overall, the study will enroll 400 subjects in 2 treatment groups, 200 subjects per group.

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

Once randomized, the subjects will enter a double-blind treatment period of a maximum duration of 14 days. This will be sequentially followed by a safety follow-up period of 24 hours and an extended follow-up period for safety and efficacy assessment terminating with an End-of-Study (EOS) visit at Week 24 post aneurysmal subarachnoid hemorrhage (aSAH).

The overall study design for the high-risk prevention group is depicted in Figure 1.

Note: The study design of the early treatment stratum is provided in Figure 2 although recruitment into this group was discontinued from protocol version 6 onwards.

Figure 1 Study design for the high-risk prevention group

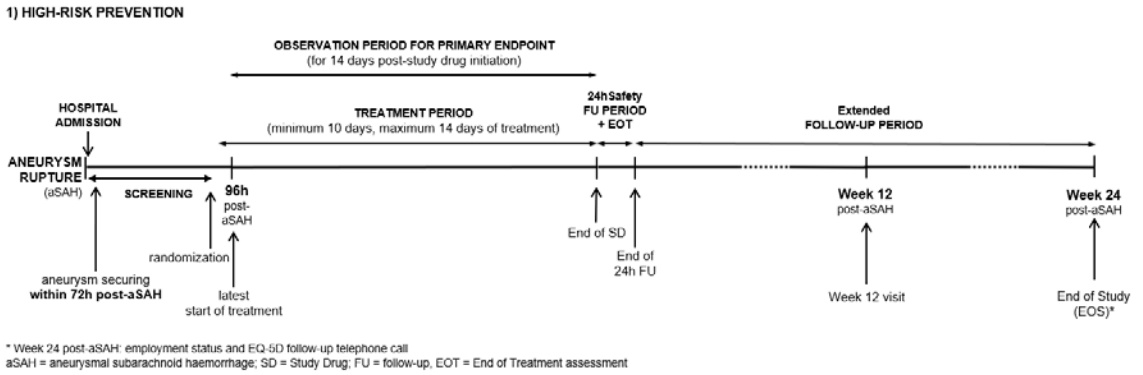
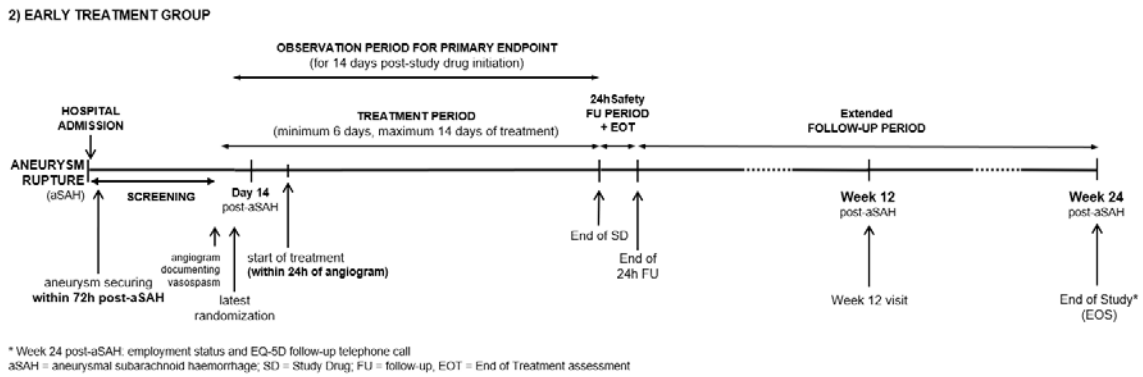


Figure 2 Study design for the early treatment stratum



2.2 Study visit and assessment schedule

The study periods and 'visits' with their respective time windows are listed in the Visit and assessment schedules [see Appendix 14.2].

2.3 Overview of analysis periods

An overview of the study periods and 'visits' is provided below.

The study comprises the following consecutive periods:

Screening period: Starts with the signature of the informed consent form (ICF) and ends with subject randomization.

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.

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.

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

The End-of-Treatment assessments are included in the 24-hour safety follow-up period. These assessments are performed within 2 hours following permanent discontinuation of study drug.

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.

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.

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

3 OBJECTIVES

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

3.1 Primary objective

To determine the efficacy of clazosentan in preventing clinical deterioration due to delayed cerebral ischemia (DCI) in subjects with aSAH.

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

3.2 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.

3.3 Other objectives

To evaluate the effect of clazosentan on healthcare resource utilization.

4 ANALYSIS SETS

4.1 Definitions of analysis sets

4.1.1 Screened analysis set

The Screened analysis set (SCR) includes all subjects for whom informed consent to participate in the study has been obtained and who have a subject identification number.

4.1.2 Randomized analysis set

The Randomized analysis set (RND) comprises all subjects who have been assigned to a study treatment.

4.1.3 Full analysis set

The Full analysis set (FAS) comprises all subjects from the RND who 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 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.

To adhere to the intent-to-treat principle, if not otherwise stated subjects will be evaluated according to their assigned study treatment (which might differ from the actual treatment received) and stratum information as recorded in the Interactive Response Technology (IRT) system.

4.1.4 Safety analysis set

The Safety analysis set (SAF) comprises all subjects who have been assigned to a study treatment and who have started the study drug.

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

In the event of an administration error, i.e., a subject was administered both placebo and active treatment, the subject will be analyzed as 'active treatment' ('clazosentan').

4.2 Usage of the analysis sets

If not otherwise stated, the listings will be produced on the FAS for efficacy and on the SAF for safety.

For the tables and figures, the sets are indicated in Table 2.

Table 2 Overview of the different analysis sets and their usage

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

Note: X: main analysis set; [x]: if RND and FAS differ by more than 5%, some tables may be replicated on the RND; [y]: if FAS and SAF differ by more than 5%, some tables may be replicated on the SAF.
FAS = Full analysis set; RND = Randomized analysis set; SAF = Safety analysis set; SCR = Screened analysis set.

5 STUDY SUBJECT VARIABLES AND ANALYSES

A listing of the randomization scheme and codes will be produced for randomized subjects only (as per ICH E3 16.1.7).

The analyses defined in this section on the FAS will be repeated on the RND if the RND and FAS differ by more than 5%.

5.1 Subject disposition

An overview of the recruitment for each country/site will be presented for the SCR and will comprise the following variables:

- N (%) of subjects screened overall
- N (%) of subjects randomized

An overview of the number of subjects randomized in each treatment group (according to the assigned treatment group) and overall for each country/site will be presented for the RND.

An overview of subject disposition over the course of the study will be presented for the RND in a table by treatment group (except for Screened, which is only summarized for the total column) and overall, and comprises the following variables:

- N (%) of randomized subjects
- N (%) of treated subjects
- N (%) of subjects who completed the study treatment
- N (%) of subjects who prematurely discontinued the study treatment
- N (%) of subjects who completed the study
- N (%) of subjects who prematurely discontinued the study

A listing will be produced with the subjects randomized but not treated.

5.1.1 Screening failures

The number and percentage of subjects who failed screening and the reasons for screening failure will be summarized for the SCR (Overall). All reasons for screening failure will be included in a listing together with the screening failure date. An additional listing will present the list of eligibility criteria not met for the screened set where the screen-failed subjects will be flagged.

5.1.2 Study completion/discontinuation

The reasons for study discontinuation will be tabulated by treatment group and overall on the randomized set.

A listing will be produced for all the subjects of the FAS who discontinued the study. It will display the EOS date, the EOS day (relative to start of study treatment), and the reason for discontinuation from the study.

5.1.3 Study treatment completion/discontinuation

The reasons for treatment discontinuation as collected in the study treatment infusion log in the electronic case report form (eCRF) will be tabulated by treatment group and overall on the FAS.

Subjects who prematurely discontinued the study treatment and subjects randomized but not treated are also included in the listing described in Section 5.1.2. The listing displays the end date of study treatment, the study day on which treatment was discontinued (relative to start of study treatment), and the reason for treatment discontinuation.

5.2 Protocol deviations

The number and percentage of subjects with at least one important protocol deviation will be summarized in a table by treatment group and overall on the FAS. The number and percentage of subjects with at least one deviation in each category and sub-category will also be presented. Similar tables will be produced for:

- subjects with at least one protocol deviation, regardless of importance (i.e., important or non-important)
- subjects with at least one important protocol deviation related to COVID-19
- subjects with at least one protocol deviation related to COVID-19, regardless of importance (i.e., important or non-important)

These tables will be repeated on the RND if the RND and FAS differ by more than 5%.

Important and non-important protocol deviations will be displayed in a listing on the screened set. It will include all deviation descriptions, identifiers and categories. Subjects without any protocol deviations will not be included in this listing.

5.3 Analysis sets

The number and percentage of subjects included in the RND and FAS will be summarized in a table, by planned treatment group (i.e., as randomized) and overall, for the RND.

A similar table will be produced for the SAF as treated.

The inclusion/exclusion of subjects for each analysis set will be listed for the SCR. A listing displaying both planned and actual treatment groups will be produced for subjects having received in error a treatment different from the one they were randomized to.

5.4 Subject characteristics

5.4.1 Demographics

Demographic characteristics will be summarized by treatment group and overall using descriptive statistics for continuous and categorical data on the FAS. It will include the following characteristics:

- Age (years) at hospital admission (continuous; categorized according to EudraCT as: adults [18–64], and elderly [65–84 and ≥ 85])
- Sex (categorized as: Male, Female)
- Race (categorized as: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Not permitted as per legislation/regulation)
- Ethnicity (categorized as: Hispanic or Latino, Not Hispanic or Latino, Unknown, Not permitted as per legislation/regulation)
- Body weight (kg) at hospital admission
- Height (cm)
- Body mass index (kg/m^2), derived as weight (kg) / (height [cm] / 100)^2
- Geographical location, derived from the country of enrollment (categorized as: USA vs non-USA, Europe vs non-Europe)

All these characteristics will be displayed in a listing.

The variables 'Woman of childbearing potential' and 'Reason for not being of childbearing potential' will not be summarized but will be listed.

This table will be repeated on the RND if the RND and FAS differ by more than 5%, and on the SAF if the FAS and the SAF differ by more than 5%.

This table will also be produced for the good neurological recovery subgroup (subjects who had mGCS ≥ 14 and aNIHSS = 0 prior to study drug start) and its complement.

5.4.2 Baseline disease characteristics

5.4.2.1 Stratification factors

The following variables will be summarized by treatment group on the FAS using descriptive statistics for categorical variables:

- Age at hospital admission categorized as: ≤ 60, > 60
- WFNS grade as assessed in the IRT system (categorized as: I–II, III–V)
- Patient population: high-risk vs early treatment

This table will be repeated on the RND if the RND and FAS differ by more than 5%, and on the SAF if the FAS and the SAF differ by more than 5%.

This table will also be produced for the good neurological recovery subgroup (subjects who had mGCS ≥ 14 and aNIHSS = 0 prior to study drug start) and its complement.

5.4.2.2 WFNS, total Glasgow Coma Scale score and motor deficit at hospital admission

WFNS grade, total Glasgow Coma Scale (GCS) score and presence of motor deficit at hospital admission will be summarized by treatment group and overall using descriptive

statistics for continuous and categorical data on the FAS. This table will include the following characteristics:

- WFNS grade as assessed in the IRT system (categorized as: I, II, III, IV, V)
- GCS score (ranges from 3 [deep coma] to 15 [fully awake person], continuous and categorized as: 3–6, 7–12, 13–14, 15])
- Motor deficit (categorized as: Present, Absent)

This table will also be repeated on the RND if the RND and FAS differ by more than 5%, and on the SAF if the FAS and the SAF differ by more than 5%.

- As 'WFNS grade at hospital admission' is collected both in the eCRF and in the IRT system. If there is a confirmed discrepancy at the time of database lock between the eCRF and the IRT system the following table will be produced: WFNS grade as assessed by investigator (categorized as: I, II, III, IV, V)
- WFNS grade as assessed by investigator (categorized as: I–II, III–V)

It will also be repeated on the RND if the RND and FAS differ by more than 5%, and on the SAF if the FAS and the SAF differ by more than 5%.

These characteristics (WFNS grade, total GCS score, and presence of motor deficit) evaluated at hospital admission, post aneurysm-securing procedure, and prior to randomization will be displayed in a listing for the FAS.

The discrepancies between WFNS collected in eCRF and in the IRT system will be flagged in the listing and the value collected in the eCRF system will also be displayed.

5.4.2.3 Neurological scales after admission and prior to Study drug initiation

The last available modified GCS (mGCS) and abbreviated National Institutes of Health Stroke Scale (aNIHSS) collected prior to study drug initiation will be summarized by treatment group and overall using descriptive statistics for continuous variable on the FAS.

This table will be repeated on the RND if the RND and FAS differ by more than 5%, and on the SAF if the FAS and the SAF differ by more than 5%.

5.4.2.4 aSAH-related characteristics

Current aSAH-related characteristics will be summarized by treatment group and overall, using descriptive statistics for continuous and categorical data on the FAS. It will include the following characteristics:

- Aneurysm-securing procedure(s) performed prior to study drug initiation (categorized as: surgical clipping, endovascular coiling, other). If the two procedures have been sequentially used, only the latest one will be used

- Time (hours, continuous) elapsed between date/time of the aneurysm rupture and stop date/time of the aneurysm-securing procedure(s) when they are both available (i.e., no imputation for missing or partial dates and times)
- Location of the ruptured aneurysm (Supraclinoid internal carotid artery segments, Middle cerebral artery segments, Anterior cerebral artery segments, Anterior communicating artery, Posterior communicating artery, Distal vertebral artery segments, Basilar artery, Posterior cerebral artery segments, Other)
- Largest diameter of the ruptured aneurysm (mm) (continuous and categorized as: ≤ 5, > 5)
- Total number of aneurysm(s) repaired (ruptured or unruptured, categorical).
- Time from aSAH to end of the securing procedure (until the end of the last procedure used)
- Number of previous aSAH episodes (categorical)
- Total number of unruptured aneurysm(s) repaired (categorical)
- Occurrence of complications of the aneurysm-securing procedure (categorical: yes, no) and by type (Intracranial hemorrhage, Intraoperative cerebral artery thrombosis, Cardiac arrest, Seizure, Intracranial hypertension, Brain edema or swelling, Cerebral infarction/ischemia, Cerebral vasospasm, Artery dissection, Severe hemodynamic event, Other coiling or other surgical complications). The categories are not mutually exclusive

This table will be repeated on the RND if the RND and FAS differ by more than 5%, and on the SAF if the FAS and the SAF differ by more than 5%.

This table will also be produced for the good neurological recovery subgroup (i.e., subjects who had mGCS ≥ 14 and aNIHSS = 0 prior to study drug start) and its complement.

Subject-level current aSAH history and the peri-operative complications will be provided in a listing. Another listing will be produced displaying the aneurysm-securing procedure(s) performed prior to study drug initiation for all subjects.

5.4.3 Other baseline characteristics

5.4.3.1 Computed tomography scan results

The following common findings at hospital admission as adjudicated by the Independent Radiology Committee (IRC) Review will be summarized by treatment group and overall on the FAS:

- Hydrocephalus
- Intraparenchymal hemorrhage
- Intraventricular hemorrhage
- Extracerebral hematoma
- Ventricular drainage

- Intracranial pressure monitoring device
- Midline shift

The number and percentage of subjects with at least one finding will also be presented.

The clot thickness will be summarized overall and separately for the good neurological recovery subgroup (i.e., subjects who had mGCS ≥ 14 and aNIHSS = 0 prior to study drug start) and its complement, according to the following categories:

- Diffuse thick, Diffuse thin, Local thick, Local thin, None, Unable to assess.
- Diffuse thick, Other, Unable to assess.

All these tables will also be repeated on the RND if the RND and FAS differ by more than 5%, and on the SAF if the FAS and the SAF differ by more than 5%.

5.4.4 **Medical history** and **concomitant diseases and/or diagnoses**

Reported terms are mapped to Preferred Terms (PTs) using MedDRA v25.

Medical history covers all diseases or diagnoses ended before or on the day of ICF signature (i.e., ongoing question is answered "No" in the eCRF).

Concomitant diseases and/or diagnoses are all diseases or diagnoses started before the day of ICF signature and ongoing at time of ICF signature (i.e., ongoing question is answered "Yes" in the eCRF).

Concomitant diseases and/or diagnoses not related to a protocol mandated procedure are all diseases or diagnoses not related to a study protocol mandated procedure started between ICF signature (included) and study drug initiation.

Medical history and concomitant diseases and/or diagnoses will be summarized separately on the FAS, by treatment group and overall. The number and percentage of subjects with at least one item of medical history are presented overall and by individual PT. Medical history and concomitant diseases and/or diagnoses will be sorted by descending frequencies of preferred name based on all treatment groups combined. This table will also be repeated on the RND if the RND and FAS differ by more than 5%.

A listing will be produced for all subjects with medical history, concomitant diseases and/or diagnoses and concomitant diseases and/or diagnoses not related to study protocol mandated procedure. The concomitant diseases and/or diagnoses not related to study protocol mandated procedure and started between ICF signature and study drug initiation will be flagged.

5.4.5 Previous and concomitant therapies

5.4.5.1 Previous/concomitant medications

Therapies collected will be coded using the WHO Drug Global reference dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system. The WHO Drug Global version used for reporting (B format 1 March 2022) will be specified in the footnote of the applicable output.

The medications will be summarized on the FAS according to the categories displayed in Table 3.

Table 3 Definition of categories for reporting previous/concomitant medications

Category	Definition
Previous medications	Start and end date before the signature of the ICF
Study concomitant medications	Ongoing or started after ICF
Study treatment concomitant medications	Ongoing at time of Study treatment initiation or Start date equal to or after study drug initiation but before or the day of study drug discontinuation
Study concomitant medications started during the 24 h follow-up period following study drug discontinuation	Start date after study drug discontinuation and up to 24 h study drug discontinuation

ICF = informed consent form.

Number (%) of subjects having taken at least one previous or concomitant medication will be presented overall and by treatment group, by ATC class (level 4 or next highest available level), and preferred name within each ATC class. A table will be produced for each category described in Table 3. Previous and concomitant medications will be sorted by ATC class and preferred name within each ATC class by descending frequency based on all treatment groups combined. These tables will also be repeated on the RND if the RND and FAS differ by more than 5%.

If the start date/time is missing, the medication will be considered as concomitant with the study and with the study treatment unless the end date is before the signature of the ICF or before study drug initiation, respectively.

If both start and end date are missing, the medication will be considered as concomitant with the study and with the study treatment.

If the start and/or end date are partially missing, the medication will be considered as concomitant with the study treatment and/or with the study unless it contradicts with the partial information available. For general rules regarding management of partial dates see Section 10.1.

A listing will be produced for all subjects with previous/concomitant medications (all categories specified in Table 3). This listing will include a flag identifying the medication started after ICF signature and before study drug initiation.

5.4.5.2 Non-drug treatments/interventions

Non-drug therapies, except rescue therapies, are defined as follows:

- Intracranial pressure monitoring
- Ventricular drainage
- Shunt (ventriculoperitoneal or ventriculoatrial)
- Subdural/epidural hematoma evacuation
- Lumbar drainage
- Mechanical ventilation
- Tracheostomy
- Intra-Aortic Balloon Counter-Pulsation

The number and percentage of subjects having started at least one non-drug treatment/intervention will be presented (i) overall and by therapies and (ii) overall and by treatment group on the FAS. It will be displayed overall and by period of emergence (prior to randomization; from randomization [included] up to hospital discharge [included]; from hospital discharge up to Week 12 [included]; after Week 12). Therapies will be sorted by descending frequency based on all treatment groups combined.

For general rules regarding management of partial dates see Section 10.1.

A listing will be produced for all subjects who received a non-drug treatment/intervention.

5.4.5.3 Rescue therapies

Rescue therapies will be summarized on the FAS according to the categories displayed in Table 4.

Table 4 Definition of categories for rescue therapies

Category	Definition
Protocol-Specific Rescue Therapy	• Non-drug treatment/intervention: balloon angioplasty reported as 'cerebral angioplasty'. • Concomitant medications reported as: (i) Intravenous vasodilators which were preceded by intra-arterial vasodilators or cerebral angioplasty, or (ii) intra-arterial/intrathecal/intra-cisternal/intraventricular administration of vasodilators or ozagrel, i.e., CM ticked as rescue medication in the eCRF and with one of the following ATC codes: C08CA, C08DA, G04BE, C01DA, C01CE, B01AC, R03DX, A03AD and those started with C04.
Local rescue therapy	• Concomitant medications reported as 'Administered as a rescue medication for vasospasm', excluding Protocol-Specific Rescue Therapy defined above. • All therapies reported as 'Other' on the 'Non-drug treatment/intervention' form.

ATC = Anatomical Therapeutic Chemical.

The incidence of protocol-specific rescue therapy and local rescue therapy within each treatment group will be displayed overall and by period of emergence together with the exact 95% confidence interval (CI) (Clopper-Pearson formula). The corresponding between-treatment group difference will be tested using a Cochran-Mantel-Haenszel (CMH) stratified by factors used in the randomization, i.e., WFNS grade (I–II vs III–V) and age (≤ 60 and > 60 years) at admission. Both will be tested at the two-sided significance level of alpha = 0.05. Treatment effect will be quantified by means of the relative risk reduction (RRR) for clazosentan together with its 95% CI.

The use of rescue therapy overview will be produced by treatment group and overall on the FAS and will display:

- Number (%) of subjects having received at least one protocol-specific rescue therapy
- Number (%) of subjects having received at least one local rescue therapy
- Number (%) of subjects having received at least one protocol-specific or local rescue therapy
- Number (%) of subjects having received at least one protocol-specific, non-drug treatment / intervention (balloon angioplasty reported as 'cerebral angioplasty')
- Total number of days with protocol-specific rescue therapy, excluding overlap, i.e., if several rescue therapies are given on the same day, then the duration under rescue therapy is one day

- Total number of days with protocol-specific rescue therapy or local rescue therapy, excluding overlap, i.e., if several rescue therapies are given on the same day, then the duration under rescue therapy is one day

The following tables will be produced by treatment group on the FAS, by period of emergence (from randomization up to hospital discharge (included), and from hospital discharge up to Week 12 (included):

- The number and percentage of subjects having received at least one protocol-specific non-drug treatment / intervention rescue therapy overall, and by ATC code
- The number and percentage of subjects having received at least one protocol-specific medication rescue therapy overall, and by ATC code
- The number and percentage of subjects having received at least one local non-drug treatment / intervention rescue therapy overall, and by ATC code
- The number and percentage of subjects having received at least one local medication rescue therapy overall, and by ATC code

Hospital discharge date (time) is defined as the latest end/discharge date (time) reported with subject location equal to 'Critical care unit or equivalent', 'Specialized care ward' or 'General care ward' among the location reported for the initial hospitalization.

For general rules regarding management of partial dates see Section 10.1.

Rescue medications will be sorted by descending frequency of the number of subjects in the clazosentan group.

Tables will also be repeated on the RND if the RND and FAS differ by more than 5%. Listings with all rescue medication defined in Table 4 will be produced on the FAS, including the category (protocol-specific vs local), the period of emergence and the number of days relative to study drug initiation.

5.5 Study treatment exposure and compliance

Study treatment duration and compliance are defined for the treatment period.

5.5.1 Exposure

Study treatment duration (in days) is defined as the number of days between the study treatment start date/time and the study treatment end date/time, regardless of treatment interruptions.

The descriptive statistics on the study treatment duration will be displayed overall and by treatment group for the SAF, Duration in subject-years will also be summarized. The definition of a year is 365.25 days.

Study treatment duration will also be summarized using the following categories ≤ 3, > 3–≤ 5, > 5–≤ 10, > 10–≤ 14 and > 14 days.

A listing will be produced displaying the study treatment duration and include the reason for permanent study treatment discontinuation.

5.5.2 Compliance with study treatment

Compliance with study treatment will be assessed using the proportion of subjects having received the study treatment for the expected duration as per the protocol: for a maximum of 14 days, for at least 10 days in the high-risk stratum, and for at least 6 days in the early treatment stratum. For each subject the observed treatment duration (difference between datetime of study drug start and stop excluding periods of temporary study drug interruptions) will be categorized as:

- 'Lower than expected' if the observed treatment duration is < 10 days or < 6 days for subjects in the in the high-risk or early treatment stratum respectively.
- 'As expected' if the observed treatment duration is ≥ 10 and ≤ 14 days or ≥ 6 and ≤ 14 days for subjects in the in the high-risk or early treatment stratum respectively
- 'Higher than expected' if the observed treatment duration is > 14.

These categories will be summarized overall and by treatment group using descriptive statistics for categorical variable on the FAS separately for the high-risk and early treatment stratum.

Number of days treated will also be summarized overall and by treatment group using a frequency table on the FAS for the high-risk and early treatment stratum separately.

6 EFFICACY VARIABLES AND ANALYSES

A listing will be produced on the FAS with the individual data used in the analyses of the primary endpoint (including sensitivity analyses), the main secondary endpoint (including the originally planned main secondary endpoint [see Section 11.1 for details]), and the other secondary endpoints (i.e., poor mRS and poor GOSE).

Tables displaying SAS procedure outputs will be produced for the main analysis of the four endpoints included in the hierarchical testing strategy.

6.1 Overview

If not otherwise stated, and according to the intent-to-treat principle, all the analyses presented in this section will be performed 'as randomized' and 'as stratified', that is, according to the treatment group and stratum allocated in the IVRS system.

If not otherwise stated, all analyses stratified/adjusted on the randomization stratification factors will be stratified/adjusted on [see Section 11.2 for details]:

- Hospital admission WFNS grade (as collected in IVRS) dichotomized as I–II vs III–V
- Age at hospital admission ≤ 60 vs > 60 years

6.1.1 Overall testing strategy

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

The first null hypothesis H_{10}, 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 groups:

$$H_{10}: p_{1,plac} = p_{1,clazo} \text{ vs } H_{1a}: p_{1,plac} \neq p_{1,clazo}$$

Here $p_{1,plac}$ and $p_{1,clazo}$ denote the incidence of clinical deterioration due to DCI in the placebo and clazosentan groups, respectively. This hypothesis will be tested at a two-sided significance level of 0.05.

Superiority will be concluded if the lower limit of the two-sided 95% CI for the RRR of clazosentan compared to placebo is greater than 0.

The second null hypothesis H_{20}, which will be tested only if H10 is rejected, is that there is 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 H2a is that there is a difference between these groups:

$$H_{20}: p_{2,plac} = p_{2,clazo} \text{ vs } H_{2a}: p_{2,plac} \neq p_{2,clazo}$$

Here $p_{2,plac}$ and $p_{2,clazo}$ 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 groups, respectively. This hypothesis will be tested at a two-sided significance level of 0.05.

Superiority will be concluded if the lower limit of the two-sided 95% CI for the RRR of clazosentan compared to placebo is greater than 0.

The third null hypothesis H_{30}, which will be tested only if H20 is rejected, is that there is no difference between clazosentan and placebo in the proportion of subjects with a poor mRS score at Week 12 post-aSAH. The alternative hypothesis H3a is that there is a difference between these groups:

$$H_{30}: p_{3,plac} = p_{3,clazo} \text{ vs } H_{3a}: p_{3,plac} \neq p_{3,clazo}$$

Here $p_{3,plac}$ and $p_{3,clazo}$ denote the proportion of subjects with a poor mRS at Week 12 post-aSAH in the placebo and clazosentan groups, respectively. This hypothesis will be tested at a two-sided significance level of 0.05.

Superiority will be concluded if the lower limit of the two-sided 95% CI for the RRR of clazosentan compared to placebo is greater than 0.

The fourth null hypothesis H_{40}, which will be tested only if H_{30} is rejected, is that there is no difference between clazosentan and placebo in the proportion of subjects with a poor Glasgow Outcome Scale – Extended (GOSE) score at Week 12 post-aSAH. The alternative hypothesis H_{4a} is that there is a difference between these groups:

$$H_{40}: p_{4,plac} = p_{4,clazo} \text{ vs } H_{4a}: p_{4,plac} \neq p_{4,clazo}$$

Here $p_{4,plac}$ and $p_{4,clazo}$ denote the proportion of subjects with a poor GOSE at Week 12 post-aSAH in the placebo and clazosentan groups, respectively. This hypothesis will be tested at a two-sided significance level of 0.05.

Superiority will be concluded if the lower limit of the two-sided 95% CI for the RRR of clazosentan compared to placebo is greater than 0.

The study will be considered successful if the first null hypothesis (H_{10}) is rejected.

6.1.2 Estimands

The estimands [ICH 2019] associated with endpoints described in Section 6.1.1 and their four attributes are given in Table 5. Estimands are defined by four attributes: Target population, Endpoint, Strategy for addressing intercurrent events (IEs), and Population-level summary.

The IEs considered in this study are:

Intercurrent Event	**Affects primary endpoint**	**Affects main secondary endpoint**	**Affects other secondary endpoints**
Death	Yes	Yes	Yes
Unevaluable for neurological status and received rescue therapy for relevant vasospasm	Yes	Yes	Yes
Unevaluable for neurological status for vasospasms-related-reason	Yes	No	No
Early discharge followed by rehospitalization due to DCI	Yes	No	No
Early discharge without follow-up at Day 14	Yes	No	No
Withdrawal of consent	Yes	Yes	Yes
Rescue therapy for non-relevant vasospasm	Yes	Yes	Yes

Permanent/temporary treatment discontinuation	Yes	Yes	Yes

DCI = delayed cerebral ischemia.

IEs considered for the primary endpoint (clinical deterioration due to DCI) can be categorized as:

- IE suggestive of a clinical deterioration: death, unevaluable for neurological status and received rescue therapy for relevant vasospasm, unevaluable for neurological status for vasospasms-related reason, early discharge followed by rehospitalization due to DCI
- IE precluding assessment of the endpoint: withdrawal of consent and early discharge without follow-up at day 14
- IE that may affect the occurrence of clinical deterioration: use of rescue therapy for non-relevant vasospasm
- IE that can impact the estimation of treatment effect: permanent/temporary treatment discontinuation

IEs considered for the main secondary endpoint (clinically relevant cerebral infarction) are:

- IE suggestive of a cerebral infarction: death
- IE precluding assessment of the endpoint: withdrawal of consent
- IE that may affect the occurrence of clinical deterioration and thus ultimately cerebral infarction: use of rescue therapy (independently of whether it was provided for a relevant or non-relevant vasospasm)
- IE that can impact the estimation of treatment effect: permanent/temporary treatment discontinuation

IEs considered for the other secondary endpoints are the same as those for the main secondary endpoint.

The strategies used in this study to address IEs are:

- Composite strategy: The IE is incorporated into the outcome variable, e.g., any subject who died is assumed to meet the endpoint
- Hypothetical strategy: When the IE occurred, the observed (or missing) values are substituted by the ones of a hypothetical scenario where the IE would have not occurred, e.g., final outcome for a subject that withdrew consent is predicted using the data collected up to the time of consent withdrawal
- Treatment policy: The data collected are analyzed irrespective of the occurrence of the IE, e.g., the final outcome of a subject is analyzed irrespective of whether the subject discontinued study treatment

Within a given estimand different strategies are employed depending on the type of IEs considered. The efficacy estimands are detailed in Table 5. The estimands' differences vs the primary or secondary estimand (as appropriate) are indicated in bold.

Table 5 Estimands for efficacy endpoints

Estimand	Target population	Endpoint	Strategy for addressing intercurrent events	Population-level summary
Primary Efficacy Endpoint				
Main Estimand	Adult subjects with aSAH as defined by the inclusion/exclusion criteria	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.	Composite strategy: Death, Unevaluable for neurological status and received Rescue therapy[c] for relevant vasospasm, Unevaluable for neurological status for vasospasm-related reason, early discharge followed by rehospitalization due to DCI Hypothetical[a] Withdrawal of consent, Early discharge without follow-up at Day 14 Treatment policy: Permanent/temporary treatment discontinuation, rescue therapy[d] for non-relevant vasospasm	Proportion of subjects meeting the endpoint as per CEC by planned treatment group. Treatment effect expressed as Relative Risk Reduction and common Odds Ratio (clazosentan vs placebo) from CMH analysis
Supplementary Estimand 1	Adult subjects with aSAH as defined by the inclusion/exclusion criteria	Occurrence of clinical deterioration due to DCI, from study drug initiation up to 14 days post-study drug initiation.	Composite strategy: Death, Unevaluable for neurological status and received Rescue therapy[c] for relevant vasospasm, Unevaluable for neurological status for vasospasm-related reason, early discharge followed by rehospitalization due to DCI Hypothetical[a]: Withdrawal of consent, Early discharge without follow-up at Day 14 Treatment policy: Permanent/temporary treatment discontinuation, rescue therapy[d] for non-relevant vasospasm	proportion of subjects meeting the endpoint as per CEC by planned treatment group. Treatment effect expressed **as adjusted Odds Ratio (clazosentan vs placebo) from logistic regression.**

Estimand	Target population	Endpoint	Strategy for addressing intercurrent events	Population-level summary
Supplementary Estimand 2	Adult subjects with aSAH as defined by the inclusion/exclusion criteria	Occurrence of clinical deterioration due to DCI, from study drug initiation up to 14 days post-study drug initiation.	Composite strategy: Death, Unevaluable for neurological status and received Rescue therapy[c] for relevant vasospasm, Unevaluable for neurological status for vasospasm-related reason, early discharge followed by rehospitalization due to DCI, **use of rescue therapy[d] for non- relevant vasospasm** Hypothetical[a]: Withdrawal of consent, Early discharge without follow-up at Day 14 Treatment policy: Permanent/temporary treatment discontinuation	Proportion of subjects meeting the endpoint by planned treatment group. Treatment effect expressed as Relative Risk Reduction and common Odds Ratio (clazosentan vs placebo) from CMH analysis
Supplementary Estimand 3	Adult subjects with aSAH as defined by the inclusion/exclusion criteria	**Occurrence of death or clinical deterioration due to DCI based on neuroscales only, from study drug initiation up to 14 days post-study drug initiation**	Composite strategy: Death Hypothetical[a]: Withdrawal of consent, Early discharge without follow-up at day 14 Treatment policy: Permanent/temporary treatment discontinuation, rescue therapy[d] for non-relevant vasospasm, Unevaluable for neurological status and received Rescue therapy[c] for relevant vasospasm, Unevaluable for neurological status for vasospasm-related reason, early discharge followed by rehospitalization due to DCI	Proportion of subjects meeting the endpoint as per CEC by planned treatment group. Treatment effect expressed as Relative Risk Reduction and common Odds Ratio (clazosentan vs placebo) from CMH analysis

Main Secondary Efficacy Endpoint				
Main Estimand	Adult subjects with aSAH as defined by the inclusion/exclusion criteria	Occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation	Composite strategy: Death Hypothetical[e]: Withdrawal of consent Treatment policy: Permanent/temporary treatment discontinuation, rescue therapy	Proportion of subjects meeting the endpoint by planned treatment group. Treatment effect expressed as Relative Risk Reduction and common Odds Ratio (clazosentan vs placebo) from CMH analysis
Supplementary Estimand 1	Adult subjects with aSAH as defined by the inclusion/exclusion criteria	Occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation	Composite strategy: Death Hypothetical[e]: Withdrawal of consent Treatment policy: Permanent/temporary treatment discontinuation, rescue therapy	Proportion of subjects meeting the endpoint by planned treatment group. Treatment effect expressed **as adjusted Odds Ratio (clazosentan vs placebo) from logistic regression**

Supplementary Estimand 2	Adult subjects with aSAH as defined by the inclusion/exclusion criteria	**Occurrence of all-cause cerebral infarction ≥ 5 cm3 at Day 16 post-study drug initiation**	Composite strategy: Death Hypothetical[e]: Withdrawal of consent Treatment policy: Permanent/temporary treatment discontinuation, rescue therapy	Proportion of subjects meeting the endpoint by planned treatment group. Treatment effect expressed as Relative Risk Reduction and common Odds Ratio (clazosentan vs placebo) from CMH analysis
Other Secondary Efficacy Endpoint (mRS)				
Main Estimand	Adult subjects with aSAH as defined by the inclusion/exclusion criteria	Long-term clinical outcome assessed by the mRS at Week 12 post-aSAH dichotomized into poor outcome (score ≥ 3) and good outcome (score < 3)	Composite strategy: Death Hypothetical[b]: Withdrawal of consent Treatment policy: Permanent/temporary treatment discontinuation, rescue therapy	Proportion of subjects with poor outcome by planned treatment group. Treatment effect expressed as Relative Risk Reduction (clazosentan vs placebo)

Other Secondary Efficacy Endpoint (mRS)				
Main Estimand	Adult subjects with aSAH as defined by the inclusion/exclusion criteria	Long-term clinical outcome assessed by the GOSE at Week 12 post-aSAH, dichotomized into poor outcome (score ≤ 4) and good outcome (score > 4)	Composite strategy: Death Hypothetical[b]: Withdrawal of consent Treatment policy: Permanent/temporary treatment discontinuation, rescue therapy	Proportion of subjects with poor outcome by planned treatment group. Treatment effect expressed as Relative Risk Reduction (clazosentan vs placebo)

[a] outcome of the patients after the occurrence of the IE is a medical judgment made by the CEC based on the totality of the data available.
[b] if the IE occurs then the observed values are replaced by the one imputed according to Section 6.4.1.3 and 6.4.2.3 for mRS and GOSE, respectively.
[c] protocol-specific rescue therapy as defined in Section 5.4.5.3
[d] protocol-specific rescue therapy or local rescue therapy as defined in Section 5.4.5.3
[e] for the first component of the endpoint [see Section 6.3.1] the outcome of the subjects after the occurrence of the IE is a medical judgment made by the CEC based on the totality of the data available. For the subjects not meeting the first component, the second component is imputed according to imputation rules for missing data defined in Section 6.3.3.
aSAH = aneurysmal subarachnoid hemorrhage; CEC = Clinical Event Committee; CMH = Cochran-Mantel-Haenszel; DCI = delayed cerebral ischemia; GOSE = Glasgow Outcome Scale Extended; IE = intercurrent event; mRS = modified Rankin Scale.

6.1.3 Overview of primary and secondary efficacy analyses including subgroups

Table 6 Overview of primary and secondary efficacy planned analyses, including subgroups

Endpoint details	Analysis	Model	Analysis set
Primary efficacy endpoint: Occurrence of clinical deterioration due to DCI from study drug initiation up to 14 days post-study drug initiation			
	Main analysis	CMH test stratified by WFNS and age at admission	FAS
	Supportive analysis (alternative model)	Logistic regression adjusted for WFNS and age at admission	FAS
	Supportive analysis (impact of rescue therapy)	CMH test stratified by WFNS and age at admission	FAS
	Supportive analysis (neurological deterioration assessed on neuroscales only)	CMH test stratified by WFNS and age at admission	FAS
	Subgroups	CMH test stratified by WFNS and age.at admission, by subgroup	FAS
	Subgroups	Logistic regression adjusted for WFNS and age at admission (treatment by subgroup interaction)	FAS
Main secondary efficacy endpoint: Occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation.			
	Main analysis	CMH test stratified by WFNS and age at admission	FAS
	Supportive analysis (alternative model)	Logistic regression adjusted for WFNS and age at admission	FAS
	Supportive analysis (initially planned analysis)	CMH test stratified by WFNS and age at admission	FAS
	Subgroups	CMH test stratified by WFNS and age.at admission, by subgroup	FAS
	Subgroups	Logistic regression adjusted for WFNS and age at admission (subgroup as a factor)	FAS
Other secondary endpoint: Long-term clinical outcome assessed by the mRS at Week 12 post-aSAH			
Good vs poor	Main analysis	CMH test stratified by WFNS, age at admission, and good neurological recovery	FAS
Good vs poor	Supportive analysis (alternative model)	Logistic regression adjusted for WFNS, age at admission, and good neurological recovery	FAS
Raw ordinal score	Supportive analysis (alternative model)	Proportional odds model adjusted for WFNS, age at admission, and good neurological recovery	FAS

Endpoint details	Analysis	Model	Analysis set
Good vs poor	Supportive analysis (out-of-window assessments)	CMH with imputation of out of time window assessments	FAS
Good vs poor	Subgroups	CMH test stratified by WFNS and age at admission	FAS
Good vs poor	Subgroups	Logistic regression adjusted on WFNS and age at admission (treatment by subgroup interaction)	FAS
Other secondary endpoint: Long-term clinical outcome assessed by the GOSE at Week 12 post-aSAH			
Good vs poor	Main analysis	CMH test stratified by WFNS, age at admission, and good neurological recovery	FAS
Good vs poor	Supportive analysis (alternative model)	Logistic regression adjusted for WFNS, age at admission, and good neurological recovery	FAS
Raw ordinal score	Supportive analysis (alternative model)	Proportional odds model adjusted for WFNS, age at admission, and good neurological recovery	FAS
Good vs poor	Supportive analysis (out-of-window assessments)	CMH with imputation of out of time window assessments	FAS
Good vs poor	Subgroups	CMH test stratified by WFNS and age at admission	FAS
Good vs poor	Subgroups	Logistic regression adjusted on WFNS and age at admission (treatment by subgroup interaction)	FAS

aNIHSS = abbreviated National Institutes of Health Stroke Scale; aSAH = aneurysmal subarachnoid hemorrhage, CMH = Cochran-Mantel-Haenszel; CT = computed tomography; DCI = delayed cerebral ischemia; FAS = Full analysis set; GOSE = Glasgow Outcome Scale – Extended; mGCS = modified Glasgow Coma Scale; mRS = modified Rankin Scale; WFNS = World Federation of Neurological Societies.

6.2 Primary endpoint

6.2.1 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.

The Clinical Event Committee (CEC) will indicate for each subject the absence/presence of clinical deterioration due to DCI according to the rules specified in the CEC charter.

During the primary review, the CEC member may answer ‘Unknown’ if and only if there is a lack of data overall or if poor imaging quality does not allow the assessment on the presence of clinical deterioration or the causality of clinical deterioration to be made with sufficient certainty.

In that case, the primary CEC reviewers will discuss the case and try to come to an agreement during the consensus meeting. If an agreement cannot be reached during the consensus meeting, an adjudication meeting will take place.

The final assessment cannot be 'Unknown'.

6.2.2 Intercurrent events for the main estimand

IEs include death, unevaluable for neurological status and received rescue therapy for relevant vasospasm, unevaluable for neurological status for vasospasms-related reason, and early discharge followed by rehospitalization due to DCI. As these events may reflect the occurrence of a clinical deterioration due to DCI, they will be addressed using a composite strategy, i.e., they will all lead the CEC to conclude (as per CEC charter) that the subject met the primary efficacy endpoint.

The withdrawal of consent and the early discharge without follow-up at day 14 are two IEs precluding further assessment of the neurological status of the subjects. However, they are not systematically associated with the occurrence of clinical deterioration. For instance, subjects in good clinical condition might be discharged early from the intensive care unit (ICU) to free up space for more severe subjects. These IEs will thus be addressed using a hypothetical strategy. The CEC will make a medical judgment based on the totality of the data available up to the time of the occurrence of the IE to determine what would have been the outcome of the subject if neuroscales had been collected up until Day 14.

Use of rescue therapy for a non-relevant vasospasm is part of standard-of-care / current practices. So far, the real efficacy of these rescue therapies has not been demonstrated. They will thus be addressed using a treatment policy strategy.

Permanent/temporary treatment discontinuation will be addressed using a treatment policy strategy.

6.2.3 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.

There will be no missing data for the stratification variables included in the analysis since these variables are used 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.

6.2.4 Hypothesis, statistical model and assumptions

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 group differs from the placebo group.

6.2.5 Main analysis

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

The observed incidence rates will be displayed together with the exact 95% confidence intervals (CIs) (Clopper-Pearson).

For the main estimand, the null hypothesis will be tested using a CMH test stratified by factors used in the randomization, i.e., WFNS grade (I–II vs III–V) and age (≤ 60 and > 60 years) at admission, at the two-sided significance level of alpha = 0.05.

The treatment effect (clazosentan vs placebo) will be expressed in terms of RRR with corresponding 95% CIs. An RRR greater than 0 will indicate a response to treatment in favor of clazosentan over placebo.

Homogeneity of the treatment effect across strata will be investigated using the Breslow-Day test. Should there be any indication that the odds ratios (ORs) are not homogeneous, emphasis will be given to the within-strata OR rather than the common OR for the interpretation of the treatment effect.

The treatment effect will be described, each with its 95% CL, with:

- The absolute difference in the rates
- The OR
- The RRR

6.2.6 Supportive analyses

6.2.6.1 Logistic regression

As a supplementary estimand, a logistic regression model will be used instead of the CMH test on the FAS.

The primary endpoint is expected to follow a binomial distribution. Accordingly, the treatment effect of clazosentan relative to the placebo will be assessed using a logistic regression adjusted for stratification factors, i.e., hospital admission WFNS grade (I–II vs III–V), and age at hospital admission (≤ 60 and > 60 years).

The generalized linear model used for estimating the treatment effect is:

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

where:

- p refers to the probability of the event (i.e., the probability of meeting the endpoint)
- treatment refers to clazosentan and placebo (reference is placebo)
- WFNS refers to hospital admission WFNS grade dichotomized as I–II vs III–V
- age refers to that at hospital admission dichotomized as ≤ 60 and > 60 years.

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

Treatment effect will be summarized by the OR, the corresponding 95% Wald CI and the p-value derived from the Wald statistic (Type III analysis of effects). Least Squares means for adjusted event rate (probability scale) by treatment group with corresponding 95% CIs will also be computed.

6.2.6.2 Rescue therapy for non-relevant vasospasms

A supplementary estimand will evaluate the robustness of the primary analysis with regards to the rescue therapies (i.e., any rescue therapy as defined in Section 5.4.5.3) that may have been given for non-relevant vasospasms. In the main analysis, this IE is addressed using a treatment policy because the efficacy of these medications has not been demonstrated. To assess the robustness of the primary efficacy analysis with regards to rescue therapy given for non-relevant vasospasms, the primary analysis will be repeated but addresses this IE using a composite strategy, i.e., all subjects having received a rescue therapy between study drug initiation and Day 14 will be considered as meeting the primary endpoint.

6.2.6.3 Deterioration due to DCI (based on neuroscales only) and death

A supplementary estimand will evaluate the robustness of the primary analysis with regards to the substitution rules defined in the CEC charter to accommodate the situation where a subject was not evaluable and, consequently, the neuroscales were not assessed. The primary analysis will be repeated but considers an alternative definition of the primary endpoint that can only be met following: (i) the occurrence of death or (ii) a clinical deterioration due to DCI based on neuroscales only. Hence, all subjects alive at Day 14 and meeting the primary endpoint according to CEC but without evidence of clinical deterioration based on the neuroscale measurements (i.e., patients having a "Yes" for question 1 "Has the primary endpoint been met?" and a "No" for question 2 "Did the patient have at least one episode of clinical deterioration due to DCI?" of the CEC eCRF) will be considered in this analysis as not meeting the primary endpoint.

6.2.7 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 following pre-specified subgroups may be considered for the analyses:

- WFNS grade at hospital admission dichotomized as I–II vs III–V
- Age (years) at hospital admission dichotomized as ≤ 60 vs > 60
- Geographical location (USA vs non-USA ; Europe vs non-Europe)
- Race (White; Black or African American; Asian).
- Sex (Female vs Male)
- Type of aneurysm-securing procedure (coiling vs clipping). If both were used, the last one is used for analysis.
- Good neurological recovery (Y/N): subjects who had mGCS ≥ 14 and aNIHSS = 0 prior to study drug start.
- Full neurological recovery (Y/N): subjects who had mGCS = 15 and aNIHSS = 0 prior to study drug start.

Results of the subgroup analyses will be displayed in a table as well as in a forest plot including:

- An estimate of the treatment effect (OR for clazosentan vs placebo) with its 95% CI for each level of each subgroup. It will be calculated using the CMH estimator of the common OR obtained separately in each subgroup level (i.e., including the subgroup and its complementary) as described for the main analysis. When a subgroup is defined by a stratification variable the corresponding stratification variable will be excluded from the analysis.
- 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 hospital admission WFNS grade (I–II vs III–V), and age at hospital admission (≤ 60 and > 60 years) and including terms for 'subgroup', 'treatment' and 'treatment by subgroup' interaction. Results will be summarized in a table and will include:

- An estimate of the treatment effect (OR for clazosentan vs placebo) with its 95% CI for each level of each subgroup (i.e., including the subgroup and its complementary)
- A p-value for the interaction tests

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

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.

6.2.8 Other analyses

If the FAS and the RND populations differ by more than 5%, then the main analysis will be repeated on the RND.

The initially planned analysis of the primary endpoint (up to protocol version 6 dated 29 April 2021) will be performed as an exploratory analysis. It will consist of repeating the primary analysis defined in Section 6.2.5 but stratified by all the factors used in the randomization, i.e., WFNS grade, age at admission, and patient population (high-risk prevention vs early treatment) at the two-sided significance level of alpha = 0.05.

Number of episodes of clinical deterioration due to DCI from study drug initiation and up to 14 days post-study drug initiation as adjudicated by the CEC will be summarized with descriptive statistics for categorical variables (from 1 up to the highest number of episodes observed) by treatment group on the FAS.

If subjects were treated accidently, at least partially, during the study with a treatment different from the one they were randomized to, the main analysis will be repeated using the actual treatment group instead of the planned treatment group, i.e., the main analysis will be repeated on the SAF.

One listing will be produced displaying both scores (mGCS and aNIHSS), the date and time of the assessment, and the day relative to study drug initiation.

One listing will present the date and time of each cerebral angiogram and cerebral computed tomography (CT) scan performed over the course of the study.

Selected information from data collected on the 'Episode of clinical deterioration' eCRF page, in the IRC Review eCRF and IRC Adjudication eCRF will be displayed in listings. Selected information from data collected in the CEC eCRF will also be displayed in listings.

6.3 Main secondary endpoint

6.3.1 Variable

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

- Component 1: all-cause cerebral infarction ≥ 5 cm^3. This will be evaluated (yes/no) for all subjects by IRC and will be confirmed by the CEC
- Component 2: for all subjects with a "no" at component 1, then the presence of cerebral infarction < 5 cm^3 (as assessed by IRC) will be evaluated in subjects with clinical deterioration due to DCI (as assessed by the CEC)

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 post-procedure. 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).

6.3.2 Intercurrent events for the main estimand

Similar to that stated for the primary endpoint regarding death and DCI, the occurrence of death prior to Day 16 may be related to cerebral infarction. Consequently, the occurrence of death will be addressed using a composite strategy, i.e., all subjects who died will be considered as meeting the main secondary endpoint.

The withdrawal of consent before Day 16 is an IE precluding the carrying out of the Day 16 CT scan. The first component of the endpoint withdrawal of consent will be addressed using a hypothetical strategy where the CEC will make a medical judgment based on the totality of the data available up to the time of consent withdrawal to determine what would have been the outcome of the subject if the Day 16 CT scan would have been available. For all subjects who (i) withdrew consent, (ii) met the primary endpoint, and (iii) do not meet the first component of the main secondary endpoint, then the second component of the main secondary endpoint cannot be derived if the Day 16 CT scan is missing. These subjects will thus be considered as meeting the main secondary endpoint (according to imputation rule for missing data defined in Section 6.3.3).

Use of rescue therapy as defined in this study are part of standard-of-care / current practices. So far, the real efficacy of these therapies/medications has not been demonstrated. Therefore, they will be addressed using a treatment policy strategy.

Permanent/temporary treatment discontinuation will be addressed using a treatment policy strategy.

6.3.3 Handling of missing data

Subjects randomized and treated

The CEC will provide a final assessment (yes/no) on the first component of the main secondary endpoint, indicating for each subject whether it has been met. Therefore, it is assumed that there will not be any missing data for this component. However, patients not meeting the first component of the endpoint may have a missing Day 16 CT scan (no CT scan performed 14 days after study drug start or later) preventing the assessment of the second component of the endpoint. If the second component of the endpoint cannot be derived, then the subjects meeting the primary endpoint will be considered as meeting the

main secondary endpoint, i.e., the worst possible outcome is assumed. As per protocol, if a subject is discharged before Day 16 but not earlier than Day 14, the "Day 16 CT scan" can be done on the day of discharge. It follows that "Day 16 CT scan" will be considered missing for the evaluation of the second component of the endpoint when there is no CT scan performed 14 days after study drug start or later.

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 primary endpoint [see Section 6.2.3] and the main secondary endpoint, i.e., the worst possible outcome is assumed.

6.3.4 Hypothesis, statistical model and assumptions

The null hypothesis (H_0) is that the occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation in subjects treated with clazosentan is not different from placebo. The alternative hypothesis (H_A) is that the event rate in the clazosentan group differs from the placebo group.

6.3.5 Main analysis

The proportion of subjects with occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation will be analyzed in a similar manner as the primary efficacy endpoint [see Section 6.2.5 for details].

The main statistical analysis for the main secondary endpoint will be performed on the FAS according to the intent-to-treat approach.

The null hypothesis will be tested using a CMH test stratified by factors used in the randomization, i.e., WFNS grade and age at admission, at the two-sided significance level of alpha = 0.05.

6.3.6 Supportive analyses

Logistic regression

As a supplementary estimand, a logistic regression model will be used on the FAS instead of the CMH test following the same approach as the one considered for the supportive analysis of the primary endpoint described in Section 6.2.6.1.

6.3.7 Subgroup analyses

Exploratory subgroup analyses may be conducted using the same approach and on the same subgroups as the ones defined for the primary endpoint analysis described in Section 6.2.7.

The study is not designed or powered to detect interactions, but an arbitrary two-sided significance level of alpha = 0.10 will be used to interpret 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.

6.3.8 Other analyses

If the FAS and the RND populations differ by more than 5%, then the main analysis will be repeated on the RND.

The initially planned primary analysis of the main secondary endpoint (up to protocol version 6 dated 29 April 2021) will be performed as an exploratory analysis. It will consist of repeating the primary analysis defined in Section 6.3.5 on the first component only of the endpoint as defined in Section 6.3.1. For this analysis the CMH will be stratified by all the factors used in the randomization, i.e., WFNS grade at hospital admission (I–II vs III–V), age (≤ 60 and > 60 years) at hospital admission, and patient population (high-risk prevention vs early treatment) at the two-sided significance level of alpha = 0.05.

If subjects were treated accidently, at least partially, during the study with a treatment different from the one they were randomized to, the main analysis will be repeated using the actual treatment group instead of the planned treatment group, i.e., the main analysis will be repeated on the SAF.

Listings will be produced on the RND displaying all the data collected in the IRC Review eCRF (e.g., common findings, clot size, vasospasm severity, reviewer's comment, total infarct volume on post-procedure CT scan, total infarct volume on Day 16 CT scan, volume of new and worsened infarcts on Day 16 CT scan).

6.4 Other secondary endpoint

The other secondary endpoint is long-term clinical outcome assessed by the mRS and the GOSE at Week 12 post-aSAH. The structured interview for the GOSE allows for simultaneous derivation of the mRS.

6.4.1 Modified Rankin Scale

6.4.1.1 Variable

The raw mRS scores range from 0 (no symptoms) to 6 (dead) and will be dichotomized for analysis into poor (a score of 3 to 6) vs good (a score of 0 to 2) outcome.

6.4.1.2 Intercurrent events for the main estimand

Deaths are included in the mRS. Therefore, the occurrence of death will be addressed using a composite strategy where all subjects that died prior to Week12 (i.e., died prior to day 84 + 21 days post-aSAH) will have a mRS score of 6 irrespective of whether a prior assessment was available.

The withdrawal of consent before the collection of the mRS assessment (Week 12) will be addressed using a hypothetical scenario. The final outcome for the subject will be derived based on the mGCS data collected up to the time of consent withdrawal as per the imputation rule for missing data defined in Section 6.4.1.3.

Use of rescue therapy as defined in this study are part of standard-of-care / current practices. So far, the real efficacy of these therapies/medications has not been demonstrated. Therefore, they will be addressed using a treatment policy strategy.

Permanent/temporary treatment discontinuation and out-of-window assessments will be addressed using a treatment policy strategy.

6.4.1.3 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 (i.e., did not die prior to day 84 + 21 days post-aSAH), the missing mRS score is replaced by the score 4 (moderately severe disability) with the following exception:

- If the patient had their mGCS score reported at least once per day, from the study drug initiation up to 14 days post-study drug initiation (or up to the time of discharge if subject is discharged before Day 14 but after having completed study treatment as per protocol), and all reported scores, regardless of day and time point, are ≥ 14 and the location where the subject was discharged 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

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).

6.4.1.4 Hypothesis, statistical model and assumptions

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

6.4.1.5 Main analysis

The proportion of subjects for each possible score value will be summarized in a table and in a figure by treatment group on the FAS.

The proportion of subjects with poor (a score of 3 to 6) clinical outcomes (mRS) at Week 12 post-aSAH will be analyzed in a similar manner as the primary efficacy endpoint [see Section 6.2.5 for details] but adding the good neurological recovery (mGCS ≥ 14 and aNIHSS = 0, Yes/No) variable as an adjustment variable.

All available assessments (including out-of-window ones) will be used in the analysis.

6.4.1.6 Supportive/sensitivity analyses

6.4.1.6.1 Out-of-window assessments

The main analysis will be repeated but replacing the assessments outside of the 84 ± 21days post-aSAH time window by imputed ones according to the imputation rule for missing data defined in Section 6.4.1.3.

6.4.1.6.2 Logistic regression

This analysis relies on a logistic regression model on the FAS instead of the CMH test. The same approach as the one considered for the supportive analysis of the primary endpoint described in Section 6.2.6.1 will be used but adding the good neurological recovery (mGCS ≥ 14 and aNIHSS = 0, Yes/No) variable as an adjustment variable.

6.4.1.6.3 Proportional odds regression model

A proportional odds model (POM) adjusted on WFNS grade (I–II vs III–V), age (≤ 60 and > 60 years) at admission and good neurological recovery (mGCS ≥ 14 and aNIHSS = 0, Yes/No) will be used as a supportive analysis to assess treatment effect on raw mRS data (i.e., on ordinal score) on the FAS. Results of the POM will be presented by the OR, the corresponding 95% Wald CL, and the p-value derived from the Wald statistic (type III analysis of effects). The validity of the proportional odds assumption will be assessed by fitting a fully non-proportional odds model. Departure from the proportional odds assumption will be evaluated on the forest plot displaying the departure of all individual slopes (and associated p-values) compared to the reference slope for each effect. If the proportional odds assumption is not satisfied for some variables, then partially proportional odds models could be considered to estimate and test treatment effect.

6.4.1.7 Subgroup analyses

The main analysis will be repeated on the following pre-defined subgroups (and corresponding complementary subgroups) but without adjusting for good neurological recovery:

- Good neurological recovery: subjects who had mGCS ≥ 14 and aNIHSS = 0 prior to study drug start.
- Full neurological recovery: subjects who had mGCS = 15 and aNIHSS = 0 prior to study drug start.

Additional exploratory subgroup analyses may also be conducted with the same approach as the one defined for the primary endpoint in Section 6.2.7.

6.4.1.8 Other analyses

If the FAS and the RAND populations differ by more than 5%, then the main analysis will be repeated on the RND analysis set.

Listings

One listing will be produced displaying both scores (GOSE and mRS), the date and time of the assessment, the number of days elapsed since aSAH, and the respondent's identity (subject and/or proxy and/or legal representative).

Figures

For the GOSE and mRS, the distribution of subjects for each level will be provided in a graphical format.

6.4.2 Glasgow Outcome Scale – Extended

6.4.2.1 Variable

The raw GOSE scores range from 1 (dead) to 8 (upper good recovery) and will be dichotomized for analysis into poor outcome (score ≤ 4) and good outcome (score > 4).

6.4.2.2 Intercurrent events for the main estimand

Death is included in the GOSE. Therefore, occurrence of death will be addressed using a composite strategy where all subjects that died prior to Week 12 (i.e., died prior to day 84 + 21 days post-aSAH) will have a GOSE score of 1 irrespective of whether a prior assessment was available.

The withdrawal of consent before the collection of the GOSE assessment (Week 12) will be addressed using a hypothetical scenario. The final outcome for the subject will be derived based on the mGCS data collected up to the time of consent withdrawal as per the imputation rule for missing data defined in Section 6.4.2.3.

Use of rescue therapy as they are defined in this study are part of standard-of-care / current practices. So far, the real efficacy of these therapies/medications has not been demonstrated. Therefore, they will be addressed using a treatment policy strategy.

Permanent/temporary treatment discontinuation will be addressed using a treatment policy strategy.

6.4.2.3 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 (i.e., did not die prior to day 84 + 21 days post-aSAH), 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 (or up to the time of discharge if subject is discharged before Day 14 but after having completed study treatment as per protocol), and all reported scores regardless of day and time point are ≥ 14, and the location where the subject was discharged 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

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).

6.4.2.4 Hypothesis, statistical model and assumptions

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 group differs from the placebo group.

6.4.2.5 Main analysis

The proportion of subjects for each possible score value will be summarized in a table and in a figure by treatment group on the FAS.

The proportion of subjects with poor (a 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 [see Section 6.2.5 for details] but adding the good neurological recovery (mGCS ≥ 14 and aNIHSS = 0, Yes/No) variable as an adjustment variable.

All available assessments (including those performed out-of-window) will be used in the analysis.

6.4.2.6 Supportive/sensitivity analyses

6.4.2.6.1 Out-of-window assessments

The main analysis will be repeated but replacing the assessments outside of the 84 ± 21days post-aSAH time window by imputed ones according to the imputation rule for missing data defined in Section 6.4.2.3.

6.4.2.6.2 Logistic regression

This analysis relies on a logistic regression model on the FAS instead of the CMH test. The same approach as the one considered for the supportive analysis of the primary endpoint described in Section 6.2.6.1 will be used but adding the good neurological recovery (mGCS ≥ 14 and aNIHSS = 0, Yes/No) variable as an adjustment variable.

6.4.2.6.3 Proportional odds regression model

A POM adjusted on WFNS grade (I–II vs III–V), age (≤ 60 and > 60 years) at admission and good neurological recovery (mGCS ≥ 14 and aNIHSS = 0, Yes/No) will be used as a supportive analysis to assess treatment effect on raw GOSE data (i.e., on ordinal score) on the FAS. Results of the POM will be presented by the OR, the corresponding 95% Wald CL, and the p-value derived from the Wald statistic (type III analysis of effects). The validity of the proportional odds assumption will be assessed by fitting a fully non-

proportional odds model. Departure from the proportional odds assumption will be evaluated on the forest plot displaying the departure of all individual slopes (and associated p-values) compared to the reference slope for each effect. If the proportional odds assumption is not satisfied for some variables, then partially proportional odds models would be considered to estimate and test treatment effect.

6.4.2.7 Subgroup analyses

The main analysis will be repeated on the following pre-defined subgroups (and their corresponding complementary) but without adjusting for good neurological recovery:

- Good neurological recovery: subjects who had mGCS ≥ 14 and aNIHSS = 0 prior to study drug start.
- Full neurological recovery: subjects who had mGCS = 15 and aNIHSS = 0 prior to study drug start.

Additional exploratory subgroup analyses may also be conducted with the same approach as the one defined for the primary endpoint on subgroups including but not limited to the ones defined in Section 6.2.7.

6.4.2.8 Other analyses

If the FAS and the RND populations differ by more than 5%, then the main analysis will be repeated on the RND.

Listings

One listing will be produced displaying both scores (GOSE and mRS), the date and time of the assessment, the number of days elapsed since aSAH, and the respondent's identity (subject and/or proxy and/or legal representative).

Figures

For the GOSE and mRS, the distribution of subjects for each level will be provided in a graphical format: one bar per treatment group and per variable, where each bar shows 100% of the discrete value.

6.5 Subject-reported endpoints

The analysis of the effect of clazosentan on long-term clinical outcome, cognition, and health-related QoL at Week 12 post-aSAH will be described together as described in this section.

To evaluate the effect of clazosentan on cognition, the following endpoints will be used:

- Cognitive status, as assessed by the change from baseline to Day 14 post-study drug initiation on the Montreal Cognitive Assessment (MoCA), for those subjects that have a score at both time points

- Cognitive status, as assessed by the change from baseline to Week 12 post-aSAH on the MoCA, for those subjects that have a score at both time points
- Cognitive status, as assessed by the change from Day 14 post-study drug initiation to Week 12 post-aSAH on the MoCA, for those subjects that have a score at both time points
- Cognitive status as assessed by the MoCA at Day 14 post-study drug initiation and at Week 12 post-aSAH

To evaluate the effect of clazosentan on health-related QoL post-aSAH, the following endpoints will be used:

- Generic QoL as measured by the EQ-5D-5L at Week 12 and Week 24 post-aSAH
- Oxford Participation and Activities Questionnaire (Ox-PAQ) at Week 12 post-aSAH
- Disease-specific QoL as measured by the Stroke-Specific Quality of Life (SS-QoL) at Week 12 post-aSAH

6.5.1 Montreal Cognitive Assessment

6.5.1.1 Variables

The MoCA will be used to detect cognitive impairment. The variables that will be analyzed are:

- The value at each assessment for the domain scores and the total score.
- The change from baseline to each post-treatment visit (i.e., Day 14 post-study drug initiation and Week 12) for the domains scores and the total score.
- The change from Day 14 post-study drug initiation to Week 12 for the domains scores and the total score.

If the assessment for one domain is missing, the total score is not computed. All assessments performed after Day 14 will be analyzed as Week 12 assessments.

6.5.1.2 Analysis

The tables, figures and listings will be produced on the FAS.

Tables

Descriptive statistics for both domain scores and the total score will be computed by treatment group on the FAS for:

- change from baseline to each visit and the corresponding actual values at each visit
- change from Day 14 post-study drug initiation to Week 12 post-aSAH and the corresponding actual values at Day 14 post-study drug initiation and at Week 12 post-aSAH
- actual values at each visit (including subjects having missing values at any visit)

A table with descriptive statistics (number and percentage of subjects) on the reason for not performing the test will also be produced.

Treatment effect in MoCA total score will be assessed using a mixed model for repeated measures for the actual values at each post-baseline visit (i.e., Day 14 post-study drug initiation and Week 12) using an unstructured variance/covariance matrix and the following covariates: WFNS grade (I–II vs III–V) at admission, age (≤ 60 and > 60 years) at admission, visit (as a factor), treatment group, and visit by treatment interaction. Least Squares means and 95% CI will be computed for each treatment group and visit and for the between-group difference at each visit.

In addition, changes from baseline to post-baseline visits will be analyzed using the same mixed model but with an additional covariate for baseline MoCA total score. Treatment effect in MoCA total score will also be assessed using an analysis of variance (ANOVA) fitted on change from Day 14 post-study drug initiation to Week 12 and including the following covariates: WFNS grade (I–II vs III–V) at admission, age (≤ 60 and > 60 years) at admission, Day 14 MoCA total score, and treatment group. This treatment effect estimate could have been derived from the mixed model for repeated measures on the change from baseline to post-baseline visits defined above but because of the missing baseline values this analysis should provide a more precise estimate of the change from Day 14 to Week 12.

Additional analyses may also be conducted using the same approaches on pre-defined subsets such as:

- Good neurological recovery: subjects who had mGCS ≥ 14 and aNIHSS = 0 prior to study drug start.
- Full neurological recovery: subjects who had mGCS = 15 and aNIHSS = 0 prior to study drug start.

Figures

The evolution of the total score over time will be provided in a graphical format from baseline to Week 12 (one boxplot per treatment group and analysis visit).

Listings

A listing will provide date and time of assessment, the reason for not performing the MoCA, the total score at each visit, the absolute change from baseline to each post-baseline visit in total score and the change from Day 14 post-study drug initiation to Week 12 post-aSAH in total score. The values taken into account for the analysis will be flagged. It will also include the day relative to study drug initiation and the number of days elapsed since aSAH.

6.5.2 EQ-5D-5L

6.5.2.1 Variables

The EQ-5D (5L version) questionnaire will be used at Week 12 and Week 24 post-aSAH to assess the subject's QoL. The variables that will be analyzed are:

- To characterize an EQ-5D **health state**: The responses of the 5 dimensions combined ranging from [redacted] (full health) to [redacted] (worst health)
- To characterize the **health utility**: The EQ-5D health state converted into a single summary index value and continuous value ranging from 0 to 1 (value less than 0 represent health states regarded as worse than death) using a crosswalk link function. Following the latest guidance of the NICE published in 2022, the value set provided by Hernández Alava et al. [Hernández-Alava 2017] for the UK will be used to derive the health utility score
- To characterize the **overall self-rated health status**: The value of the visual analog scale (VAS) score, ranging from 0 (worst imaginable health) to 100 (best imaginable health)

All assessments performed before Day 126 (midpoint between Week 12 and Week 24) will be analyzed as Week 12 assessments and all those performed after will be analyzed as Week 24 assessments. If a subject has two assessments allocated to the same week then only the last assessment will be used for analysis.

6.5.2.2 Analysis

The tables, figures and listing will be produced on the FAS.

Tables

The health state and corresponding respondent (e.g., subject, proxy) will be summarized by visit and treatment group, using descriptive statistics for categorical and continuous data. The health utility and VAS will be summarized by visit and treatment group, using descriptive statistics for continuous data.

Change from Week 12 to Week 24 in health utility and VAS will be summarized by treatment group, using descriptive statistics for continuous data.

For the health state, between-group comparison domain by domain will be performed using a POM (unadjusted). It will provide the OR and corresponding 95% CI (normal approximation) for each domain.

For the overall health status (VAS score) and the health utility, between-group comparisons at Week 12 and Week 24 will be performed using ANOVAs with factors for WFNS grade (I–II vs III–V) at admission, age (≤ 60 and > 60 years) at admission, and treatment group. Least Squares means and 95% CLs will be computed for each treatment group and for the difference between clazosentan and placebo groups. Between-group comparison of the

change from Week 12 to Week 24 will be done using the same model but adding the assessment at Week 12 as an adjustment variable.

If the assumptions underlying the ANOVA model (normality of the residuals, homogeneity of the variance) are not fulfilled, the same comparisons between treatment groups will also be performed by means of a non-parametric one-way ANOVA (Wilcoxon-Mann-Whitney test).

Figures

For each domain, the distribution of subjects in each level will be provided in a graphical format.

For the VAS score, the distribution will also be provided in a graphical format: one histogram per treatment group.

For the utility index, the distribution will also be provided in a graphical format: one histogram per treatment group.

All the figures will be provided for both Week 12 and Week 24.

Listings

One listing will be produced displaying the health profile (the value for each domain), health status (VAS score) and index value. It will also include the number of days elapsed since aSAH.

6.5.3 Ox-PAQ

6.5.3.1 Variables

The Ox-PAQ at Week 12 post-aSAH will be used to assess health-related QoL and in particular to assess participation, activities, and level of independence. The variables that will be analyzed are:

- The value for each item, ranging from 0 (never) to 4 (always)
- The raw score **for each domain**, calculated as the sum of the scores for the items in that domain
  - Routine activities (14 items): [redacted]
  - Emotional well-being (5 items): [redacted]
  - Social engagement (4 items): [redacted]
- The re-scaled score **for each domain**, ranging from 0 to 100, calculated according to the following formula:

– 100 × raw score / maximum score

The missing data will be imputed as recommended in the Ox-PAQ manual. If a single item within any domain is unanswered it is considered reasonable to impute the mean value representing all of the respondent's other item responses (the series mean) within that

domain to the missing item. If two or more questions on any domain are unanswered, the overall score for that domain/respondent should not be calculated.

6.5.3.2 Analysis

The tables, figures and listings will be produced on the FAS.

Tables

Descriptive statistics on the raw and re-scaled scores will be presented by domain and treatment group. The table will also include descriptive statistics (number and percentage of subjects) on missing data (imputed, missing).

Between-group comparison (clazosentan vs placebo) will be performed for each domain on the transformed score by means of ANOVAs with factors for WFNS grade (I–II vs III–V) at admission, age (≤ 60 and > 60 years) at admission and treatment group. Least Squares means and 95% CLs will be computed for each treatment group and for the difference between clazosentan and placebo groups.

If the assumptions underlying the ANOVA model (normality of the residuals, homogeneity of the variance) are not fulfilled, the same comparison between treatment groups will also be performed by means of a non-parametric one-way ANOVA (Wilcoxon-Mann-Whitney test).

Figures

For each domain score, the distribution/dispersion of the values will be displayed as boxplots: one figure per score and one boxplot per treatment group.

Listings

A listing will provide the raw score for each of the 3 domains together with the transformed scores. It will also include the number of days elapsed since aSAH.

6.5.4 Stroke-Specific Quality of Life

6.5.4.1 Variables

The SS-QoL [Williams 1999] is evaluated at Week 12 post-aSAH to measure health-related QoL specific to patients with stroke. For the first part of the questionnaire (49 items), the following scores will be computed:

- Domain scores, **computed** [redacted]
- Total score, **computed** [redacted]
- Physical component, **computed** [redacted]
- Psychosocial component, **compute** [redacted]

Missing items are handled in the following way: if more than half of the items in a given domain are missing, that domain is not scored and the resulting overall SS-QoL score is an average of the remaining domain scores. If fewer than half of the items in a given domain are missing, the scored items are averaged and rounded to the nearest integer. This imputed item score is then substituted for the missing item(s).

Overall SS-QoL score is an unweighted average of domain scores and ranges from 1.0 (worst) to 5.0 (best). [redacted]

For the second part of the questionnaire collecting information regarding patient status prior to aSAH, the following scores are used:

- Domain scores, [redacted]
- Total score, [redacted]

No imputation for missing data will be performed.

6.5.4.2 Analysis

The tables, figures and listings will be produced on the FAS.

Tables

For the first part of the questionnaire, descriptive statistics for each computed score will be presented by treatment group on the FAS. The table will also include descriptive statistics (number and percentage of subjects) on missing data (imputed, missing).

Between-group comparison (clazosentan vs placebo) will be performed for each domain and on the total score by means of ANOVAs with factors for WFNS grade (I–II vs III–V) at admission, age (≤ 60 and > 60 years) at admission and treatment group. Least Squares means and 95% CLs will be computed for each treatment group and for the difference between clazosentan and placebo groups.

If the assumptions underlying the ANOVA model (normality of the residuals, homogeneity of the variance) are not fulfilled, the same comparisons between treatment groups will also be performed by means of a non-parametric one-way ANOVA (Wilcoxon-Mann-Whitney test).

The variables collected in the second part of the questionnaire will be summarized using descriptive statistics for categorical variables by treatment groups on the FAS.

Figures

In the first part of the questionnaire, the distribution/dispersion of the values will be provided by means of boxplots for each computed score: one figure per score and one boxplot per treatment group.

In the second part of the questionnaire, a bar plot will be produced by variable and treatment group displaying the proportions of subjects for each category.

Listings

A listing will be produced to display all computed scores. A second listing will provide the answers to the second part of the questionnaire and related reported scores. It will also include the number of days elapsed since aSAH.

6.6 Multivariate long-term outcome

6.6.1 Variables

The long-term clinical outcome of the patients will be evaluated by jointly analyzing the following variables:

- GOSE total score at Week 12
- mRS total score at Week 12
- EQ-5D utility value at Week 12
- EQ-5D utility value at Week 24
- Ox-PAQ raw domain scores at Week 12
- SS-QoL total score at Week 12
- MoCA at Week 12
- Change from baseline to Week 12 in MoCA

6.6.2 Analysis

All Week 12 assessments will be analyzed jointly using a normed Principal Component Analysis (PCA). This analysis will be done in R [R Core Team 2020] using the function "dudi.pca" of the R-package 'ade4" [Chessel 2004]. As the PCA requires complete cases, subjects with at least one missing value will be excluded from the analysis. The treatment effect will be characterized using a between-class analysis [Dolédec 1987] and tested using a permutation test [Romesburg 1985] at the two-sided significance level of alpha = 0.05 on the between-groups inertia (i.e., multi-dimensional between-treatment group variance) percentage. This analysis will be repeated but imputing missing assessment with the observed overall mean of the corresponding variable. The analysis might also be repeated excluding the variables with the highest frequencies of missing values and/or including change from baseline to Week 12 in MoCA and Week 24 assessment of EQ-5D.

The following outputs will be produced:

- Distribution of the eigen values of the PCA
- Contribution of the variables to the principal components of the PCA
- Factorial maps of the PCA
- Factorial maps of the between-class analysis
- Permutation test on the between-group inertia percentage

6.7 Analysis of pharmaco-economic variables

The tables, figures and listings will be produced on the FAS.

- Number and type of episodes of rescue therapy, from randomization up to hospital discharge and from hospital discharge up to Week 12 [see Section 5.4.5.3]
- 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 [see Section 5.4.5.2]
- Length (in days) of initial and total ICU stay, length (in days) of total hospitalization, and duration (in days) in different hospital 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 (in days) of home care support post-initial hospital discharge
- Employment status at Week 24 (6 months) post-aSAH

6.7.1 Rescue therapies

See Section 5.4.5.3 for details.

6.7.2 Specific (pre-specified) medical treatments and therapies

See Section 5.4.5.2 for details.

6.7.3 Subject location/rehabilitation

6.7.3.1 Variables

For each subject, the following variables will be derived:

- Length of initial ICU stay, defined as the time (days) elapsed between date of start/admission and date of end/discharge when location is recorded as ‘Critical care unit or equivalent’ (earliest record)
- Length of total ICU stay, defined as the sum of the lengths (days) of each stay recorded as ‘Critical care unit or equivalent’
- Length of total hospitalization (in days), defined as the sum of the lengths of each stay recorded as ‘Critical care unit or equivalent’ or ‘Specialized care ward’ or ‘General care ward’
- Length of stay in ‘Specialized care ward’ defined as the total time (days) elapsed between date of start/admission and date of end/discharge for each location recorded as ‘Specialized care ward’
- Length of stay in ‘General care ward’ defined as the total time (days) elapsed between date of start/admission and date of end/discharge for each location recorded as ‘General care ward’
- Intensity of rehabilitation care up to Week 12 post-aSAH, defined as the cumulative number of hours in each category (none, light, moderate, intense)

- Post-hospital discharge location, defined as the first location the subject is admitted to other than 'Critical care unit or equivalent' or 'Specialized care ward' or 'General care ward'
- Duration (days) of home care support post-hospital discharge, defined as the sum of the lengths of each stay in 'Inpatient rehabilitation facility' and 'Assisted living facility' or 'Home partially independent'

Other locations recorded as a free text will not be taken into account for the computation of any of these durations.

Duration in hours (for the intensity of rehabilitation care) will be derived by multiplying the duration of the rehabilitation in weeks by the mid class of rehabilitation intensity: 3.5, 10.5, 17.5 hours per week.

To compute duration in the event of a missing end date, when the question 'Ongoing at end of study' was ticked in the eCRF then the missing end date should be imputed with EOS date.

6.7.3.2 Analysis

Descriptive statistics will be provided for each of the aforementioned variables by treatment group.

A first listing will present the inpatient and outpatient locations (e.g., critical care unit or equivalent, specialized care ward, nursing facility) with corresponding date (time) of start/admission and date (time) of end/discharge as well as the various lengths of stay.

A second listing will present the intensity of the rehabilitation course and the corresponding start and end date as well as the corresponding duration.

6.7.4 Employment status

6.7.4.1 Assessments

At Week 24 post-aSAH, 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 via telephone or postal questionnaire and captured in the clinical database.

The employment status is collected as follows:

- Employed full time
- Employed part time
- Student full time
- Student part time
- On work disability
- Homemaker

- Retired
- Not employed
- Unknown

For both time points (pre-aSAH and Week 24 post-aSAH), the subject may select multiple possibilities.

6.7.4.2 Variables

The following variables will be derived:

- The employment status at the given time point (including the reported combinations (e.g., Student part time/ Employed part time)
- The time (days) from aSAH to return to work, the time (days) from aSAH to return to education
- The change from pre- to post-aSAH status (fully back to pre-aSAH, partially back to pre-aSAH, not back to pre-aSAH) defined as the worst observed transition (see transition matrix in Appendix 14.3) between pre-aSAH and post-aSAH status.

6.7.4.3 Analysis

Tables and listings will be produced on the FAS.

A table will provide the number and percentage of subjects in each category (and reported combinations) by treatment group for each time point.

A table will provide the number and percentage of subjects in each category of change from pre- to post-aSAH status (fully back, partially back, not back) by treatment group with 95% Clopper-Pearson CI.

Employment status will also be described on the FAS using descriptive statistics for the following variables:

- Time from aSAH to return to work
- Time from aSAH to return to education
- Proportion of subjects fully back to pre-aSAH status, partially back to pre-aSAH status, not back to pre-aSAH

A listing will provide the status for each time point. It will also display the date of return to work (or to an educational institution, for students, as applicable) and the corresponding number of days elapsed since aSAH.

6.8 Biomarker endpoints analysis

The biomarker endpoints are:

- Presence of abnormal S100b protein concentration defined as the max observed concentration between study drug start and day14 in S100b being greater than or equal to 0.4 µg/L

6.8.1 Variables

The presence of abnormal concentration of S100b between study drug start and Day 14 will be derived.

6.8.2 Analysis

Tables

Descriptive statistics for the level of S100b protein at baseline will be tabulated by treatment group on the FAS. The table will also display the percentages of subjects with S100b protein greater or equal to 0.4 µg/L at any time between study drug start and Day 14 with corresponding 95% Clopper-Pearson CI.

Figures

Values over time will be provided in graphical format (boxplots) by treatment group.

Listings

One listing will be provided for the FAS. It will include all results from the central laboratory. The maximum concentration observed that will be used to derive the endpoint will be flagged. It will also include the day relative to study drug initiation.

7 SAFETY VARIABLES AND ANALYSES

If not otherwise stated:

- All tables and listings will be produced on the SAF
- Subjects will be evaluated according to the actual treatment they received, which may differ from the randomly assigned treatment

In the event of an administration error, i.e., a subject was administered both placebo and active treatment, the subject will be analyzed as active treatment (‘clazosentan’).

For partial date handling see Section 10.1.

7.1 Adverse events

The original terms used by the investigators to describe adverse events (AEs) in the Adverse Events eCRF are assigned a PT and a System Organ Class (SOC) for classification and tabulation using MedDRA v25.

Subjects who experienced the same AE more than once (as qualified by the same PT) are counted only once.

7.1.1 Variables

All adverse events

All AEs are those occurring from signature of the ICF until EOS visit, which are believed to be related to a protocol-mandated procedure as well as treatment-emergent adverse events (TEAEs).

Treatment-emergent adverse events

An AE is treatment-emergent if the onset date/time ≥ start date/time of study treatment up to 24 hours after study treatment discontinuation.

An incomplete (time, day or month missing) or missing AE date will be imputed as described in the Table 7. The 'lower limit' and 'upper limit' refer to the earliest and latest possible date/times, respectively. As an example: If AE onset date is MAR2017 (time and day missing), the lower limit is 01MAR2017 T00:00:01 and the upper limit is 31MAR2017 T23:59:59; if AE onset date is 2017 (time, day and month missing), the lower limit is 01JAN2017T00:00:01 and the upper limit is 31DEC2017T23:59:59.

Table 7 Imputation rules for an incomplete or missing AE datetime

Field	Incomplete datetime	Missing datetime
AE resolution datetime	The upper limit.	No imputation: the AE is considered as ongoing.
AE onset datetime	The rules below apply in the order presented: 1. If the (imputed) AE end datetime is on or after the start of study treatment, and if the study treatment start falls within the upper and lower limits (inclusive), the study treatment start datetime is used. 2. If the AE resolution datetime is missing, and: if the study treatment start falls within the upper and lower limits (inclusive), the study treatment start datetime is used. 3. In all the other cases, the lower limit is used.	Whichever is the earlier of the AE resolution datetime or study treatment start datetime.

AE = adverse event.

If the emergence of an AE cannot be determined based on the above imputation rules, the AE will be considered as treatment-emergent.

The purpose of imputing AE dates is only to determine the treatment emergence of an AE for the summary tables and listings. However, only the actual dates as reported in the eCRF will be listed. No imputed date is considered in the medical evaluation of an AE.

Treatment-emergent adverse events related to study treatment

An AE is considered related to the study treatment if the investigator answered "related" to the question "Relationship to study treatment". If the relationship is missing, the AE is considered 'related'.

Treatment-emergent adverse events by intensity

The intensity of an AE is determined by the investigator as 'mild', 'moderate' or 'severe'.

Subjects who experienced the same AE more than once (as qualified by the same PT), but with different intensities, are counted only once, using the worst reported intensity. If the intensity is missing, the event is considered severe.

Serious adverse events

An AE is considered serious if the investigator answered, "Yes" on the question "Serious?".

Serious treatment-emergent adverse events

Serious AEs (SAEs) are considered treatment-emergent if their onset date/time ≥ start date/time of study treatment up to 24 hours after study treatment discontinuation.

Serious adverse events during the long-term follow-up

SAEs with an onset date/time ≥ end date/time of study drug + 24 hours and up to EOS.

Adverse events leading to death

An AE is considered fatal if the investigator ticked "Fatal" on the question "Outcome".

Adverse events leading to premature discontinuation of study treatment

An AE is considered leading to premature discontinuation of study treatment if the investigator ticked "Permanently discontinued" on the question "Action taken with study treatment".

Adverse events of special interest

An AE is considered an AE of special interest (AESI) if it is treatment-emergent and belongs to any of the categories listed below (the corresponding MedDRA PTs/SMQs using MedDRA v25 are provided in Appendix 14.4):

- Brain oedema
- Cerebral haemorrhage
- Anaemia
- Lung complications
- Hypotension
- Oedema and fluid retention
- Tachyarrhythmia

- Hepatic disorders

Rescue therapy-specific adverse events

An AE is considered related to the rescue therapy if the investigator answered "related" to the question "Relationship to rescue therapy" in the AE page.

7.1.2 Analysis

An overview of the AEs by treatment group will be produced on the SAF. It will include the N (%) of subjects having at least one treatment-emergent:

- AE
- AE related to study treatment
- AE of severe intensity
- SAE
- SAE related to study treatment
- AE of special interest
- AE with a fatal outcome
- AE with a fatal outcome and related to study treatment
- AE leading to temporary interruption of study treatment
- AE leading to permanent discontinuation of study treatment

It will also include the N (%) of subjects having at least one:

- SAE during the long-term follow-up
- SAE during the long-term follow-up with fatal outcome

The tables specified in Table 8 will summarize the number (%) of subjects by treatment group based on the SAF.

Table 8 Summary of adverse event analyses

Category	Approach
All AEs	
All TEAEs	- N (%) of subjects having at least one event by SOC and PT (overall and by patient population high-risk prevention vs early treatment) - N (%) of subjects having at least one event by PT - N (%) of subjects having at least one event by SOC and PT and maximum intensity
TEAEs of severe intensity	- N (%) of subjects having at least one event by SOC and PT
TEAEs related to study treatment	- N (%) of subjects having at least one event by and PT
TEAEs leading to temporary interruption of study treatment	- N (%) of subjects having at least one event by SOC and PT - N (%) of subjects having at least one event by PT

Category	Approach
TEAEs leading to permanent discontinuation to study treatment	- N (%) of subjects having at least one event by SOC and PT - N (%) of subjects having at least one event by PT
TEAEs with fatal outcome	- N (%) of subjects having at least one event by SOC and PT - N (%) of subjects having at least one event by PT
TEAEs with fatal outcome and related to study treatment	- N (%) of subjects having at least one event by SOC and PT - N (%) of subjects having at least one event by PT
Serious TEAEs	- N (%) of subjects having at least one event by SOC and PT (overall and by patient population high-risk prevention vs early treatment) - N (%) of subjects having at least one event by PT
SAEs during long-term follow-up	- N (%) of subjects having at least one event by SOC and PT - N (%) of subjects having at least one event by PT
Serious TEAEs related to study treatment	- N (%) of subjects having at least one event by SOC and PT - N (%) of subjects having at least one event by PT
SAEs with fatal outcome during long-term follow-up	- N (%) of subjects having at least one event by SOC and PT - N (%) of subjects having at least one event by PT
TEAEs of special interest	- N (%) of subjects having at least one event by category of interest and PT
Rescue therapy-specific AEs	- N (%) of subjects having at least one event by PT

AE = adverse event; PT = preferred term; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event.

A table will display the most frequent TEAE (at least 5% in placebo or active group) by treatment group and by PT. The PTs will be sorted by decreasing frequency in the active group.

A table will display the primary cause of death for all deaths up to EOS by treatment group and by PT. The PTs will be sorted by decreasing frequency in the active group.

For disclosure to public database purposes the following table will also be produced:

- Treatment-emergent SAEs (including occurrences)
- Treatment-emergent SAEs related to study treatment (including occurrences)
- Most frequent (threshold to be defined at time of reporting) non-serious TEAEs (including occurrences)

For tables presented by SOC and PT, SOCs/PTs are sorted by descending frequency of the number of subjects in the clazosentan group. If the frequencies of SOCs or PTs are the same, alphabetical order is used.

For tables presented by PT, PTs are sorted by descending frequency of the number of subjects in the clazosentan group. If the frequencies of PTs are the same, alphabetical order is used.

All AEs captured from signature of ICF up to EOS will be reported in the subject listings, which include data collected in the eCRF as well as the coded terms (SOC, PT), a flag for treatment-emergent and a flag for waived event as defined in protocol section 9.1.3 [D-22.069].

The following additional listings will be produced:

- All deaths and associated primary cause of death will be listed
- All AEs of subjects randomized but not treated (RND)
- All the previous/concomitant medications for subjects with a waived SAE.
- All medical histories for subjects with a waived SAE.

7.2 Laboratory tests

Laboratory analyses are based on data received from the central laboratory. Laboratory data will be converted into Standard International (SI) units. Unless noted otherwise, summaries and listings will include scheduled, re-test, and unscheduled assessments.

Consistent with the AE emergence period, the study treatment period considered for the laboratory measurements analyses is defined as start date/time of study treatment up to 24 hours after study treatment discontinuation.

Descriptive summary statistics on the observed values and the change from baseline to last value (re-test and unscheduled assessments included) in the study treatment period for hematology and blood chemistry parameters will be summarized.

Marked laboratory abnormalities are defined in Table 9 in Appendix 14.5.

Treatment-emergent marked laboratory abnormalities (MLAs) are those which are not present at baseline (e.g., change from no marked abnormality to any marked abnormality) or if a worsening occurred from study drug initiation up to 24 hours after study drug discontinuation, as compared to the corresponding value at baseline (e.g., change from a pre-existing abnormality at baseline to a worse category of abnormality).

The number (%) of subjects with newly occurring or worsening MLAs during study treatment period will be tabulated. A subject will be counted only once but may be reported in more than one MLA criterion of a given parameter. Percentages will be based on the number of subjects at risk, i.e., those having at least one post-baseline value and not meeting the criteria at baseline (or having a missing baseline value) for a given parameter.

Treatment-emergent liver function abnormalities occurring at any time post-baseline are identified according to the following criteria; a subject is considered to have met the criteria if they have at least one abnormality based on the worst post-baseline value measured:

- ALT > 3, > 5, > 8 × ULN, > 10 × ULN
- AST > 3, > 5, > 8 × ULN, > 10 × ULN

- AST or ALT > 3, > 5, > 8 × ULN, > 10 × ULN
- TBL > 2 × ULN
- TBL > 2 × ULN combined with ALT or AST > 3 × ULN
- ALT or AST > 3 × ULN + TBL ≥ 2 × ULN + ALP < 2 × ULN

For criteria combining several parameters, the abnormality must be reported at the same visit (same sample date).

The number (%) of subjects meeting the criteria defined above will be tabulated by treatment group. Percentages will be based on the number of subjects at risk, i.e., those having at least one post-baseline value and not meeting the criteria at baseline for a given parameter. In the event a subject's baseline value is missing:

- the subject will be considered 'at risk' for an abnormality formulated as a post-baseline value, but:
- the subject will be considered not 'at risk' for an abnormality formulated as a change from baseline.

A similar table will be produced on all post-baseline marked abnormalities.

Individual results will be listed by category (e.g., Hematology, Blood chemistry), by subject number and by visit / study day for all subjects, including central laboratory results.

All laboratory data for subjects with at least one MLA during study treatment will be listed. Any local laboratory data collected will be listed separately.

7.3 Electrocardiography

Descriptive summary statistics on the observed values and the change from baseline to last value (re-test and unscheduled assessments included) in the study treatment period for the 12 lead ECG parameters will be summarized by treatment group on the SAF.

The QT corrected with Fridericia's formula (QTcF) will be derived from the reported QT and RR using the following formula:

$$QTcF\ (msec) = QT\ (msec) / RR^{1/3}$$

For this parameter, additional flags will be defined:

Marked ECG abnormalities are defined below for QTcF:

- Value > 450, Value > 480, Value > 500
- Increase from baseline > 30, Increase from baseline > 60
- Value > 450 and increase from baseline > 30
- Value > 450 and increase from baseline > 60
- Value > 500 and increase from baseline > 30
- Value > 500 and increase from baseline > 60.

Number (%) of subjects with a marked QTcF abnormality during the study treatment period will be tabulated by treatment group. Percentages will be based on the number of subjects at risk, i.e., those having at least one post-baseline value and not meeting the criteria at baseline for a given parameter. In the event a subject's baseline value is missing:

- the subject will be considered 'at risk' for an abnormality formulated as a post-baseline value, but:
- the subject will be considered not 'at risk' for an abnormality formulated as a change from baseline.

All data (values and changes) will be listed by assessment. The listing will include date and time of measurements as well as the day, relative to study drug initiation.

7.4 Vital signs

Descriptive summary statistics on the average daily values and the change from baseline to each daily average post-baseline value in the study treatment period will be summarized for the following parameters:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (beats/min)
- Central venous pressure (mmHg)
- Intracranial pressure (mmHg)
- Body temperature (°C)

All data (values and changes) will be listed by assessment. The listing will include date and time of measurements as well as the day, relative to study drug initiation.

7.5 Other safety variables and analyses

7.5.1 Fluid balance

Daily fluid balance will be computed by subtracting the daily input and the daily output when they are both available and will be categorized according to the following classes:

Imbalance categories	1	2	3	4	5	6	7
Class boundaries (L)	>0,≤1	> 1,≤2	>2,≤3	>3,≤4	>4, ≤5	>5, ≤6	>6

Negative fluid balance will not be categorized. For each subject the periods of at least two consecutive days with fluid balance of category 2 or higher will be flagged.

A table displaying the proportion of subjects with at least one episode of fluid balance of category 2 or higher lasting for at least two consecutive days by treatment group will be produced on the SAF. A listing displaying daily fluid balance for all subjects will be

produced on the SAF. Periods of at least two consecutive days with fluid balance of category 2 or higher will be flagged.

7.6 Subgroup analysis of safety variables

The following subgroups will be used for safety analyses:

- WFNS grade at hospital admission, dichotomized as I–II vs III–V
- Age (years) at hospital admission, dichotomized as < 60 and ≥ 60
- Geographical location (USA vs non-USA, Europe vs non-Europe)
- Race (White; Black or African American; Asian). Subjects in the "Other" category will be excluded from the analysis given the small number of subjects.
- Sex
- Type of aneurysm-securing procedure (coiling vs clipping). If both were used, the last one is used for analysis.
- Good neurological recovery (mGCS ≥ 14 and aNIHSS = 0 *vs.* complement)

The following tables [see Table 8 for details] will be repeated on the subgroups (and their complements) defined above:

- TEAEs
- TEAEs of special interest
- TEAEs leading to premature discontinuation of study treatment
- Serious TEAEs

8 GENERAL STATISTICAL METHODOLOGY

Descriptive statistics will be provided by treatment group depending on the nature of the variable:

- For continuous variables: number of observed values, mean, standard deviation, minimum, first quartile, median, third quartile and maximum
- For dichotomous or categorical variables: number of observed values, and frequency with percentage per level/ category

Data are listed and summarized as described below.

The tables will use the following header structure (label and order):

Clazosentan 15 mg/h *N = xxx*	*Placebo* *N = xxx*

Where N indicates the total number randomized or treated appropriate to the analysis set in the corresponding treatment group, unless otherwise specified.

9 INTERIM ANALYSES AND DATA MONITORING COMMITTEES

Not applicable, IDMC analyses are described in a separate SAP.

10 GENERAL DEFINITIONS AND DERIVATIONS

10.1 Handling of missing date

This section describes some general principles to be followed in the case of missing or incomplete dates.

Missing dates will not necessarily be replaced (e.g., medical history). Unless specified otherwise, partially known dates will be defined as:

- Partially known start date:
  - If only the day is missing, and month and year of the episode = month and year of study drug initiation, then Start date = date of study drug initiation,
    otherwise Start date = yyyy-mm-01.
  - If month and day are missing, and year of the episode = year of study drug initiation, then Start date = date of study drug initiation,
    otherwise Start date = yyyy-01-01
- Partially known end date:
  - If only the day is missing, and month and year of the episode = month and year of study drug discontinuation, then End date = date of study drug discontinuation,
    otherwise End date = yyyy-mm-28 or 29 or 30 or 31
  - If month and day are missing, and year of the episode = year of study drug discontinuation, then if start date is less than or equal to study drug discontinuation then End date = date of study drug discontinuation,
    otherwise End date = yyyy-12-31

The original dates without estimation will be presented in the listings.

Any missing EOS date will be substituted with the date of database lock.

10.2 General analysis variables

Baseline value is defined as the last non-missing value before study drug initiation based on date and time (when collected).

Analysis value is defined as the value at the visit (numeric result in standard units).

Absolute change from baseline is defined as post-baseline value minus baseline value, i.e., a positive sign indicates an increase as compared to baseline.

Percent change from baseline is defined as the absolute change from baseline divided by the baseline value (if the baseline value is > 0) and then multiplied by 100.

Ratio to baseline is defined as the value at the visit divided by the value at baseline (if the baseline value is $\neq 0$).

Analysis date is defined as the numeric SAS date derived from the date/time of assessment. It may be an imputed date.

Analysis start date is defined as the numeric SAS date derived from the start date/time of an event. It may be an imputed date.

Analysis end date is defined as the numeric SAS date derived from the end date/time of an event. It may be an imputed date.

Analysis relative day is estimated for several assessments (e.g., vital signs, laboratory data). It refers to the number of days elapsed since study drug initiation date plus 1 (e.g., Day 1 is the day of study drug initiation). For dates prior to study drug initiation, study day is the negative number of days elapsed between the date under consideration and the day of study drug initiation. Therefore, the study day is never 0.

Analysis day relative to aSAH is estimated for several assessments performed during screening period and at EOS visit (e.g., MoCA, EQ-5D-5L). It refers to the number of days elapsed since aneurysm rupture (aSAH) date plus 1 (e.g., Day 1 is the day of aSAH).

Analysis end relative day is estimated for several assessments, including AE end, treatment interruptions, concomitant medication end. It refers to the number of days between the end of the specific event and the study drug initiation.

Hospital discharge date (time) is defined as the latest end/discharge date (time) reported with subject location equal to 'Critical care unit or equivalent', 'Specialized care ward' or 'General care ward' among the location reported for the initial hospitalization.

Discharge home is defined as being discharged home fully or partially independent.

Day 14 is defined as per protocol as 14th day after study drug start. This corresponds to the analysis relative day 15.

10.3 Study treatment administration error

In the event of an administration error, i.e., a subject was administered both placebo and active treatment, the subject will be analyzed as active treatment ('clazosentan') in all analyses based on the SAF (i.e., in all analyses based on the actual treatment group).

10.4 Other derivations

Length/Duration: Lengths and durations based on dates will be computed as end date minus start date plus 1.

Good and Full neurological recovery subgroup variable: If one of these subgroups cannot be derived for a given subject due to missing data then the subject will be considered to be in the corresponding complementary subgroup.

11 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

11.1 Changes in the conduct of the study / data collection

Addition of the EQ-5D questionnaire at Week 24 post-aSAH:

In order to have at least one QoL assessment performed later than 12 weeks after aSAH subjects will be interviewed for the EQ-5D questionnaire at a second timepoint, Week 24 post-aSAH (from protocol version 4 dated 7 January 2020). Accordingly, the study duration was adjusted from 3 to 6 months for the collection of the employment status, the EQ-5D and SAE data collection.

Early treatment stratum:

Following decision of the IDMC held on 2 April 2021, the recruitment into the early treatment stratum was stopped. This decision was based on 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.

Main secondary endpoint definition:

In protocol version 7 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 [see Section 6.3.1 for details]. The initially planned analysis (up to and including protocol version 6) will still be performed but as an exploratory analysis [see Section 6.3.8 for details].

Other secondary endpoint and testing strategy:

Since protocol version 7 the mRS has been formally included in the statistical hierarchical testing strategy, just before the GOSE [see Section 6.1.1 for details].

11.2 Changes to the analyses planned in the study protocol

Early treatment stratum:

The number of subjects randomized in this stratum being very low, and according to IDMC decision considering the contribution of these subjects to the overall study futile, this stratum was no longer considered as an adjustment/stratification variable in all the analyses adjusted/stratified on the stratification factors used for randomization. The initially planned analysis of the primary endpoint (i.e., stratified on the 3 stratification factors) will be done, but as an exploratory analysis [see Section 6.2.8 for details].

Estimands:

As the study started before the ICH E9 (R1) guidance became effective [ICH 2019], the estimands were not described in the protocol or in the CSR SAP version 1. They are now

defined in Section 6.1.2. Redefining the analyses with the estimand framework led to no longer using a Per-protocol analysis set and to rather defining the list of the IEs, and the different strategies considered to address them.

Biomarker endpoints analysis:

In the protocol, the biomarker endpoints are the area under the plasma concentration-time curve of S100b protein from baseline to Day 10 and from baseline to Day 14 post-study drug initiation. To accommodate the heterogeneity of the timing of the assessment, because some subjects may have been discharged early, and to align with previous studies, the following endpoint definition will be used: presence of abnormal S100b protein concentration defined as the max observed concentration between study drug start and Day 14 being greater or equal to 0.4µg/L.

GOSE/mRS:

In the protocol, the main analysis of the dichotomized GOSE and mRS was specified as a CMH test stratified on the variables used in the randomization (i.e., WFNS grade [I–II vs III–V] and age [≤ 60 and > 60 years] at admission). However, in previous studies it was found that subjects who had recovered well from their initial bleeding episode and aneurysm-securing procedure had on average a better GOSE/mRS score. This subgroup of subjects called "good neurological recovery" is defined as subjects with an mGCS ≥ 14 and an aNIHSS = 0 (absence of motor deficit) within 60 minutes prior to study drug initiation. The complement subgroup is called "neurological impairment". To gain further precision in treatment effect estimates, the analyses of GOSE and mRS will, in addition, be adjusted for good neurological recovery variable (mGCS ≥ 14 and aNIHSS = 0, Yes/No).

11.3 Clarifications concerning endpoint definitions and related variables or statistical methods

In protocol version 7 dated 18 February 2022, 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 [see Section 6.3.1 for details].

The protocol defines that the treatment effect for the main efficacy analyses will be summarized using: the absolute difference in the rates, the OR, the RR and the RRR. However, to avoid redundancy as RRR = 1 – RR the RR will not be presented in statistical outputs.

The protocol defines the following pharmaco-economic endpoint: Number and type of episodes of rescue therapy, from randomization up to hospital discharge and from hospital discharge up to Week 12 post-aSAH. Total duration in days, rather than the number of episodes of rescue therapy, will be analyzed, and more specifically: (i) the total number of

days with protocol-specific rescue therapy and (ii) the total number of days with protocol-specific rescue therapy or local rescue therapy [see Section 5.4.5.3 for details].

11.4 Additional analyses to those planned in the study protocol

Not applicable.

12 LIST OF TABLES, LISTINGS AND FIGURES

The complete list of Tables, Listings and Figures is stored in the Idorsia Electronic Document Management System.

For the mock-up catalog to be used during programming, please refer to the document stored in the Biometry Computing Environment.

Since all Tables, Listings and Figures are produced using SAS®, the output actually generated may slightly differ from the mock-ups presented in the study specific mock-up catalog.

13 REFERENCES

[D-22.069] 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). Idorsia Pharmaceuticals Ltd; Protocol Version 7 ID-054-304, 18 February 2022.

[Chessel 2004] Chessel D, Dufour A, Thioulouse J. The ade4 Package - I: One-Table Methods. R News. 2004;4(1):5-10 Available from: https://cran.r-project.org/doc/Rnews/Rnews_2004-1.pdf

[Dolédec 1987], Dolédec S, Chessel, D. Rythmes saisonniers et composantes stationnelles en milieu aquatique I- Description d'un plan d'observations complet par projection de variables. Acta Oecologica, Oecologia Generalis, 8, 3, 403–426. French.

[Hernández-Alava 2017] Hernández-Alava M, Pudney, S. Econometric modelling of multiple self-reports of health states: the switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. J Health Econ. 2017;55:139-152.

[ICH 2019] ICH Harmonised Tripartite Guideline. Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials – E9 (R1). 20 November 2019 [accessed on 25 July 2022]. Available from: https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

[R Core Team 2020] R-project.org [Internet]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2020 [cited 25 July 2022]. Available from: https://www.R-project.org/

[Romesburg 1985] Romesburg HC. Exploring, confirming and randomization tests. Computers & Geosciences. 1985;11(1):19–37.

[Williams 1999] Williams LS, Weinberger M, Harris LE, Clark DO, Biller J. Development of a stroke-specific quality of life scale. Stroke. 1999 Jul;30(7):1362-9.

14 APPENDICES

14.1 Revision History

Version Date	Version	Implemented Change(s)
31-OCT-2018	1.0	Initial version
26-JUL-2022	2.0	• Definition of Estimands added • Incorporate changes in protocol: – New/revised exploratory endpoints were added (protocol version 3) – EQ-5D questionnaire was added at Week 24 post-aSAH, EOS visit was moved from Week 12 to Week 24, SAEs collected until Week 24 (protocol version 4) – Follow-up visit / phone call was added for subject discharged prior to Day 14 to allow assessment of primary endpoint (protocol version 5) – Discontinuation of the recruitment into the early treatment group following a recommendation received by the study IDMC on 2 April 2021 (protocol version 6) – Revised definition of main secondary endpoint, mRS explicitly added to the overall testing strategy (protocol version 7) • Imputation rules for missing CT scan at Day 16 (to address FDA comment from November 2018 on SAP Version 1)
27-SEP-2022	3.0	• GOSE/mRS: All GOSE/mRS analyses are now also adjusted for the partial neurological recovery variable (mGCS ≥ 14 and aNIHSS = 0, Yes/No). • Subgroup analyses for safety variables were added. • Minor updates/corrections/clarifications throughout the document.
26-JAN-2023	4.0	• Name of the subgroup “partial neurological recovery” changed to “good neurological recovery subgroup”. • New table displaying main cause of death. • New table displaying SAS procedure outputs.

Version Date	Version	Implemented Change(s)
		• EQ-5D: Rule to reallocate visit was added. • Update definition of marked abnormalities for ALT and AST. • Minor updates/corrections/clarifications throughout the document.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; aNIHSS = abbreviated National Institutes of Health Stroke Scale; aSAH = aneurysmal subarachnoid hemorrhage; CT = computed tomography; EOS = End-of-Study; EQ-5D = Euro Quality of Life-5D; GOSE = Glasgow Outcome Scale – Extended; IDMC =Independent Data Monitoring Committee; mGCS = modified Glasgow Coma Scale; mRS = modified Rankin Scale; SAE = serious adverse event.

14.2 Schedule of events

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)			24 h safety FU Period	Extended FU Period (From end of 24 h safety FU Period until EOS)	
			TREATMENT Period (min. 10, max. 14 days of treatment)						
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**	**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]							
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. 10, max. 14 days of treatment)						
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
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.

Visit and assessment schedule for subjects in the early treatment stratum (recruitment in this stratum was discontinued from protocol version 6, dated 29 April 2021 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.

14.3 Change from pre-aSAH to post-aSAH status

Pre-aSAH \ Post-aSAH	Employed full time	Employed part time	Employed full time - not yet returned	Employed part time - not yet returned	Employed full time - on work disability	Employed part time - on work disability	Retired	Unemployed	Homemaker	Student full time	Student part time	Student not yet returned	Unknown
Employed full time	F	P	NB	NB	NB	NB	P	P	P	P	P	NB	M
Employed part time	F	F	NB	NB	NB	NB	P	P	P	P	P	NB	M
Employed full time - on work disability	F	P	NB	NB	NB	NB	P	P	P	P	P	NB	M
Employed part time - on work disability	F	F	NB	NB	NB	NB	P	P	P	P	P	NB	M
Retired	F	F	NB	NB	NB	NB	F	F	F	F	F	NB	M
Unemployed	F	F	NB	NB	NB	NB	P	F	F	F	F	NB	M
Homemaker	F	F	NB	NB	NB	NB	P	F	F	F	F	NB	M
Student full time	P	P	NB	NB	NB	NB	P	P	P	F	P	NB	M
Student part time	P	P	NB	NB	NB	NB	P	P	P	F	F	NB	M
Unknown	M	M	M	M	M	M	M	M	M	M	M	NB	M

F = Fully Back; P = Partially Back; NB = Not Back; M = Missing.

14.4 Adverse events of special interest

This appendix contains the search criteria (provided as MedDRA PTs and PT codes) for the following AESIs:

- Brain oedema
- Cerebral hemorrhage
- Anaemia
- Lung complications
- Hypotension
- Oedema and fluid retention
- Tachyarrhythmia
- Hepatic disorders

Overview of search criteria for clazosentan AESI

MedDRA v25.0
Brain oedema
Cerebral hemorrhage
Anaemia
Lung complications
Hypotension
Oedema and fluid retention
Tachyarrhythmia
Hepatic disorders

Brain oedema

MedDRA v25.0	MedDRA v25.0 code
The case will be included in this subgroup if it contains an event within the MedDRA HLGT "Increased intracranial pressure and hydrocephalus" (primary or secondary path), i.e., any of the following MedDRA PTs:	
Aqueductal stenosis	10067575
Benign enlargement of the subarachnoid spaces	10078477
Brain compression	10006112
Brain dislocation syndrome	10082220
Brain herniation	10006126
Brain oedema	10048962
Cerebral ventricle collapse	10073706
Cerebrospinal fluid circulation disorder	10075604
Cerebrospinal fluid retention	10065532
Cerebrospinal thrombotic tamponade	10052173
Congenital aqueductal stenosis	10066084
Congenital hydrocephalus	10010506
Cytotoxic oedema	10067276
Dandy-Walker syndrome	10048411
Dialysis disequilibrium syndrome	10059256
External hydrocephalus	10076670
Hydrocephalus	10020508
Hypertensive hydrocephalus	10058025
Idiopathic intracranial hypertension	10078904
Intracranial pressure increased	10022773
Normal pressure hydrocephalus	10029773
Oval pupil	10085734
Papilloedema	10033712
Posthaemorrhagic hydrocephalus	10079859
Vasogenic cerebral oedema	10067275

Cerebral haemorrhage

MedDRA v25.0	MedDRA v25.0 code
All PTs from the Haemorrhagic central nervous system vascular conditions (SMQ): The case will be included in this subgroup if it contains an event within the "Haemorrhagic central nervous system vascular conditions" SMQ, i.e., if it contains an event with any of the following MedDRA PTs:	
Basal ganglia haematoma	10077031
Basal ganglia haemorrhage	10067057
Basal ganglia stroke	10071043
Basilar artery perforation	10075736
Brain stem haematoma	10073230
Brain stem haemorrhage	10006145
Brain stem microhaemorrhage	10071205
Brain stem stroke	10068644
Carotid aneurysm rupture	10051328
Carotid artery perforation	10075728
Central nervous system haemorrhage	10072043
Cerebellar haematoma	10061038
Cerebellar haemorrhage	10008030
Cerebellar microhaemorrhage	10071206
Cerebellar stroke	10079062
Cerebral aneurysm perforation	10075394
Cerebral aneurysm ruptured syphilitic	10008076
Cerebral arteriovenous malformation haemorrhagic	10008086
Cerebral artery perforation	10075734
Cerebral cyst haemorrhage	10082099
Cerebral haematoma	10053942
Cerebral haemorrhage	10008111
Cerebral haemorrhage foetal	10050157
Cerebral haemorrhage neonatal	10008112
Cerebral microhaemorrhage	10067277
Cerebrovascular accident	10008190
Cerebrovascular disorder	10008196
Epidural haemorrhage	10073681
Extra-axial haemorrhage	10078254
Extradural haematoma	10015769
Extradural haematoma evacuation	10082797
Extraischaemic cerebral haematoma	10080347
Foville syndrome	10082594
Haemorrhage intracranial	10018985
Haemorrhagic cerebellar infarction	10085944
Haemorrhagic cerebral infarction	10019005
Haemorrhagic stroke	10019016
Haemorrhagic transformation stroke	10055677
Intracerebral haematoma evacuation	10062025
Intracranial haematoma	10059491

Intracranial haemorrhage neonatal	10086946
Intracranial tumour haemorrhage	10022775
Intraventricular haemorrhage	10022840
Intraventricular haemorrhage neonatal	10022841
Meningorrhagia	10052593
Perinatal stroke	10073945
Periventricular haemorrhage neonatal	10076706
Pituitary apoplexy	10056447
Pituitary haemorrhage	10049760
Putamen haemorrhage	10058940
Ruptured cerebral aneurysm	10039330
Spinal cord haematoma	10076051
Spinal cord haemorrhage	10048992
Spinal epidural haematoma	10050162
Spinal epidural haemorrhage	10049236
Spinal stroke	10082031
Spinal subarachnoid haemorrhage	10073564
Spinal subdural haematoma	10050164
Spinal subdural haemorrhage	10073563
Stroke in evolution	10059613
Subarachnoid haematoma	10076701
Subarachnoid haemorrhage	10042316
Subarachnoid haemorrhage neonatal	10042317
Subdural haematoma	10042361
Subdural haematoma evacuation	10042363
Subdural haemorrhage	10042364
Subdural haemorrhage neonatal	10042365
Thalamus haemorrhage	10058939
Vertebral artery perforation	10075735
Vertebrobasilar stroke	10082484

Anaemia

MedDRA v25.0	MedDRA v25.0 code
The case will be included in this subgroup if it contains an event within the "Haematopoietic erythropenia" SMQ or the "Haematopoietic cytopenias affecting more than one type of blood cell" SMQ, or it contains an event with any MedDRA Preferred Term containing the text "anaemia" (with the exception of the PT "Melanaemia"), or with the PT "Haemodilution" i.e., any of the following MedDRA PTs:	
Anaemia	10002034
Anaemia folate deficiency	10002043
Anaemia Heinz body	10002058
Anaemia macrocytic	10002064
Anaemia megaloblastic	10002065
Anaemia neonatal	10002068
Anaemia of chronic disease	10002073
Anaemia of malignant disease	10049105
Anaemia of pregnancy	10066468
Anaemia postoperative	10048861
Anaemia prophylaxis	10050250
Anaemia splenic	10049009
Anaemia vitamin B12 deficiency	10002080
Anaemia vitamin B6 deficiency	10002081
Aplasia pure red cell	10002965
Aplastic anaemia	10002967
Aspiration bone marrow abnormal	10003506
Autoimmune anaemia	10080243
Autoimmune aplastic anaemia	10071576
Autoimmune haemolytic anaemia	10073785
Autosomal recessive megaloblastic anaemia	10081878
Bicytopenia	10058956
Biopsy bone marrow abnormal	10004738
Blood disorder	10061590
Blood incompatibility haemolytic anaemia of newborn	10056369
Blood loss anaemia	10082297
Blood loss anaemia neonatal	10005644
Bone marrow disorder	10061729
Bone marrow failure	10065553
Bone marrow infiltration	10075173
Bone marrow myelogram abnormal	10057528
Bone marrow necrosis	10058822
Cardiac haemolytic anaemia	10072202
Cold type haemolytic anaemia	10009868
Congenital anaemia	10010329
Congenital aplastic anaemia	10053138
Congenital dyserythropoietic anaemia	10081457

Coombs negative haemolytic anaemia	10010940
Coombs positive haemolytic anaemia	10010941
Cytopenia	10066274
Deficiency anaemia	10061101
Erythroblast count abnormal	10058508
Erythroblast count decreased	10058505
Erythroid dysplasia	10086470
Erythroid maturation arrest	10015279
Erythropenia	10015287
Erythropoiesis abnormal	10049467
Erythropoietin deficiency anaemia	10083258
Febrile bone marrow aplasia	10053213
Foetal anaemia	10077577
Full blood count decreased	10017413
Gelatinous transformation of the bone marrow	10078097
Haematocrit abnormal	10049221
Haematocrit decreased	10018838
Haematotoxicity	10061188
Haemodilution	10059484
Haemoglobin abnormal	10018879
Haemoglobin decreased	10018884
Haemolytic anaemia	10018916
Haemolytic anaemia enzyme specific	10018919
Haemolytic icteroanaemia	10054920
Hand and foot syndrome secondary to sickle cell anaemia	10048775
Hereditary haemolytic anaemia	10060893
Hereditary microcytic anaemia	10085905
Hereditary sideroblastic anaemia	10019902
Hexokinase deficiency anaemia	10020022
Hyperchromic anaemia	10020605
Hypochromic anaemia	10020969
Hypoplastic anaemia	10021074
Immune-mediated cytopenia	10084828
Iron deficiency anaemia	10022972
Leukoerythroblastic anaemia	10053199
Microangiopathic haemolytic anaemia	10027527
Microcytic anaemia	10027538
Myelodysplastic syndrome	10028533
Myelodysplastic syndrome transformation	10067387
Myelofibrosis	10028537
Myeloid metaplasia	10028561
Myelosuppression	10028584
Nephrogenic anaemia	10058116
Normochromic anaemia	10029782
Normochromic normocytic anaemia	10029783
Normocytic anaemia	10029784
Pancytopenia	10033661
Panmyelopathy	10050026
Pernicious anaemia	10034695

Plasmablast count decreased	10058774
Primary myelofibrosis	10077161
Proerythroblast count abnormal	10060227
Proerythroblast count decreased	10060229
Protein deficiency anaemia	10037006
Pyruvate kinase deficiency anaemia	10037682
Radiation anaemia	10085644
Red blood cell count abnormal	10038151
Red blood cell count decreased	10038153
Refractory anaemia with an excess of blasts	10038270
Refractory anaemia with ringed sideroblasts	10038272
Reticulocyte count abnormal	10038788
Reticulocyte count decreased	10038790
Reticulocyte percentage decreased	10059921
Reticulocytopenia	10038795
Scan bone marrow abnormal	10053504
Scorbutic anaemia	10086662
Sickle cell anaemia	10040641
Sickle cell anaemia with crisis	10040642
Sideroblastic anaemia	10040661
Spherocytic anaemia	10041509
Spur cell anaemia	10052483
Warm autoimmune haemolytic anaemia	10087091

Lung complications

MedDRA v25.0	MedDRA v25.0 code

The case will be included in this subgroup if it contains an event **with the PTs "Bronchospasm", "Bronchospasm paradoxical", "Unilateral bronchospasm",**
or with a PT containing "pneumonia" from within the following MedDRA High Level terms:
Bacterial lower respiratory tract infections
Fungal lower respiratory tract infections
Lower respiratory tract and lung infections
Lower respiratory tract infections NEC
Lower respiratory tract inflammatory and immunologic conditions
Viral lower respiratory tract infections
Or with a PT within any of the following MedDRA HLTs:
Conditions associated with abnormal gas exchange
Parenchymal lung disorders NEC
Pneumothorax and pleural effusions NEC
Pulmonary oedemas
Pulmonary thrombotic and embolic conditions
Respiratory failures (excl neonatal)

i.e. any of the following MedDRA PTs (exact match):

Acute interstitial pneumonitis	10066728
Acute lung injury	10069351
Acute pulmonary oedema	10001029
Acute respiratory distress syndrome	10001052
Acute respiratory failure	10001053
Alveolar aeration excessive	10001874
Alveolar lung disease	10073344
Alveolar proteinosis	10001881
Anaemic hypoxia	10051899
Anaphylactoid syndrome of pregnancy	10067010
Anoxia	10002660
Antisynthetase syndrome	10068801
Asphyxia	10003497
Atelectasis	10003598
Atypical mycobacterial pneumonia	10071075
Atypical pneumonia	10003757
Brain hypoxia	10006127
Bronchopulmonary disease	10053420
Bronchospasm	10006482
Bronchospasm paradoxical	10006486
Candida pneumonia	10053158
Capnothorax	10070771
Cardiopulmonary failure	10051093
Cardio-respiratory arrest	10007617
Cardio-respiratory distress	10049874
Catamenial pneumothorax	10086100

Cement embolism	10050484
Chronic respiratory failure	10009126
Chylothorax	10051228
Combined pulmonary fibrosis and emphysema	10076515
Complications of transplanted lung	10010187
Confirmed e-cigarette or vaping product use associated lung injury	10085189
Congenital chylothorax	10078770
Congenital emphysema	10010456
Congenital pneumonia	10010594
COPA syndrome	10083948
Coronavirus pneumonia	10084381
COVID-19 pneumonia	10084380
Cyanosis	10011703
Cyanosis central	10011704
Cystic lung disease	10078811
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	10082591
Embolic pneumonia	10065680
Emphysema	10014561
Engraftment syndrome	10050684
Enterobacter pneumonia	10054218
Eosinophilic pleural effusion	10080148
Eosinophilic pneumonia	10014962
Eosinophilic pneumonia acute	10052832
Eosinophilic pneumonia chronic	10052833
Haemorrhagic pneumonia	10077933
Haemothorax	10019027
Hepatic hydrothorax	10067365
Herpes simplex pneumonia	10065046
Hydrothorax	10048612
Hypercapnia	10020591
Hypercapnic coma	10072597
Hyperoxia	10058490
Hypobarism	10077606
Hypocapnia	10020952
Hypoxia	10021143
Hypoxia intolerance	10080129
Hypoxic ischaemic encephalopathy neonatal	10086943
Hypoxic-ischaemic encephalopathy	10070511
Idiopathic interstitial pneumonia	10078268
Idiopathic pneumonia syndrome	10063725
Idiopathic pulmonary fibrosis	10021240
Interstitial lung disease	10022611
Leukostasis syndrome	10074608
Low lung compliance	10086117
Lung consolidation	10025080
Lung cyst	10068749
Lung induration	10057261
Lung infiltration	10025102
Lung perforation	10076279

Lymphangioleiomyomatosis	10049459
MacLeod's syndrome	10025375
Metapneumovirus pneumonia	10085550
Metastatic pulmonary embolism	10069909
Middle lobe syndrome	10056652
Miliary pneumonia	10055088
Multifocal micronodular pneumocyte hyperplasia	10057109
Negative pressure pulmonary oedema	10080589
Neonatal pneumonia	10053584
Neonatal pneumothorax	10082056
Neuroendocrine cell hyperplasia of infancy	10072968
Non-cardiogenic pulmonary oedema	10029538
Obstetrical pulmonary embolism	10029925
Oesophageal-pulmonary fistula	10083015
Organising pneumonia	10067472
Paracancerous pneumonia	10080986
Paraneoplastic pleural effusion	10075715
Parasitic pneumonia	10078883
Pleural effusion	10035598
Pleuroparenchymal fibroelastosis	10084305
Pleuroperitoneal communication	10068641
Pneumocystis jirovecii pneumonia	10073755
Pneumonia	10035664
Pneumonia acinetobacter	10079866
Pneumonia adenoviral	10035665
Pneumonia anthrax	10035667
Pneumonia aspiration	10035669
Pneumonia bacterial	10060946
Pneumonia bordetella	10035672
Pneumonia chlamydial	10035673
Pneumonia cryptococcal	10067565
Pneumonia cytomegaloviral	10035676
Pneumonia escherichia	10035699
Pneumonia fungal	10061354
Pneumonia haemophilus	10035702
Pneumonia herpes viral	10035703
Pneumonia influenzal	10035714
Pneumonia klebsiella	10035717
Pneumonia legionella	10035718
Pneumonia lipoid	10035720
Pneumonia measles	10035722
Pneumonia moraxella	10035723
Pneumonia mycoplasmal	10035724
Pneumonia necrotising	10055672
Pneumonia parainfluenzae viral	10035727
Pneumonia pneumococcal	10035728
Pneumonia proteus	10079867
Pneumonia pseudomonal	10035731
Pneumonia respiratory syncytial viral	10035732

Pneumonia salmonella	10035733
Pneumonia serratia	10079868
Pneumonia staphylococcal	10035734
Pneumonia streptococcal	10035735
Pneumonia tularaemia	10035736
Pneumonia viral	10035737
Pneumothorax	10035759
Pneumothorax spontaneous	10035763
Pneumothorax traumatic	10035765
Polymer fume fever	10077266
Post procedural pneumonia	10066590
Post procedural pulmonary embolism	10063909
Postoperative respiratory distress	10054809
Postoperative respiratory failure	10072651
Probable e-cigarette or vaping product use associated lung injury	10085188
Procedural pneumothorax	10077574
Progressive massive fibrosis	10036805
Pulmonary air leakage	10067826
Pulmonary alveolar haemorrhage	10037313
Pulmonary alveolar microlithiasis	10037315
Pulmonary amyloidosis	10063945
Pulmonary artery thrombosis	10037340
Pulmonary atypical adenomatous hyperplasia	10084570
Pulmonary bullae rupture	10086936
Pulmonary calcification	10051200
Pulmonary cavitation	10051738
Pulmonary congestion	10037368
Pulmonary contusion	10037370
Pulmonary embolism	10037377
Pulmonary fibrosis	10037383
Pulmonary fistula	10065873
Pulmonary haemosiderosis	10037396
Pulmonary infarction	10037410
Pulmonary interstitial emphysema syndrome	10037415
Pulmonary microemboli	10037421
Pulmonary necrosis	10058824
Pulmonary nodular lymphoid hyperplasia	10077412
Pulmonary oedema	10037423
Pulmonary oedema neonatal	10050459
Pulmonary oedema post fume inhalation	10037427
Pulmonary oil microembolism	10069388
Pulmonary ossification	10070310
Pulmonary pneumatocele	10063749
Pulmonary thrombosis	10037437
Pulmonary toxicity	10061924
Pulmonary tumour thrombotic microangiopathy	10079988
Pulmonary venous thrombosis	10037459
Reexpansion pulmonary oedema	10064715
Respiratory acidosis	10038661

Respiratory alkalosis	10038664
Respiratory failure	10038695
Respiratory gas exchange disorder	10062105
Respiratory paralysis	10038708
Restrictive allograft syndrome	10077506
Restrictive pulmonary disease	10048667
Rheumatoid arthritis-associated interstitial lung disease	10085517
Septic pulmonary embolism	10083093
Transfusion-related acute lung injury	10052235
Traumatic haemothorax	10074487
Traumatic lung injury	10069363
Unilateral bronchospasm	10072338
Varicella zoster pneumonia	10074254

Hypotension

MedDRA v25.0	MedDRA v25.0 code

The case will be included in this subgroup if it contains an event with a PT containing ("Blood pressure" AND "decreased"), or with the PT "Blood pressure immeasurable", "Mean arterial pressure decreased", "Circulatory collapse", "Hypotensive crisis", **"Peripheral circulatory failure"** or with a PT containing "hypotension" (with the exception of the PTs Dialysis hypotension, Intracranial hypotension, Neonatal hypotension"), or with any of the following selected PTs containing "shock" (Cardiogenic shock, Distributive shock, Hypovolaemic shock, Procedural shock, Shock, Shock haemorrhagic, Shock symptom), i.e., if it contains any of the following MedDRA PTs:

Blood pressure ambulatory decreased	10005731
Blood pressure systolic inspiratory decreased	10005761
Blood pressure systolic decreased	10005758
Blood pressure orthostatic decreased	10053356
Blood pressure diastolic decreased	10005737
Blood pressure decreased	10005734
Blood pressure immeasurable	10005748
Mean arterial pressure decreased	10026983
Circulatory collapse	10009192
Peripheral circulatory failure	10034567
Hypotensive crisis	10083659
Hypotension	10021097
CT hypotension complex	10078280
Diastolic hypotension	10066077
Procedural hypotension	10062300
Post procedural hypotension	10084013
Orthostatic hypotension	10031127
Shock	10040560
Cardiogenic shock	10007625
Distributive shock	10070559
Hypovolaemic shock	10021138
Procedural shock	10080894
Shock haemorrhagic	10049771
Shock symptom	10040581

Oedema and fluid retention

MedDRA v25.0	MedDRA v25.0 code
The case will be included in this subgroup if it contains an event within the SMQ "Haemodynamic oedema, effusions and fluid overload (SMQ)" or with the PTs Swelling of eyelid, Swelling face, Eyelid oedema, Face oedema, i.e. the case will be included if it contains an event with any of the following MedDRA PTs:	
Acute pulmonary oedema	10001029
Administration site joint effusion	10075944
Administration site oedema	10075104
Administration site swelling	10075107
Amyloid related imaging abnormalities	10072599
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	10072601
Amyloid related imaging abnormality-oedema/effusion	10072260
Application site joint effusion	10076010
Application site joint swelling	10076016
Application site oedema	10003050
Application site swelling	10053424
Ascites	10003445
Bone marrow oedema	10051763
Bone marrow oedema syndrome	10064269
Bone swelling	10053631
Brain oedema	10048962
Bronchial oedema	10056695
Capillary leak syndrome	10007196
Catheter site oedema	10055909
Cerebral mass effect	10067086
Cerebral oedema management	10008128
Cervix oedema	10063817
Circumoral swelling	10081703
Compression garment application	10079209
Cytotoxic oedema	10067276
Durotomy procedure	10081615
Effusion	10063045
Elephantiasis nostras verrucosa	10071025
Extensive swelling of vaccinated limb	10065106
Eyelid oedema	10015993
Face oedema	10016029
Flood syndrome	10084797
Fluid retention	10016807
Gallbladder oedema	10017637
Gastrointestinal oedema	10058061
Generalised oedema	10018092
Gestational oedema	10063412
Gravitational oedema	10018713

Heat oedema	10019340
Hydraemia	10060374
Hydrothorax	10048612
Hydrovarium	10081546
Hypervolaemia	10020919
Hypoosmolar state	10074867
Implant site oedema	10063776
Implant site swelling	10063867
Inadequate peritoneal dialysis	10085005
Incision site oedema	10065614
Incision site swelling	10074758
Infusion site joint effusion	10076072
Infusion site joint swelling	10076078
Infusion site oedema	10053998
Infusion site swelling	10053505
Injection site joint swelling	10049260
Injection site oedema	10022085
Injection site swelling	10053425
Instillation site oedema	10073619
Joint effusion	10023215
Joint swelling	10023232
Lipoedema	10063955
Localised oedema	10048961
Lumbar subcutaneous oedema	10086593
Lymphoedema	10025282
Lymphovenous bypass	10084980
Medical device site joint effusion	10076117
Medical device site joint swelling	10076123
Modified Rodnan skin score abnormal	10081776
Mouth swelling	10075203
Muscle oedema	10071759
Muscle swelling	10064470
Myocardial oedema	10064966
Negative pressure pulmonary oedema	10080589
Non-cardiogenic pulmonary oedema	10029538
Non-pitting oedema	10083903
Oedema	10030095
Oedema blister	10080039
Oedema due to cardiac disease	10049632
Oedema due to hepatic disease	10049631
Oedema due to renal disease	10049630
Oedema mucosal	10030111
Oedema neonatal	10061317
Oedema peripheral	10030124
Oedematous kidney	10073381
Oesophageal oedema	10064342
Omental oedema	10087030
Oropharyngeal oedema	10078783
Pelvic fluid collection	10065388

Pericardial effusion	10034474
Perinephric collection	10059209
Perinephric oedema	10078818
Peripheral oedema neonatal	10049779
Peripheral swelling	10048959
Pleural effusion	10035598
Prevertebral soft tissue swelling of cervical space	10074880
Pulmonary oedema	10037423
Pulmonary oedema neonatal	10050459
Puncture site oedema	10074069
Reexpansion pulmonary oedema	10064715
Retroperitoneal effusion	10063637
Retroperitoneal oedema	10038983
Scleroedema	10055953
Second impact syndrome	10084563
Skin oedema	10058679
Skin swelling	10053262
Spinal cord oedema	10063036
Subdural effusion	10054797
Swelling	10042674
Swelling face	10042682
Swelling of eyelid	10042690
Tendon sheath effusion	10086724
Testicular swelling	10043354
Vaccination site joint effusion	10076172
Vaccination site joint swelling	10076178
Vasogenic cerebral oedema	10067275
Visceral oedema	10065768

Tachyarrhythmia

MedDRA v25.0	MedDRA v25.0 code
A case will be included in this subgroup if it contains an event within the following SMQ: Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ) including all its sub-SMQs, or within the SMQ Torsade de pointes/QT prolongation (broad scope), i.e., any of the following MedDRA PTs:	**contains duplicate PTs**
Arrhythmic storm	10067339
Cardiac arrest	10007515
Cardiac death	10049993
Cardiac fibrillation	10061592
Cardio-respiratory arrest	10007617
Electrocardiogram QT interval abnormal	10063748
Electrocardiogram QT prolonged	10014387
Electrocardiogram repolarisation abnormality	10052464
Electrocardiogram U wave inversion	10062314
Electrocardiogram U wave present	10057913
Electrocardiogram U-wave abnormality	10055032
Long QT syndrome	10024803
Long QT syndrome congenital	10057926
Loss of consciousness	10024855
Sudden cardiac death	10049418
Sudden death	10042434
Syncope	10042772
Torsade de pointes	10044066
Ventricular arrhythmia	10047281
Ventricular fibrillation	10047290
Ventricular flutter	10047294
Ventricular tachyarrhythmia	10065341
Ventricular tachycardia	10047302
Accelerated idioventricular rhythm	10049003
Anomalous atrioventricular excitation	10002611
Arrhythmia supraventricular	10003130
Arrhythmic storm	10067339
Atrial fibrillation	10003658
Atrial flutter	10003662
Atrial parasystole	10071666
Atrial tachycardia	10003668
Cardiac fibrillation	10061592
Cardiac fibrillation	10061592
Cardiac flutter	10052840
Congenital supraventricular tachycardia	10082343
Early repolarisation syndrome	10086230
ECG P wave inverted	10057526
Electrocardiogram P wave abnormal	10050384
Extrasystoles	10015856
Frederick's syndrome	10082089

Junctional ectopic tachycardia	10074640
Parasystole	10033929
Retrograde p-waves	10071187
Rhythm idioventricular	10039111
Sinus tachycardia	10040752
Supraventricular extrasystoles	10042602
Supraventricular tachyarrhythmia	10065342
Supraventricular tachycardia	10042604
Tachyarrhythmia	10049447
Torsade de pointes	10044066
Ventricular arrhythmia	10047281
Ventricular extrasystoles	10047289
Ventricular fibrillation	10047290
Ventricular flutter	10047294
Ventricular parasystole	10058184
Ventricular pre-excitation	10049761
Ventricular tachyarrhythmia	10065341
Ventricular tachycardia	10047302

Hepatic disorders SMQ

MedDRA v25.0	MedDRA v25.0 code
The case will be included in this subgroup if it contains an event within the "Hepatic disorders" SMQ.	
5'nucleotidase increased	10000028
Accessory liver lobe	10052752
Acquired antithrombin III deficiency	10074561
Acquired factor IX deficiency	10082747
Acquired factor V deficiency	10086006
Acquired factor VIII deficiency	10082745
Acquired factor XI deficiency	10082746
Acquired hepatocerebral degeneration	10080860
Acquired protein S deficiency	10068370
Acute fatty liver of pregnancy	10000746
Acute graft versus host disease in liver	10066263
Acute hepatic failure	10000804
Acute hepatitis B	10059193
Acute hepatitis C	10065051
Acute on chronic liver failure	10077305
Acute yellow liver atrophy	10070815
Adenoviral hepatitis	10056885
Alagille syndrome	10053870
Alanine aminotransferase abnormal	10001547
Alanine aminotransferase increased	10001551
Alcoholic encephalopathy	10085656
Alcoholic liver disease	10001627
Allergic hepatitis	10071198
Alloimmune hepatitis	10080576
Ammonia abnormal	10001942
Ammonia increased	10001946
Anorectal varices	10068924
Anorectal varices haemorrhage	10068925
Anti factor X activity abnormal	10077670
Anti factor X activity decreased	10077674
Anti factor X activity increased	10077671
Anti-liver cytosol antibody type 1 positive	10086970
Antithrombin III decreased	10049547
Ascites	10003445
Aspartate aminotransferase abnormal	10003477
Aspartate aminotransferase increased	10003481
AST to platelet ratio index increased	10084175
AST/ALT ratio abnormal	10082832
Asterixis	10003547
Asymptomatic viral hepatitis	10063838
Autoimmune hepatitis	10003827
Bacterascites	10068547
Benign hepatic neoplasm	10004269

Benign hepatobiliary neoplasm	10077922
Benign recurrent intrahepatic cholestasis	10087038
Bile output abnormal	10051344
Bile output decreased	10051343
Biliary ascites	10074150
Biliary cirrhosis	10004659
Biliary fibrosis	10004664
Bilirubin conjugated abnormal	10067718
Bilirubin conjugated increased	10004685
Bilirubin excretion disorder	10061009
Bilirubin urine present	10077356
Biopsy liver abnormal	10004792
Blood alkaline phosphatase abnormal	10059571
Blood alkaline phosphatase increased	10059570
Blood bilirubin abnormal	10058477
Blood bilirubin increased	10005364
Blood bilirubin unconjugated increased	10005370
Blood cholinesterase abnormal	10005429
Blood cholinesterase decreased	10005430
Blood fibrinogen abnormal	10005518
Blood fibrinogen decreased	10005520
Blood thrombin abnormal	10005818
Blood thrombin decreased	10005820
Blood thromboplastin abnormal	10005824
Blood thromboplastin decreased	10005826
Bromosulphthalein test abnormal	10006408
Cardiohepatic syndrome	10082480
Cerebrohepatorenal syndrome	10053684
Child-Pugh-Turcotte score abnormal	10077020
Child-Pugh-Turcotte score increased	10068287
Cholaemia	10048611
Cholangiosarcoma	10077861
Cholestasis	10008635
Cholestasis of pregnancy	10049055
Cholestatic liver injury	10067969
Cholestatic pruritus	10064190
Chronic graft versus host disease in liver	10072160
Chronic hepatic failure	10057573
Chronic hepatitis	10008909
Chronic hepatitis B	10008910
Chronic hepatitis C	10008912
Cirrhosis alcoholic	10009208
Coagulation factor decreased	10009736
Coagulation factor IX level abnormal	10061770
Coagulation factor IX level decreased	10009746
Coagulation factor V level abnormal	10061771
Coagulation factor V level decreased	10009754
Coagulation factor VII level abnormal	10061772
Coagulation factor VII level decreased	10009761

Coagulation factor X level abnormal	10061774
Coagulation factor X level decreased	10009775
Coma hepatic	10010075
Complications of transplanted liver	10010186
Computerised tomogram liver abnormal	10078360
Congenital absence of bile ducts	10010317
Congenital hepatic fibrosis	10056533
Congenital hepatitis B infection	10010496
Congenital hepatitis C infection	10084252
Congenital hepatobiliary anomaly	10061065
Congenital hepatomegaly	10051130
Congenital viral hepatitis	10084251
Congestive hepatopathy	10084058
Cryptogenic cirrhosis	10063075
Cystic fibrosis hepatic disease	10068289
Cytokeratin 18 increased	10068471
Cytomegalovirus hepatitis	10011830
Deficiency of bile secretion	10071634
Diabetic hepatopathy	10071265
Dilatation intrahepatic duct congenital	10013003
Drug-induced liver injury	10072268
Duodenal varices	10051010
Fatty liver alcoholic	10016262
Flood syndrome	10084797
Focal nodular hyperplasia	10052285
Foetor hepaticus	10052554
Galactose elimination capacity test abnormal	10059710
Galactose elimination capacity test decreased	10059712
Gallbladder varices	10072319
Gamma-glutamyltransferase abnormal	10017688
Gamma-glutamyltransferase increased	10017693
Gastric variceal injection	10076237
Gastric variceal ligation	10076238
Gastric varices	10051012
Gastric varices haemorrhage	10057572
Gastrooesophageal variceal haemorrhage prophylaxis	10066597
Gianotti-Crosti syndrome	10053842
Glutamate dehydrogenase increased	10049483
Glycocholic acid increased	10080824
Glycogen storage disease type I	10018464
Glycogen storage disease type III	10053250
Glycogen storage disease type IV	10053249
Glycogen storage disease type VI	10053240
Graft versus host disease in liver	10064676
Granulomatous liver disease	10018704
Guanase increased	10051333
Haemangioma of liver	10018821
Haemorrhagic ascites	10059766
Haemorrhagic hepatic cyst	10067796

HBV-DNA polymerase increased	10058937
Hepaplastin abnormal	10019621
Hepaplastin decreased	10019622
Hepatectomy	10061997
Hepatic adenoma	10019629
Hepatic amoebiasis	10063741
Hepatic angiosarcoma	10067388
Hepatic artery flow decreased	10068997
Hepatic atrophy	10019637
Hepatic calcification	10065274
Hepatic cancer	10073069
Hepatic cancer metastatic	10055110
Hepatic cancer recurrent	10073070
Hepatic cancer stage I	10059318
Hepatic cancer stage II	10059319
Hepatic cancer stage III	10059324
Hepatic cancer stage IV	10059325
Hepatic candidiasis	10049653
Hepatic cirrhosis	10019641
Hepatic cyst	10019646
Hepatic cyst infection	10051705
Hepatic cyst ruptured	10053973
Hepatic cytolysis	10049199
Hepatic echinococciasis	10019659
Hepatic encephalopathy	10019660
Hepatic encephalopathy prophylaxis	10066599
Hepatic enzyme abnormal	10062685
Hepatic enzyme decreased	10060794
Hepatic enzyme increased	10060795
Hepatic failure	10019663
Hepatic fibrosis	10019668
Hepatic fibrosis marker abnormal	10074084
Hepatic fibrosis marker increased	10074413
Hepatic function abnormal	10019670
Hepatic gas gangrene	10077055
Hepatic haemangioma rupture	10054885
Hepatic hamartoma	10079685
Hepatic hydrothorax	10067365
Hepatic hypertrophy	10076254
Hepatic hypoperfusion	10084751
Hepatic infection	10056522
Hepatic infection bacterial	10065215
Hepatic infection fungal	10065217
Hepatic infection helminthic	10065216
Hepatic infiltration eosinophilic	10064668
Hepatic lesion	10061998
Hepatic lipoma	10086088
Hepatic lymphocytic infiltration	10079686
Hepatic mass	10057110

Hepatic necrosis	10019692
Hepatic neoplasm	10019695
Hepatic neuroendocrine tumour	10085864
Hepatic pain	10019705
Hepatic perfusion disorder	10083840
Hepatic sarcoma	10086958
Hepatic sequestration	10066244
Hepatic steato-fibrosis	10077215
Hepatic steatosis	10019708
Hepatic vascular resistance increased	10068358
Hepatic venous pressure gradient abnormal	10083172
Hepatic venous pressure gradient increased	10083171
Hepatitis	10019717
Hepatitis A	10019719
Hepatitis A antibody abnormal	10019722
Hepatitis A antibody positive	10019725
Hepatitis A antigen positive	10058751
Hepatitis A immunity confirmed	10086044
Hepatitis A virus test positive	10070216
Hepatitis acute	10019727
Hepatitis alcoholic	10019728
Hepatitis B	10019731
Hepatitis B antibody abnormal	10019733
Hepatitis B antibody positive	10019736
Hepatitis B antigen positive	10063411
Hepatitis B core antibody positive	10071344
Hepatitis B core antigen positive	10052328
Hepatitis B DNA assay positive	10060047
Hepatitis B DNA increased	10068379
Hepatitis B e antibody positive	10071348
Hepatitis B e antigen positive	10052329
Hepatitis B immunity confirmed	10086043
Hepatitis B reactivation	10058827
Hepatitis B surface antibody positive	10071346
Hepatitis B surface antigen positive	10019742
Hepatitis B virus test positive	10070217
Hepatitis C	10019744
Hepatitis C antibody positive	10019747
Hepatitis C core antibody positive	10077052
Hepatitis C RNA increased	10068377
Hepatitis C RNA positive	10019750
Hepatitis C virus test positive	10070218
Hepatitis cholestatic	10019754
Hepatitis chronic active	10019755
Hepatitis chronic persistent	10019759
Hepatitis D	10019762
Hepatitis D antibody positive	10059528
Hepatitis D antigen positive	10058436
Hepatitis D RNA positive	10059540

Hepatitis D virus test positive	10070626
Hepatitis E	10019768
Hepatitis E antibody abnormal	10057994
Hepatitis E antibody positive	10057985
Hepatitis E antigen positive	10060049
Hepatitis E immunity confirmed	10086045
Hepatitis E RNA positive	10086906
Hepatitis E virus test positive	10070220
Hepatitis F	10019771
Hepatitis fulminant	10019772
Hepatitis G	10019773
Hepatitis H	10019776
Hepatitis infectious mononucleosis	10019781
Hepatitis mumps	10019783
Hepatitis neonatal	10019785
Hepatitis non-A non-B	10019786
Hepatitis non-A non-B non-C	10019787
Hepatitis post transfusion	10019791
Hepatitis syphilitic	10019794
Hepatitis toxic	10019795
Hepatitis toxoplasmal	10019798
Hepatitis viral	10019799
Hepatitis viral test positive	10072748
Hepatobiliary cancer	10073073
Hepatobiliary cancer in situ	10073074
Hepatobiliary cyst	10079889
Hepatobiliary disease	10062000
Hepatobiliary infection	10056523
Hepatobiliary neoplasm	10061203
Hepatobiliary scan abnormal	10066195
Hepatoblastoma	10062001
Hepatoblastoma recurrent	10019823
Hepatocellular carcinoma	10073071
Hepatocellular damage neonatal	10019834
Hepatocellular foamy cell syndrome	10053244
Hepatocellular injury	10019837
Hepato-lenticular degeneration	10019819
Hepatomegaly	10019842
Hepatopulmonary syndrome	10052274
Hepatorenal failure	10019845
Hepatorenal syndrome	10019846
Hepatosplenic abscess	10077631
Hepatosplenic candidiasis	10051590
Hepatosplenomegaly	10019847
Hepatosplenomegaly neonatal	10019848
Hepatotoxicity	10019851
Hereditary haemochromatosis	10057873
Herpes simplex hepatitis	10067389
Hyperammonaemia	10020575

Hyperbilirubinaemia	10020578
Hyperbilirubinaemia neonatal	10020580
Hypercholia	10051924
Hyperfibrinolysis	10074737
Hypertransaminasaemia	10068237
Hypoalbuminaemia	10020942
Hypocoagulable state	10020973
Hypofibrinogenaemia	10051125
Hypoprothrombinaemia	10021085
Hypothrombinaemia	10058517
Hypothromboplastinaemia	10058518
Icterus index increased	10021209
Immune-mediated cholangitis	10083406
Immune-mediated hepatic disorder	10083521
Immune-mediated hepatitis	10078962
Increased liver stiffness	10082444
International normalised ratio abnormal	10022592
International normalised ratio increased	10022595
Intestinal varices	10071502
Intestinal varices haemorrhage	10078058
Intrahepatic portal hepatic venous fistula	10072629
Ischaemic hepatitis	10023025
Jaundice	10023126
Jaundice cholestatic	10023129
Jaundice hepatocellular	10023136
Jaundice neonatal	10023138
Kayser-Fleischer ring	10023321
Kernicterus	10023376
Leucine aminopeptidase increased	10024275
Liver abscess	10024652
Liver and pancreas transplant rejection	10051603
Liver carcinoma ruptured	10050842
Liver dialysis	10076640
Liver disorder	10024670
Liver function test abnormal	10024690
Liver function test decreased	10077677
Liver function test increased	10077692
Liver induration	10052550
Liver injury	10067125
Liver iron concentration abnormal	10074352
Liver iron concentration increased	10074354
Liver opacity	10084071
Liver operation	10062040
Liver palpable	10075895
Liver sarcoidosis	10068664
Liver scan abnormal	10061947
Liver tenderness	10024712
Liver transplant	10024714
Liver transplant failure	10083175

Liver transplant rejection	10024715
Liver-kidney microsomal antibody positive	10060107
Lupoid hepatic cirrhosis	10025129
Lupus hepatitis	10067737
Magnetic resonance imaging hepatobiliary abnormal	10085121
Magnetic resonance proton density fat fraction measuremen	10082443
Mitochondrial aspartate aminotransferase increased	10064712
Mixed hepatocellular cholangiocarcinoma	10027761
Mixed liver injury	10066758
Model for end stage liver disease score abnormal	10077291
Model for end stage liver disease score increased	10077292
Molar ratio of total branched-chain amino acid to tyrosine	10066869
Multivisceral transplantation	10082450
Necrolytic acral erythema	10084061
Neonatal cholestasis	10056528
Neonatal hepatomegaly	10049995
Nodular regenerative hyperplasia	10051081
Non-alcoholic fatty liver	10029530
Non-alcoholic steatohepatitis	10053219
Non-cirrhotic portal hypertension	10077259
Ocular icterus	10058117
Oedema due to hepatic disease	10049631
Oesophageal varices haemorrhage	10030210
Omental oedema	10087030
Osteopontin increased	10082708
Parenteral nutrition associated liver disease	10074151
Perihepatic discomfort	10054125
Perinatal HBV infection	10075233
Peripancreatic varices	10073215
Periportal oedema	10068821
Peritoneal fluid protein abnormal	10069000
Peritoneal fluid protein decreased	10068999
Peritoneal fluid protein increased	10068998
Peritoneovenous shunt	10052716
Pneumobilia	10066004
Polycystic liver disease	10048834
Porphyria acute	10036182
Porphyria non-acute	10036186
Portal fibrosis	10074726
Portal hypertension	10036200
Portal hypertensive colopathy	10079446
Portal hypertensive enteropathy	10068923
Portal hypertensive gastropathy	10050897
Portal pyaemia	10036202
Portal shunt	10036204
Portal shunt procedure	10077479
Portal tract inflammation	10075331
Portal vein cavernous transformation	10073979
Portal vein dilatation	10073209

Portal vein flow decreased	10067337
Portal vein pressure increased	10064936
Portal venous system anomaly	10076609
Portopulmonary hypertension	10067281
Primary biliary cholangitis	10080429
Progressive familial intrahepatic cholestasis	10076033
Protein C decreased	10037005
Protein S abnormal	10051736
Protein S decreased	10051120
Prothrombin level abnormal	10037048
Prothrombin level decreased	10037050
Prothrombin time abnormal	10037057
Prothrombin time prolonged	10037063
Prothrombin time ratio abnormal	10061918
Prothrombin time ratio increased	10037068
Radiation hepatitis	10051015
Regenerative siderotic hepatic nodule	10080679
Renal and liver transplant	10052279
Retinol binding protein decreased	10048473
Retrograde portal vein flow	10067338
Reye's syndrome	10039012
Reynold's syndrome	10070953
Schistosomiasis liver	10039610
Small-for-size liver syndrome	10069380
Spider naevus	10041519
Splenic artery embolisation	10083795
Splenic varices	10067823
Splenic varices haemorrhage	10068662
Splenorenal shunt	10041661
Splenorenal shunt procedure	10077281
Spontaneous bacterial peritonitis	10061135
Spontaneous intrahepatic portosystemic venous shunt	10076239
Steatohepatitis	10076331
Stomal varices	10075186
Subacute hepatic failure	10056956
Sugiura procedure	10083010
Sustained viral response	10076041
Thrombin time abnormal	10051319
Thrombin time prolonged	10051390
Total bile acids increased	10064558
Transaminases abnormal	10062688
Transaminases increased	10054889
Ultrasound liver abnormal	10045428
Urine bilirubin increased	10050792
Urobilinogen urine decreased	10070480
Urobilinogen urine increased	10070479
Varices oesophageal	10056091
Varicose veins of abdominal wall	10072284
Viral hepatitis carrier	10047458

Weil's disease	10047903
White nipple sign	10078438
Withdrawal hepatitis	10071220
X-ray hepatobiliary abnormal	10056536
Yellow skin	10048245
Zieve syndrome	10048255

14.5 Definitions of marked abnormalities

Where more than one assessment falls on the same day, the scheduled assessment is used above any non-scheduled (repeat or re-test or local) assessment for that parameter.

Laboratory analyses are based central laboratory data.

Marked laboratory abnormalities are displayed in Table 9, as described in the company standards

Table 9 Marked abnormalities in laboratory parameters for reporting

Laboratory parameter	Criteria for marked laboratory abnormalities
Hematology (SI unit)	
Hemoglobin (g/L)	< 80 < 100 > 20 above ULN or > 20 above baseline if baseline > ULN > 40 above ULN or > 40 above baseline if baseline > ULN
Hematocrit (L/L)	< 0.20 < 0.32 (Male) or < 0.28 (Female) > 0.60 (Male) or > 0.55 (Female) > 0.65
Platelets (10^9/L)	< 50 < 75 > 600 > 999
Leukocytes (10^9/L)	< 2.0 < 3.0 > 20.0 > 100.0
Lymphocytes (10^9/L)	< 0.5 < 0.8 > 4.0 > 20.0
Blood chemistry (SI unit)	
Alkaline phosphatase (U/L)	> 2.5 × ULN > 5 × ULN
Alanine aminotransferase (U/L)	> 3 × ULN > 5 × ULN > 8 × ULN > 10 × ULN
Aspartate aminotransferase (U/L)	> 3 × ULN > 5 × ULN

Laboratory parameter	Criteria for marked laboratory abnormalities
	> 8 × ULN > 10 × ULN
Total bilirubin (µmol/L)	> 2 × ULN > 5 × ULN
Creatinine (µmol/L)	> 1.5 × ULN or > 1.5 × baseline if baseline < ULN > 3 × ULN or > 3 × baseline if baseline < ULN
Potassium (mmol/L)	< 3.0 < 3.2 > 5.5 > 6.0
Sodium (mmol/L)	< 130 > 150 > 155
Gamma-glutamyl transferase (U/L)	> 2.5 × ULN > 5 × ULN
Urea nitrogen (mmol/L)	> 2.5 × ULN > 5 × ULN

SI = standard international; ULN = upper limit of normal.