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BAF312

CBAF312X2207 / NCT03338998

A phase II, patient and investigator-blinded, randomized, placebo-controlled study to evaluate efficacy, safety and tolerability of BAF312 in patients with stroke due to intracerebral hemorrhage (ICH)

Statistical Analysis Plan (SAP)

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List of tables

List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
aPHE	absolute Perihematoma Edema
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
BMI	Body Mass Index
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
C-SSRS	Columbia-Suicide Severity Rating Scale
DBL	Database Lock
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
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FAS	Full Analysis Set
FIR	First Interpretable Results
GCS	Glasgow Coma Scale
HLT	High level terms
i.v.	Intravenous
IA	Interim Analysis
ICH	Intracerebral hemorrhage
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MedDRA	Medical Dictionary for Drug Regulatory Affairs
mRS	modified Rankin Scale
NF-L	Neurofilament light
NIBR	Novartis Institute for BioMedical Research
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PAS	Pharmacokinetics Analysis Set
PDT	Programming Deliverables Tracker
PHE	Perihematoma Edema
PK	Pharmacokinetics
PPS	Per-Protocol Set
PT	Preferred Terms
p.o.	Oral
PRO	Patient-reported Outcomes
QD	Qua'que di'e / once a day
RAP	Report and Analysis Process
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SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System

SOPs	Standard Operating Procedures
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TFLs	Tables, Figures, Listings

WHO	World Health Organization

1 Introduction

1.1 Scope of document

This document details the planned statistical analysis for data collected in the study CBAF312X2207.

Clinical Study Report (CSR) deliverables (tables, figures, listings - TFLs) and further programming specifications are described in separate documents.

This statistical analysis plan (SAP) describes the primary analysis for which a CSR is planned. Interim analyses (IA) may be conducted to support decision making concerning the current clinical study. Nevertheless, a Data Monitoring Committee (DMC) will review unblinded safety and efficacy data on a regular basis and three DMC is planned for this study.

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1.2 Study reference documentation

The SAP is finalized under the amended study protocol version v02 dated on 25-Mar-2019.

The Novartis Institutes for BioMedical Research (NIBR) standard SAP and TLFs shells templates version Final 3.0, 24-Mar-2017 (Effective 3-Apr-2017) and Final 3.0, 04-Jul-2017 (Effective 01-Aug-2017), are respectively used.

The electronic Case Report Form (eCRF) version 5.0 dated on 11-Nov-2019 version is used for TLFs shells development. The DMC charter used for this study is: nibr-BAF312 DMC charter.pdf dated 28-Aug-2020.

1.3 Study objectives

The purpose of the study is to investigate the initial efficacy and safety of BAF312 administered on top of standard-of-care compared to placebo in patients with stroke due to ICH; and to determine if the overall clinical profile of BAF312 warrants further clinical development in ICH.

1.3.1 Primary objective

Primary objective	Endpoints related to primary objective	Analysis
To obtain the first efficacy estimate of CCI BAF312 daily (7 days i.v. with titration followed by 7 days p.o.) compared to placebo on reducing absolute perihematoma edema (aPHE) volume on Day 14 after ICH.	aPHE volume measured by CT scan on Day 14 after ICH	

1.3.2 Secondary objective

The secondary objectives are:

Secondary objective(s)	Endpoints related to secondary objective(s)	Analysis

To assess the safety profile of BAF312 in ICH patients.	Continuous assessment of Adverse events (AEs)/Serious AEs during the course of the study (90 days).	Refer SAP section 5.2
To evaluate the pharmacokinetics (PK) of BAF312 in ICH patients.	PK measurements of plasma BAF312 concentrations at 0.5, 2 and 6 h after start of infusion during i.v. titration on Day 1; and before p.o. dosing on Days 8 and 14.	Refer SAP section 5.2 and Section 6

1.3.3 Exploratory objective(s)

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1.4 Study design and treatment

This is a randomized, patient- and investigator-blinded, placebo-controlled, parallel group study of BAF312 (siponimod) on top of standard-of-care for intracerebral hemorrhage (ICH), consisting of 3 epochs: **Screening/Baseline, Treatment, and Follow-Up** as indicated in Figure 1-1.

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Approximately 33 patients per treatment group (~65 patients in total) will be randomized, with an expected drop-out rate of approximately 10% to obtain at least 60 completed study subjects (Day 14). Patients will be assigned to one of the following 2 treatment arms, BAF312 or Placebo, in a ratio of 1:1.

Reduction of perihematoma edema (PHE) measured by CT imaging at 14 days after ICH is the primary endpoint for measuring BAF312 efficacy in this study.

Regular DMC will occur in order to provide recommendations to the sponsor to continue the trial according to the protocol and any relevant amendments, or to make changes or adjustments to the study.

2 First interpretable results (FIR)

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3 Interim/DMC analyses

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4 Statistical methods

4.1 Analysis sets

All randomized subjects:

They correspond to all patients included in the study who fulfilled the inclusion/exclusion criteria.

Full Analysis Set (FAS):

The FAS will include all patients who are randomized and received any amount of study drug.

Safety Set (SAF):

The Safety Analysis Set will include all patients that received any amount of study drug.

Per Protocol Set (PPS):

The PPS will include all patients in the FAS having received at least 2 full days of I.V. treatment and no protocol deviations listed in Table 4.1 with relevant impact on efficacy data.

PK Analysis Set (PAS):

The PAS will include all patients with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations listed in table 4.1 with relevant impact on PK data.

For all analysis sets, patients will be analyzed per the study treatment(s) received.

All listings will use Randomized patients.

Frequency counts and percentages (using FAS as denominator) of patients in each of the above defined analysis sets will be summarized. In addition, listings of patients excluded from each of the analysis sets will be provided.

The analysis sets and protocol deviation are related to this study as follows:

Table 4-1 Protocol deviation and analysis sets

Text description of deviation
Subjects are excluded from Per protocol analysis set in case of these PDs:
• Any protocol deviation from the category “Eligibility and Entry Criteria” which are all at least major (except if not considered by clinical team before the database lock).

Text description of deviation
• Any protocol deviation from the category “IP Compliance” corresponding to the major or critical deviation below: ▪ Wrong medication pack dispensed resulting in injection of placebo during the whole i.v. phase followed by intake of BAF312 in the oral part. • Any intake of prohibited medication corresponding to a protocol deviation category “Concomitant Medications Criteria” and taken during a certain period and likely to impact efficacy analysis.

Subjects are excluded from PK analysis in case of same PDs as PPS except
• Any intake of prohibited medication corresponding to a protocol deviation category “Concomitant Medications Criteria” and taken during a certain period and likely to impact PK analysis.

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to data base lock (DBL). The list of deviation will be review regularly to make sure the analysis set definition is as needed.

Prior to the locking of the database for final blind data reviews a blinded data review report will be written in order to establish analysis set assignment and to identify the potential reason(s) for exclusion of subjects from one or more of the analysis sets. As one of the criteria will request unblinded information a second version of the blind data review report will be created post database lock in order to indicate the final analysis set assignment as per IQVIA best practice.

4.2 Data analysis general information:

Data will be analyzed by IQVIA Biostatistics and Statistical Programming personnel according to the data analysis section 11 of the study protocol as detailed in this analysis plan. IQVIA standard operating procedures (SOPs) will be followed and some of the Novartis SOPs will be used, if deemed appropriate. Few analyses may be performed by NIBR Biostatistics group which is specified in advance in appropriate section.

SAS® version 9.4 (or later version if available at time of database lock) will be used for all analyses.

Data from all patients who signed informed consent will be used in the analysis; no center effect will be assessed as it is expected to have small sample size of enrollment at each individual centers. Each analysis will use all data in the database up to the analysis cut-off date, determined prior to database lock.

General presentation of descriptive summaries and listings

The following summary statistics will be presented unless otherwise stated specifically. Qualitative/categorical data (e.g., gender, race) will be summarized by frequency counts and percentages. Percentages will be calculated using the number of patients in the relevant treatment arm or subgroup as the denominator.

Continuous data (e.g., age, body weight) will be summarized using appropriate descriptive statistics (i.e. mean, standard deviation (SD), lower quartile (q1), median, upper quartile (q3),

minimum, and maximum) by treatment arm. Based on the nature of the data, few analyses requires additional statistics such as geometric mean, geometric coefficient of variation (CV) and it will be specifically requested respective section.

In general, listings will be presented

- with country/center/subject identifier and age/sex/race as a mandatory column unless otherwise specified
- by treatment and patient

4.3 Subgroup of interest -

Result to swallowing test (success or fail) will be used as a covariate and as a subgroup for descriptive summary of mRS score.

4.4 General definitions

Study Treatment:

Patients will be assigned to one of the two treatment (BAF312/Placebo) arms in a ratio of 1:1. Study treatment will be noted as BAF312/Placebo throughout this document and CSR deliverables.

Patients and investigators (including all site staff) will remain blinded to study treatment throughout the study.

Study Day:

The study day for safety/efficacy assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, Electrocardiogram (ECG), PK sampling mRS scores, etc.,) will be calculated using the first administration of i.v. dose date as the reference date. For assessments occurring:

on or after the first administration of i.v. dose date, the study day will be calculated as (date of assessment/occurrence) – (date of first administration of i.v. dose) + 1. Then study day 1 will be the day of first administration of i.v. dose.

before the first administration of i.v. dose date, the study day will be calculated as (date of assessment/occurrence) – (date of first administration of i.v. dose).

For example, if a serious adverse event starts 1 day before the first administration of i.v. dose date, the study day displayed on the listing will be negative, i.e. -1.

Baseline:

For all evaluations, the last available assessment before or on the date/time of first dose is taken as 'baseline' value or 'baseline' assessment.

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Unscheduled Assessment:

In general, descriptive summary statistics will not include unscheduled/repeat assessment.

For all analyses regarding abnormal assessments or analyses based on worst post–baseline value (e.g. laboratory, ECGs, vital signs), all post-baseline values will be included (scheduled, unscheduled, repeat). All unscheduled and repeat measurements will be included in listings.

Analysis visit window:

No time-window will be applied in this study.

In summary by visit the scheduled EOS visit will be included. If appropriate EOS visit could be mapped to the next scheduled visit.

On treatment:

It corresponds to any event or any assessment occurring between the 1st study drug injection date and the last injection/intake date.

5 Statistical methods for primary objective

5.1 Primary objective

To obtain the first efficacy estimate of CCI BAF312 daily (7 days i.v. with titration followed by 7 days p.o.) compared to placebo on reducing absolute perihematoma edema (aPHE) volume on Day 14 after ICH.

5.1.1 Variables

The primary efficacy variable is the aPHE volume measured on Day 14, which. will be measured from the CT images by a central reading lab.

The primary analysis will be done on the PPS. A sensitivity analysis will be done on the FAS.

5.1.2 Descriptive analyses

Summary statistics of aPHE will be presented by treatment at Day 14 in the same output as the inferential result.

5.1.3 Statistical model, assumptions and hypotheses

It is expected that the distribution of aPHE is right-skewed (as it is a positive-valued measurement), so a log-transformation will be applied. The log-transformed absolute PHE volume on Day 14 will be analyzed using analysis of covariance (ANCOVA) model, with

treatment as a classification factor and the baseline log-transformed aPHE as covariate. The mean difference (BAF312 vs. placebo) and its two-sided 90% CI will be calculated, and these estimates will be back-transformed to give adjusted geometric mean and the respective CV along with a geometric mean ratio and two-sided 90% CI of BAF312 vs. placebo. One-sided p-value will be provided to test superiority of BAF312 to placebo.

5.1.3.1 Handling of Missing Data

Every effort will be made to obtain complete data during clinical conduct of the study.

The analysis will be done on the available data recorded on the Day 14 CT scan.

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5.1.3.2 Supportive Analyses

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5.1.3.3 Graphical presentation of results

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Percentage of ordinal mRS score at Day 90 will be displayed by treatment.

5.2 Secondary objectives

The secondary objectives are to assess the safety profile, and to evaluate the pharmacokinetics of BAF312 in ICH patients.

5.2.1 Variables

- Safety profile of BAF312 in ICH patients will be evaluated by continuous assessment of AEs/SAEs during the course of the study (90 days). Safety set will be used for this analysis.
- PK of BAF312 in ICH patients will be evaluated by PK measurements of plasma BAF312 concentrations at 0.5, 2 and 6 h after start of infusion during i.v. titration on Day 1; and before p.o. dosing on Days 8 and 14. PK Analysis set will be used.

5.2.2 Descriptive analyses

Both secondary endpoints are descriptive in nature, there will not be any inferential statistics presented. Descriptive statistics will be presented for concentration vs time by treatment arm.

5.2.3 Statistical model, assumptions and hypotheses

The analyses will be descriptive. No hypothesis will be tested.

Safety profile of BAF312:

The incidence of any treatment emergent adverse events (TEAEs), serious TEAEs overall and by severity will be summarized by treatment using frequency counts, percentages of patients and 95% Confidence Intervals (CIs) for percentages obtained using Clopper – Pearson method.

Treatment emergent adverse events are defined as any event starting or worsening on treatment (i.e. between the 1st study drug injection date and the last study drug injection/intake date).

These secondary safety endpoints will be summarized by treatment arm for the safety analysis set.

PK of BAF312:

Refer SAP section 6.

5.2.3.1 Model checking procedures

There will be no imputation for missing values.

5.2.3.2 Graphical presentation of results

Graphical presentation may be provided for most frequent TEAEs sorted by relative risk. For PK, refer section 6.

6 Statistical methods for Pharmacokinetic (PK) parameters

One of the secondary objectives is to evaluate the pharmacokinetics of BAF312 in ICH patients.

6.1 Secondary Objective:

PK of BAF312 in ICH patients will be evaluated by PK measurements of plasma BAF312 concentrations at 0.5, 2 and 6 h after start of infusion during i.v. titration on Day 1; and before p.o. dosing on Days 8 and 14. All PK analyses will be performed based on the PAS.

6.2 Variables

As only sparse PK samples will be collected in the study, no PK parameters will be estimated. PK samples will be pooled with PK data of other available studies in order to assess the effect of various covariates on the plasma concentrations of BAF312 in patients with stroke due to ICH through a population pharmacokinetic analysis and it is not scope of this SAP.

Only evaluable PK concentration data will be used in the analyses and summary statistics.

Unscheduled samples will not be used for descriptive statistics. It will be flagged in the corresponding concentration listing.

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6.3 Descriptive analyses

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Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below the limit of quantification will be treated as zero in summary statistics and excluded from geometric mean and geometric Coefficient of Variation (CV%) computation. Linear mean concentration vs. time will be graphically presented. In addition, individual patient concentration vs. time will also be presented.

BAF312 plasma concentration data will be listed by treatment, patient, and visit/sampling time point. All individual data will be listed on all randomized subjects and those excluded from the PK analysis will be flagged. Statistical model, assumptions and hypotheses

The analyses will be descriptive. No hypothesis will be tested.

7 Exploratory objectives

7.1.1 Variables

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7.1.2 Descriptive analyses

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8 Statistical methods for safety and tolerability data

The following safety analyses will be performed based on the Safety Set.

8.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

8.2 Descriptive analyses

Subject demographics and other baseline characteristics

The FAS will be used for all patient demographic and baseline characteristic summaries and listings, unless otherwise specified.

All data for background and demographic variables will be listed by treatment and patient. Summary statistics will be provided by treatment. Descriptive statistics, frequency counts and percentages will be tabulated by treatment arm, as appropriate.

Baseline demographic includes following,

- Age (in years)
- Age category in years (<70; >=70)
- Sex (Male, Female)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other)
- Ethnicity (Hispanic or Latino, East Asian, Southeast Asian, South Asian, West Asian, Russian, Mixed Ethnicity, Not Reported, Unknown, Other)
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) – calculated as weight (kg) / (height (m))^2

Other baseline characteristics includes,

- Glasgow Coma Scale (GCS) total score
- GCS total score in categories (<13 a.u., >=13 a.u.)
- Baseline blood pressure includes systolic (mmHg), diastolic (mmHg), pulse (Beats/min), and Temperature (°C)

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- Baseline aPHE volume (mL)
- Baseline location of hematoma
- Time from first symptoms of ICH or last seen neurologically normal status (day). This time will be computed up to the start of study drug.

Patients who signed study informed consent and pharmacogenetic informed consent with date will be presented in listings by treatment and patient.

Medical History

Medical history and ongoing conditions will be listed by treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Patient disposition

The FAS will be used for the patient disposition summaries. The summary by treatment arm will show:

- Number (%) of randomized patients who were not treated;
- Number (%) of randomized patients who were treated;
- Number (%) of patients who completed the study treatment;
- Number (%) of patients who discontinued the study treatment;
- Reasons for study treatment discontinuation.

Frequency counts and percentages of patients for each of analysis set will be presented separately by treatment. Any protocol deviation (selection criteria not met, patient not withdrawn as per protocol, key procedures not performed as per protocol, treatment deviation, prohibited concomitant medication, other Good Clinical Practice (GCP) deviation) will be tabulated by the deviation type and treatment.

All protocol deviations will be presented in a listing by treatment and patient. Summary of protocol deviation with categories will be presented by treatment.

Data presented for screen failure patients

- Screen failure patients will not be included any analysis.

Study drug exposure and compliance

The total treatment lasts 14 days with two treatment phases (i.v. to p.o.) based on dose administration.

7 days of i.v. BAF312 with titration to the final daily dose Commercially Confidential Information

During the 7 days of i.v. infusion treatment, all patients must undergo a swallowing safety evaluation per the treating hospital's institutional guidelines and practices.

If the patients pass the swallowing safety evaluation, 7 days of CCI BAF312 p.o. QD.

Patients who do not successfully pass a swallowing safety evaluation must not be transitioned to the p.o. phase of treatment, and BAF312 must be discontinued after Day 7; but they should not be terminated from the study. These patients should continue to be followed as per the protocol assessment schedule.

Eligible patients who pass a swallowing safety evaluation will continue with 7-day p.o. phase of treatment with BAF312 CCI QD.

Information on the dose administration, amount, frequency (includes dose titration), reason for the dose change, start date and end date in eCRF pages collected for each of the treatment phase.

Overall study drug exposure, study drug exposure for individual phase (i.v. and p.o.) will be calculated as follows,

Overall drug exposure (days) =[date of last study treatment – date of first study treatment+1]

Study drug exposure in i.v. phase (days) =[date of last dose in i.v. phase– date of first dose in i.v. phase +1]

Study drug exposure in p.o. phase (days) =[date of last dose in p.o. phase– date of first dose in p.o. phase +1]

Overall drug exposure, study drug exposure in i.v. and p.o. phase will be summarized by treatment. In addition, frequency counts and percentages of patients who have dose decreases, increases in planned dose or dose interruptions, the corresponding reasons and average length of dose interruptions will be summarized separately for i.v. phase and p.o. phase.

Listing of drug administration will be presented with i.v. treatment phase on day 1-7 and another listing for p.o. phase on day 8-14.

During the 7 days of i.v. infusion treatment, all patients will undergo a swallowing safety evaluation. A listing will be provided for swallowing test by treatment.

Compliance using pill count in p.o. phase:

Study drug compliance of patients who transitioned from i.v. to p.o. phase will be evaluated using “Drug Accountability Oral Medication” eCRF page.

The relative consumed tablet count (%) is defined as the ratio of total count consumed to total count prescribed. Where the total count consumed is calculated as the sum of counts dispensed minus the sum of counts returned and where the prescribed count corresponds to the count prescribed by the investigator for a p.o. phase that the patient should have taken during this phase.

The relative consumed tablet will be summarized by treatment.

Prior, concomitant and post therapies

Prior and concomitant therapies are defined as any medication, and significant non-drug therapies administered to a subject preceding or coinciding with the study assessment period.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List (WHO DRL), which employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Concomitant therapies will include medications and significant non-drug therapies taken during treatment phase. Prior therapies will include medications or significant non-drug therapies starting and ending prior to the start of study treatment.

Concomitant and prior therapies will be summarized by ATC class, preferred term and treatment arm using safety set. Medications starting prior to the start of study treatment and continuing after the start of study treatment will be counted in both summaries.

All prior and concomitant therapies will be listed.

Vital signs

Vital signs will include pulse rate, systolic and diastolic blood pressure in supine position and temperature which will be assessed at the all visits from screening/baseline to 90 days.

Summary statistics of vital sign results and change from baseline will be provided by treatment and visit/time.

Change from baseline will only be summarized for patients with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value.

Table 8-1 Notable vital signs and body weight

Vital Sign Variable	Notable Criteria
Pulse (beats/min)	>120 bpm or < 50 bpm
Systolic BP (mmHg)	≥ 160 mmHg or ≤ 90 mmHg
Diastolic BP (mmHg)	≥ 100 mmHg or ≤ 50 mmHg
Temperature (°C)	>38.3 °C/ 101°F
Body weight (kg)	More than 7% decrease from baseline weight

Listing will be provided with vital signs results and notable values will be flagged by treatment and patients. Box plot will be presented for each of vital sign parameter over visits by treatment.

ECG evaluations

Standard 12-lead ECGs will be performed for all patients at screening/baseline, day 1-3, day 7. ECGs measurement HR, PR, QT, QRS, and QTcF will be listed by treatment, patient and visit/time, abnormalities will be flagged. Summary statistics of raw value and change from baseline will be provided by treatment and visit/time.

Change from baseline will only be summarized for patients with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline values – baseline value.

Additionally, the number and proportion of patients with abnormal values below will be summarized:

- QT > 500 ms;
- QTcF > 500 ms;
- QTcF > 480 ms;

- QTc F> 450 ms;
- QTcF changes from baseline > 30 ms;
- QTcF changes from baseline > 30 ms and QTcF>450 ms;
- QTcF changes from baseline > 30 ms and QTcF>480 ms;
- QTcF changes from baseline > 30 ms and QTcF>500 ms;
- QTc changes from baseline > 60 ms;
- QTcF changes from baseline > 60 ms and QTcF>450 ms;
- QTcF changes from baseline > 60 ms and QTcF>480 ms;
- QTcF changes from baseline > 60 ms and QTcF>500 ms;
- HR decrease >25% to a HR <50 bpm
- HR increase >25% to a HR >100 bpm
- PR > 220 ms.
- PR increase >25% to PR >220 ms
- QRS>120 ms
- QRS increase > 25% to QRS > 120 ms

Cardiac monitoring will be performed from 1 hour before dosing and up to 48 hours after the first drug administration. Any abnormalities in the continuous monitoring (i.e., pre-dose to 48 hours) will be reported in AE eCRF page, but will not be presented separately in listings.

Clinical laboratory evaluations

Due to the emergency setting of the patient, screening/baseline laboratory evaluation can be performed by locally. A central laboratory will be used for all other timepoints for the analysis of all specimens collected.

Laboratory data from all sources (central and local laboratories) will be combined. All laboratory values will be converted into International System (SI) units.

Raw values as well as absolute and relative change from baseline values for hematology, biochemistry and urinalysis (quantitative and qualitative) laboratory parameters will be summarized descriptively per time point and treatment arm.

Urinalysis parameters will be listed.

Change from baseline will only be summarized for patients with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline values – baseline value

Shift tables based on normal ranges to compare baseline to the worst post-baseline value will be provided by parameter and treatment arm for hematology, biochemistry and urinary laboratory data.

A listing of all laboratory values with values flagged to show the corresponding range classifications (High, Low) relative to the laboratory reference ranges will be provided by laboratory category and treatment arm.

Normal ranges by laboratory parameter will be provided in a separate listing.

Liver event definition:

The liver event criteria Table 8-2 will be evaluated using clinical chemistry parameters.

Table 8-2 Liver event definition

Definition
ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN (Potential Hy's law cases)
ALT or AST > 3 × ULN and INR > 1.5
ALT or AST > 3 × ULN
ALP > 2 × ULN
AST = Aspartate aminotransferase; also known as SGOT, ALT = Alanine aminotransferase; also known as SGPT, INR=International Normalized Ratio, ALP = Alkaline phosphatase, TBL = Total bilirubin, DBL = conjugated (direct) bilirubin.

For all patients with liver values (AST, ALT, ALP, TBL) matching the thresholds of 5xULN or any criteria of the above table (Table 8-2), single patient LFT profile graphs will be generated showing all AST, ALT, ALP, TBL lab values reported for this study and the time of study treatment for these patients a listing of patients with these liver abnormalities will be provided.

Nephrotoxicity (Specific Renal Criterion)

Patients who meet renal toxicity criteria will be diagnosed/followed up and captured eCRF will be reported in listing as well as summarized.

Pregnancy test and assessments of fertility

Pregnancy testing will be done for all female patients of childbearing potential at screening/baseline and follow-up visits (Day 30 or Day 90). Listing will be produced by treatment and patients.

Adverse events (AEs)

All information obtained (e.g. relatedness to study drug, action taken etc.) on adverse events will be displayed by treatment and patient. AEs will be coded using the latest version of MedDRA available at the time of clinical database lock.

AEs summarized will be all events recorded during the study. Any AE with a missing start date will be considered as starting in the study.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A patient with multiple AEs within a body system is only counted once towards the total of this body system.

The following AE summaries will be produced by treatment:

- AEs, regardless of study drug relationship by primary system organ class and preferred term
- AEs, regardless of study drug relationship by primary system organ class and preferred term and severity
- AEs, regardless of study drug relationship by primary system organ class and preferred term and maximum CTCAE grade (all grades and grade 3/4)

- AEs, with suspected study drug relationship by primary system organ class and by preferred term
- Serious adverse events (SAEs), regardless of study drug relationship, by primary system organ class and preferred term
- SAEs, with suspected study drug relationship, by primary system organ class and preferred term
- AEs leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class and preferred term
- AEs requiring dose adjustment or study-drug interruption, regardless of study drug relationship, by primary system organ class and preferred term
- AEs requiring additional therapy, regardless of study drug relationship, by primary system organ class and preferred term
- Non-serious AEs (ie, AEs excluding serious AEs), regardless of study drug relationship, by primary system organ class and preferred term

Fatal AEs suspected to be related to study treatment will be provided by SOC and PT.

- Fatal SAEs regardless of study drug relationship will be provided by SOC and PT.

AEs will be summarized by presenting the number and percentage of patients having at least one AE, and having at least one AE by system organ class and/or preferred, severity and relation to study drug by treatment arm.

An overall summary of type of AEs (e.g. serious, leading to study drug discontinuation, requiring dose adjustment or/and interruption) will be presented by treatment (overall and severe). The overall summary will present the number and percentage of patients having at one AE and the occurrence of event. If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the (non missing) end date of the preceding AE and the (non missing) start date of the consecutive AE.
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE, or if start date or end date are missing.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block (e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE).

Any information collected (e.g. relation to study drug, action taken etc.) will be listed as well as the duration of the AE. If start date or end date is partially missing, it will be imputed as described in this SAP appendix, before to compute the duration of the AE.

The listings of all deaths, serious adverse events, adverse events leading to study drug discontinuation, and adverse events requiring dose adjustment or interruption will also be provided.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables will be provided by system organ class and preferred term on the safety set population. The first one will be on non-serious treatment emergent adverse events (non-serious TEAEs) with an incidence greater than 1%. The second one will be on serious treatment emergent adverse events (serious TEAEs) or SAEs suspected to be related to study treatment. These two tables will be produced by Novartis.

Deaths

Deaths will be summarized by primary system organ class and preferred term by treatment. Listing of all death will be produced for patient who signed informed consent and randomized.

Other safety evaluations

Not Applicable.

Immunogenicity

All immunogenicity results will be listed by subject and visit/time.

8.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be presented. An evaluation of Drug Induced Serious Hepatotoxicity (eDISH) plot will also be presented.

10 Sample size consideration

The detailed sample size calculation of primary and secondary endpoint provided in protocol section 11.7.

11 Reference list

[1] CPMP (2001) Points to consider on clinical investigation of medicinal products for the treatment of acute stroke. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003342.pdf

[2] D. Spiegelhalter, K. Abrams, J. Myles Bayesian Approaches to Clinical Trials and Health-Care Evaluation John Wiley & Sons, Malden MA (2004)

12 Appendix

12.1 SAS code

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

12.2 Definition of benefit for individual endpoints

Measurement	Endpoint	Direction of benefit*
Questionnaire	mRS	Decrease
	Commercially Confidential Information	
Computed tomography scan	HV	Decrease

* In the direction of

Personal Protected Data