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BAF312

Clinical Trial Protocol CBAF312X2207 / NCT03338998

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

Document type:	Amended Protocol Version
EUDRACT number:	2015-005738-23
Version number:	v02 (Clean)
Clinical Trial Phase:	II
Release date:	25-Mar-2019

Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not form part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO&PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

ACR	Albumin-creatinine ratio
AE	adverse event
AHA	American Heart Association
ALT	alanine aminotransferase
aPHE	absolute perihematoma edema
ASA	American Stroke Association
AST	aspartate aminotransferase
bICH	blood intracerebral hemorrhage model
cICH	collaginase intracerebral hemorrhage model
C-SSRS	Columbia Suicide Severity Rating Scale
CFR	U.S. Code of Federal Regulations
CMO&PS	Chief Medical Office & Patient Safety
CNS	Central nervous system
COAs	Clinical outcome assessments
CPK	Creatinine phosphokinase
CPRC	Clinical Pharmacology Review Committee
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CT	computed tomography, refers to X-ray CT in this study
CTCAE	Common Toxicity Criteria for Adverse Events
CV	coefficient of variation
DAR	dose administration record
DDE	direct data entry
DIBD	Development International Birth Date
DIC	Disseminated intravascular coagulation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRFs	Electronic case report forms
EDC	Electronic Data Capture
EMA	European Medicines Agency

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ESO	European Stroke Organisation
eSource	Electronic Source
EVD	External ventricular drain
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GEE	Generalized estimating equation
GGT	Gamma-glutamyl transferase
h	hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HR	heart rate
i.v.	Intravenous
IB	Investigators brochure
ICH	intracerebral hemorrhage
ICU	intensive care unit
IEC	Independent Ethics Committee
IN	Investigators notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
IVH	Intraventricular hemorrhage
LDL	Low-density lipoprotein
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MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)

mL	milliliter(s)
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NIHSS	National Institutes of Health Stroke Scale
NPO	nil per os, or nothing by mouth
oGS	Original Graeb Score
p.o.	Oral
PD	pharmacodynamic(s)
PHE	perihematoma edema
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PPS	per protocol set
PT	prothrombin time
QD	Once daily
QM	Quality management
rPHE	relative perihematoma edema
RRMS	Relapsing remitting multiple sclerosis
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBI	Traumatic brain injury
TBL	total bilirubin
ULN	upper limit of normal
VZV	varicella zoster virus
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Pharmacokinetic definitions and symbols

AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
T1/2	The terminal elimination half-life [time]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Patient	An individual with the condition of interest
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.

Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Run in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's medications or other intervention)
Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

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Protocol Summary

Protocol number	CBAF312X2207
Full Title	A phase II, patient- and investigator-blinded, randomized, placebo-controlled study to evaluate efficacy, safety and tolerability of BAF312 (siponimod) in patients with stroke due to intracerebral hemorrhage (ICH).
Brief title	Study of efficacy, safety and tolerability of BAF312 in patients with intracerebral hemorrhage (ICH)
Sponsor and Clinical Trial Phase	Novartis; Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	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.
Primary Objective(s)	To obtain the first efficacy estimate of 2 weeks of BAF312 daily (7 days i.v. with up-titration followed by 7 days p.o.) on reducing perihematoma edema (PHE) compared to placebo on day 14 after ICH.
Secondary Objectives	To assess the safety profile of BAF312 in ICH patients. To evaluate the pharmacokinetics of BAF312 in ICH patients.
Study design	This is a randomized, patient- and investigator-blinded, placebo-controlled, parallel group study of BAF312 on top of standard-of-care for ICH.
Population	The study population consists of adult male or female patients with stroke due to ICH between age of 18 and 85 years (inclusive). Approximately 33 patients per treatment group (BAF312 or placebo) will be randomized for a total of 60 patients completing the protocol.
Key Inclusion criteria	1. Male or female patients aged 18 to 85 years (inclusive). 2. Written informed consent obtained before any study assessment is performed. If the patient is not able to give the informed consent personally, consent by a relative or legal representative is acceptable. 3. Spontaneous, supratentorial intracerebral hemorrhage in cerebral cortex or deep brain structures (putamen, thalamus, caudate, and associated deep white matter tracts) with a volume ≥ 10 mL but ≤ 60 mL (calculated by the ABC/2 method, after Kothari et al 1996) determined by routine clinical MRI or CT. 4. Patients with the onset of ICH witnessed and/or last seen healthy no longer than 24 hrs previously. 5. Patients with Glasgow Coma Scale (GCS) motor score no less than 5 (brings hand above clavicle on stimulus to head or neck).

Key Exclusion criteria	1. Infratentorial (midbrain, pons, medulla, or cerebellum) ICH. 2. Secondary ICH due to aneurysm, brain tumor, arteriovenous malformation, thrombocytopenia, coagulopathy, acute sepsis, traumatic brain injury (TBI), or disseminated intravascular coagulation (DIC). 3. Prior disability due to other disease compromising mRS evaluation, thereby interfering with the primary outcome, operationally defined as an estimated mRS score (by history) of ≥ 3 before ICH for patients ≤ 80 years of age. For ICH patients 81-85 years of age, estimated mRS by history prior to ICH **must** be ≤1 (no significant disability despite symptoms). 4. [Criterion withdrawn by protocol amendment # 2] 5. Candidates for surgical hematoma evacuation or other urgent surgical intervention (i.e., surgical relief of increased intracranial pressure) on initial presentation. 6. Patients with intraventricular hemorrhage (IVH) having a Graeb score of >3 on initial presentation. Patients **must not** have blood in the 4th ventricle (0 points), and may only have blood in the 3rd ventricle in the absence of ventricular expansion (≤1 point). Trace or mild hemorrhage in either or both lateral ventricles (≤1 point each) is permitted. Patients with hydrocephalus determined radiographically on initial presentation are excluded regardless of Graeb score. 7. Patients with active systemic bacterial, viral or fungal infections. 8. Current use of concomitant medications with potent CYP2C9/3A4 inhibitory or induction potential; intravenous immunoglobulin, immunosuppressive and/or chemotherapeutic medications; 9. Cardiovascular exclusion criteria: • Cardiac conduction or rhythm disorders including sinus arrest or sino-atrial block, heart rate <50 bpm, sick-sinus syndrome, Mobitz Type II second degree AV block or higher grade AV block, or preexisting atrial fibrillation (either by history or observed at screening). • PR interval >220 msec. Long QT syndrome or QTcF prolongation >450 msec in males or >470 msec in females on screening electrocardiogram (ECG). • Patients receiving treatment with QT-prolonging drugs having a long half-life (e.g., amiodarone).
Study treatment	Treatment should start as soon as possible, Commercially Confidential Information after the time of onset of ICH symptoms, defined as the time the patient was last witnessed healthy. The total treatment will last 14 days: 7 days of BAF312 i.v. infusion, titrated Commercially Confidential Information followed by 7 days of CCI BAF312 p.o. daily if the patient passes a swallowing safety evaluation. ICH patients who do **not** pass a swallowing safety evaluation per participating institutional standards will **not** be transitioned to the p.o. phase of treatment, and BAF312 must be discontinued after Day 7. These patients should continue to be followed for the remainder of the Assessment schedule; they should **not** be terminated from the study.

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Pharmacokinetic assessments	Pharmacokinetic (PK) samples will be collected on Days 1, 8 and 14.
Efficacy/PD assessments	CT imaging of the brain will be performed 24-48 hours after the initial diagnostic scan and on Days CCI 14. Commercially Confidential Information Modified Rankin Scale (mRS) and neurological examinations will be assessed on Days CCI 90. Commercially Confidential Information
Key safety assessments	• Adverse event monitoring • ECGs • Vital signs • Physical and neurological examinations • Monitoring of laboratory markers in blood and urine
Other assessments	• N/A
Data analysis	The primary analysis will be performed on the Per Protocol analysis set (PPS) defined as all patients having received at least the first infusion on Day1 and with no major protocol deviations impacting the analysis of efficacy. The primary endpoint is reduction of absolute perihematoma edema (aPHE) volume based on CT imaging at Day 14 after ICH. The objective is to compare the mean aPHE between the BAF312 and placebo treatment groups. Commercially Confidential Information
Key words	Stroke, intracerebral hemorrhage (ICH), BAF312, siponimod, sphingosine-1-phosphate (S1P) receptor, efficacy, safety, tolerability

1 Introduction

1.1 Background

1.1.1 Unmet Medical Need

Stroke remains one of the leading causes of adult death and disability worldwide. Intracerebral hemorrhage (ICH) occurs when diseased blood vessels rupture, causing hemorrhage into brain tissue. The most common risk factors associated with ICH are hypertension, smoking, and diabetes mellitus. ICH constitutes 10-15% of all strokes, and is a common cause of morbidity and mortality (Qureshi et al 2001). Although ICH, or hemorrhagic stroke, accounts for a minority of all cases of stroke, it results in 50% of stroke deaths, contributing disproportionately to stroke morbidity and mortality (Qureshi et al 2001, Asuzu et al 2016). No pharmacological interventions have demonstrated significant efficacy to improve functional outcomes after ICH; and less than one third of ICH patients attain functional independence by 6 months after ICH. As such, treatment options for ICH are limited, and there is an enormous unmet medical need for agents that may improve neurological recovery and reduce disability.

1.1.2 Pathophysiology of ICH

ICH triggers a complex cascade of events in the affected tissue, including inflammatory processes and edema formation (Urday et al 2015). Neuroinflammation after ICH involves the early activation of resident microglia, release of proinflammatory mediators, and the influx of peripheral lymphocytes; and is thought to have a major role in the pathophysiology of secondary brain damage. Lymphocytes were found in human cerebrospinal fluid early, starting at 6 hours post ICH, and were also detected in perihematoma edema (PHE) in ICH patients. It was found that CD4+ T cells are the predominating lymphocyte population in mice on day 1. Along with other T cell populations, proinflammatory and immunosuppressive regulatory T cells infiltrate the hemorrhagic brain (Mracsko and Veltkamp 2014). Despite this information on the infiltration pattern of lymphocytes in experimental ICH, less is known about the interactions among these immune cells. Because of the delayed nature of secondary brain damage after ICH, adaptive immune cells may play an important role in the subacute and the regenerative phases after ICH.

1.1.3 Pharmacology of Sphingosine-1-Phosphate (S1P) Receptors

BAF312 (siponimod) acts as a selective modulator of two of the five sphingosine-1-phosphate (S1P) receptors: $S1P_1$ and $S1P_5$. T cells selectively require $S1P_1$ activation for emigration from the thymus, and both T- and B cells require this receptor for egress from peripheral lymphoid organs (Matloubian et al 2004, Brinkmann et al 2004).

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Two open label trials with another S1P-receptor modulator, fingolimod (Fu et al 2014a, Fu et al 2014b), suggest an impact on edema formation and improved neurological outcome in ICH and ischemic stroke. However, limitations of the Fu et al. studies include lack of randomization, lack of placebo controls, and small sample sizes.

BAF312 is a second generation S1P receptor modulator that reduces peripheral lymphocyte counts approximately 4 – 6 hours (h) after the first dose. The half-life of BAF312 is approximately 30 h, which allows reversal of pharmacodynamic effects and recovery of the baseline lymphocyte counts within a week after treatment withdrawal. BAF312's mode of action is believed to include $S1P_1$-mediated prevention of effector lymphocyte recirculation from lymphatic tissue to sites of inflammation, such as the central nervous system (CNS). In addition, there may be direct beneficial effects in the CNS mediated by $S1P_1$ and/or $S1P_5$. Evidence from preclinical models suggests that BAF312 may target $S1P_1$ on astrocytes and/or $S1P_5$ on oligodendrocytes (Choi et al 2011).

We seek to evaluate whether reducing peripheral leukocyte count acutely after ICH would reduce PHE and decrease secondary injury after ICH, thereby improving outcomes in a prospective, randomized study with another S1P-receptor modulator, BAF312.

For more details, please see the Investigator's Brochure.

1.2 Nonclinical data

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1.3 Clinical data

1.3.1 Human safety and tolerability data

S1P receptor modulators are known to cause dose dependent transient decrease in heart rate within 2-3 h of drug intake (Legangneux et al 2013, Hoch et al 2014).

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As of 05-Mar-2018, approximately 3279 unique subjects have been enrolled into the siponimod clinical program (inclusive of Phase 1, Phase 2 and Phase 3), of which approximately 2742 unique subjects (912 healthy volunteers, 1787 patients with MS, 43 patients with PM or DM) have received siponimod and 925 subjects (297 healthy subjects and 628 patients) have received placebo. This includes subjects who sequentially received placebo and siponimod. In addition, 1 ICH patient has been enrolled in ongoing placebo-controlled study CBAF312X2207 (this study) and 363 subjects (all healthy volunteers) were exposed to other drugs.

The cumulative exposure of clinical trial subjects to siponimod since the Development International Birth Date (DIBD) of 05-Mar-2009 is estimated to be approximately 4840 patient-years. Healthy subjects have received siponimod as single doses or as multiple doses (single doses: 0.1 mg to 75 mg, multiple doses: 0.25 mg to 20 mg). Patients with MS have received siponimod (0.25 mg to 10 mg) daily from 1 day to 73 months during the clinical development program (please see Investigators Brochure).

The safety profile of BAF312 includes the following identified risks: transient effects on heart rate and rhythm (bradyarrhythmia and 2nd degree AV block) at treatment initiation that are completely avoided by initial up-titration; liver enzyme elevation; lymphopenia due to lymphocyte redistribution (main targeted PD effect of BAF312); seizures; hypertension; macular edema; and varicella zoster (VZV) infection reactivation.

A placebo-controlled Phase II study of BAF312 in 297 patients with relapsing remitting MS (RRMS) showed significant dose-response relationship at Month 3. BAF312 treatment reduced the combined unique active lesion count by up to 80% vs. placebo, with the 2 mg dose providing near-maximal efficacy. Five transient symptomatic bradyarrhythmic events without sequelae were observed with the two highest doses (3/40 on 2 mg, and 2/50 on 10 mg) without titration. Serious adverse events (SAEs) included one death 27 days post-study drug discontinuation, likely due to previously unrecognized coronary artery disease. Other safety findings included liver enzyme elevations that were thought to be dose-related (4.3% of patients at higher dose

levels, 2 and 10 mg, had transaminases >3x upper limit of normal) and one case of macula edema in a patient with history of uveitis (Selmaj et al 2013), which has been recognized with longer-term BAF312 exposure.

The most common AEs were headache, bradycardia, dizziness and nasopharyngitis. A dose-dependent effect of BAF312 treatment on the occurrence of headache, bradycardia and dizziness reported as AEs was demonstrated. Common types of infections observed included nasopharyngitis, sinusitis, influenza and urinary tract infections, although no apparent treatment relationship was evident.

For more details, please see the Investigator's Brochure.

1.3.2 Human pharmacokinetic data

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1.3.3 Human pharmacodynamic data

BAF312 is a second generation S1P receptor modulator that leads to the reduction of peripheral lymphocyte counts at approximately 4 – 6 hours after dose on Day 1. The half-life of BAF312 is approximately 30 h, which allows reversal of pharmacodynamic effects and recovery of the baseline lymphocyte counts within a week after treatment withdrawal. The mode of action of BAF312 is believed to include $S1P_1$-mediated prevention of effector lymphocyte recirculation from lymphatic tissue to sites of inflammation, including the central nervous system (CNS). In addition, evidence from preclinical models suggests that there may be direct beneficial effects in the CNS mediated by $S1P_1$ and/or $S1P_5$ (Choi et al 2011).

1.4 Study purpose

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.

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	***Endpoints related to primary objective(s)***
• 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.

2.2 Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To assess the safety profile of BAF312 in ICH patients.	• Continuous assessment of AEs/SAEs during the course of the study (90 days).
• To evaluate the pharmacokinetics 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.

2.3 Exploratory objective(s)

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3 Investigational plan

3.1 Study design

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

Screening/Baseline Epoch

The screening/baseline epoch lasts no longer than 24 hours from the time of onset of ICH, defined as the time the patient was last witnessed to be at their normal neurological baseline, and consists of:

- The initial diagnostic neuroimaging study (CT or MRI) to determine the cause of stroke
- Obtaining informed consent
- Determining the Glasgow Coma Scale (GCS, Appendix 6) score (see Section 20) on presentation
- Obtaining medical history, including current medications
- Hospital admission laboratory studies
- Electrocardiogram (ECG)
- Pregnancy test for premenopausal female patients
- Vital signs and physical examination, including neurological examination, and

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Please see Assessment schedule for details.

Treatment Epoch

Patients fulfilling all eligibility criteria must be randomly allocated to one of two treatment groups in a ratio of 1:1. The treatment should start as soon as possible, Commercially Confidential Information after the time of the ICH, defined as the time the patient was last witnessed to be healthy, defined as functioning at their normal, pre-event neurological baseline.

The total treatment lasts 14 days (see Figure 3-1):

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

Patients must be monitored with CV telemetry or continuous bedside monitoring for the first 48 hours of i.v. BAF312 treatment. 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 a swallowing safety evaluation, the 7-day i.v. phase is followed by 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 for the remainder of the Assessment schedule.

i.v. Dose Titration

The dose titration schedule is based on estimations of the cardiovascular effects of BAF312 balanced with the therapeutic need to achieve fast, effective BAF312 concentrations in ICH patients, where the timely achievement of expected therapeutic concentrations may be of great importance.

The BAF312 i.v. titration schedule, specified in Section 6.2 (Treatment arms), is designed to minimize the effects of rapid exposure to high concentrations of S1P receptor modulators on heart rate by gradually increasing the BAF312 concentration in the infusion over the first two days of treatment.

As described in the accompanying Pharmacy Manual, syringe pump changes must occur every 6 hours, with a window of -15/+30 minutes.

During the i.v. up-titration period patients must be closely monitored. Special attention should be given to monitoring of the HR and cardiac rhythm by continuous CV telemetry in the Stroke Unit/Neurointensive Care Unit (Stroke/NICU) setting. In case of symptomatic bradycardia or cardiac rhythm abnormalities (e.g. atrioventricular blocks or sinus pauses), the Investigator must follow the guidance given in Section 6.6. Under those predefined conditions a dose may be postponed or skipped, but not more than 2 times in a row.

p.o. Dose

Eligible patients who pass a swallowing safety evaluation will continue with the 7-day p.o. phase of treatment with BAF312 CCI QD. The daily dose is delivered as CCI 2 mg tablets (BAF312 or placebo), to be taken in the morning, with or without food.

During the Treatment Epoch, all patients must undergo study-specific assessments according to the Assessment schedule.

Follow-Up Epoch

Patients must return for scheduled outpatient (or inpatient, if still in rehabilitation facility) follow-up visits after being discharged from the Stroke/NICU or inpatient hospital floor, according to the Assessment schedule. The Follow-Up Epoch will last through the Day 90 visit after ICH.

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3.2 Rationale of study design

The study uses a randomized, patient and investigator-blinded, parallel-group design on top of standard-of-care, which has been used in other clinical trials investigating new treatments in patients with acute stroke due to ICH. Treatments are randomized, and blinded to patients and investigators to avoid potential reporting bias. Parallel groups are used because strokes are usually one-time events.

Perihematoma edema (PHE) has attracted significant attention as a mechanism of secondary injury after ICH, thereby contributing to both short-term morbidity and long-term disability (Selim and Norton 2018).

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The modified Rankin Scale (mRS) is a widely-used clinical instrument, and is considered the current standard assessment for stroke outcomes by most Health Authorities. The follow-up observation period of 90 days for assessing improvement in functional disability is a well-established time point for stroke studies, including trials in ICH (CPMP Points to Consider 2001). The 90-day mRS score has been used as an endpoint in many contemporary clinical stroke trials, including INTERACT2 (Anderson et al 2013), ATACH (Qureshi et al 2010), SAMURAI-ICH (Koga et al 2014), and ENOS (The ENOS Trial Investigators 2015).

Studies published by Fu et al (2014a, 2014b) with fingolimod showed reduction of PHE and potential clinical benefit in stroke treatment with an S1P receptor modulator. The pilot data published by Fu et al (2014a) with fingolimod need to be reproduced under more rigorous trial conditions in a larger population and in another geography. Despite this earlier study with fingolimod, the sponsor has selected BAF312 (siponimod) for further development, as the considerably shorter half-life of BAF312 may be advantageous in an acute setting, such as ICH.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

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Dose titration is introduced with the aim to reduce the bradycardic effects of $S1P_1$ modulators during treatment initiation. The proposed i.v. dose-titration scheme is based on estimations of the HR effects of BAF312 and therapeutic need to achieve fast, effective concentrations in ICH patients. There is currently no knowledge to predict the duration of treatment necessary to reduce secondary brain damage due either to perihematomal edema (PHE) or to other potential mechanisms. The choice of i.v. administration in the Stroke Unit/NICU setting is based on the standard practice of maintaining acute stroke patients NPO on admission until the presence or absence of dysphagia can be determined.

3.4 Rationale for choice of comparator

Placebo is the only possible comparator given the absence of any approved treatment for acute stroke due to ICH.

3.5 Rationale for choice of background therapy

All patients in the study should receive supportive standard-of-care treatment for ICH, as laid down in the guidance publications of the American Heart Association and the American Stroke Association (Hemphill et al 2015), and the European Stroke Organisation (Steiner et al 2014).

3.6 Purpose and timing of interim analyses/design adaptations

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3.7 Risks and benefits

The risk to patients in this trial must be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and clear instructions to the Investigator on how to manage symptomatic bradycardia if it occurs.

Bradyarrhythmic effect – Treatment initiation with BAF312 results in transient decrease in HR in a dose-dependent manner, with nadir ~3-4 h after the first dose. In a clinical study in MS patients (CBAF312A2201) without dose titration, five cases of second degree AV blocks were reported: 3/29 in the 2 mg group and 2/50 in the 10 mg group. Implementation of dose titration effectively mitigated the occurrence of bradyarrhythmic events. In this study, the dose is titrated to the target daily dose of CCI BAF312. The need to achieve fast therapeutic concentration was carefully weighed against the need to prevent bradyarrhythmic effects. Unlike ischemic stroke, in which reflex tachycardia and increased blood pressure is typically allowed to persist (to some extent) to maximize perfusion of the ischemic penumbra, in hemorrhagic stroke most supportive therapies are aimed at lowering blood pressure to minimize likelihood of acute expansion of the initial hematoma. Given this, transient bradycardia carries significantly less risk in the ICH patient population than in patients with ischemic stroke.

During the first 48 hours of treatment, all patients will be on continuous CV telemetry in Stroke Units/Neurointensive Care Units, and special attention will be given to the monitoring of the HR. In case of symptomatic bradycardia, the Investigator should follow the guidance given in Section 6.6. Under those predefined conditions, BAF312 treatment must be interrupted. When the heart rate has recovered, the treatment may be started again, as judged by the Investigator.

Risk of infection - The core PD effect of BAF312 is dose-dependent reduction of peripheral lymphocyte counts to 20-30 % of baseline due to their sequestration in the lymphoid tissues. As a consequence, there is an increased risk of infections. Patients with low baseline lymphocyte count are excluded from the study. There were no reports of increased bacterial infections between drug and placebo in the MS population with $S1P_1$ modulators (fingolimod

and BAF312). Although the risk of infection is considered small given the short treatment duration of 14 days, in this critically-ill population this risk might be higher.

Cases of progressive multifocal leukoencephalopathy (PML), have been reported with another S1PR modulator, fingolimod, but is extremely unlikely in this population due to the short treatment duration. Nevertheless, signs of CNS infections will be routinely monitored, promptly investigated, and treated as per standard medical practice. Although not the preferred imaging modality for PML *per se*, all study patients will have CT imaging of the brain performed at 7 and 14 days after ICH, as well as ongoing neurological examinations (see Assessment schedule). Effective diagnostic and therapeutic strategies should be employed in patients with infections.

Aspiration pneumonia – Respiratory tract infections were reported only in 3 patients with MS on BAF312 (N=235) and none on placebo (N=61). While the risk of aspiration pneumonia cannot be excluded in this population, it is not believed to be increased by BAF312 treatment. All ICH patients must be monitored in the Stroke Unit/NICU setting for at least the first 48 hours after ICH, and standard-of-care treatment interventions should be implemented in cases of aspiration pneumonia.

Urinary tract infections – In the clinical trials conducted in MS patients, the incidence of overall infections was not different between placebo and BAF312 (5% in BAF312 and 3.5% in placebo). Patients with ICH requiring urinary catheterization might be at a higher risk of urinary infections, which should be treated per the standard-of-care in the Stroke Unit/NICU.

Blood pressure – In the healthy volunteer and MS population, the blood pressure lowering effect of BAF312 was very weak upon initiation. Small elevations in blood pressure were seen with siponimod treatment. The mechanism of these effects is unclear, but is potentially the result of unopposed natural sphingosine-1-phosphate ligand stimulation of S1PR type 2/3 (S1P2/3) endothelial receptors, owing to the strong functional antagonism of S1P1 by siponimod (Brinkmann et al 2010). Even taking into account that the population for this study is likely to be older, minimal effects are nonetheless expected with this BAF312 dose and short treatment duration.

Elevated liver function tests – In the Phase 2 dose-finding study in MS patients, elevated liver function tests > 3 x ULN were noted in 4.3% of patients in BAF312 (10 mg and 2 mg) groups. However, the short treatment duration of this study will likely reduce the frequency of treatment-related liver enzyme elevations.

Macular edema – The occurrence of macular edema with BAF312 in the present study is unlikely given the short treatment duration. However, the Investigator should be aware that patients with diabetes mellitus and previous uveitis might be at risk of developing macular edema. If the patient reports vision disturbances, they should be referred to an ophthalmologist for OCT measurement.

Radiation dose considerations from CT scans – Patients enrolled in this trial will have CCI non-contrast head CT scans- two as part of routine standard-of-care for ICH determination and follow-up (one at presentation/inclusion and another 24-48 hours later- corresponding to V1 and V2 in the Assessment schedule) and CCI follow-up study scans CCI at Days CCI 14 (V10). Scans from CCI Day 14 will be used for quantitative assessment of efficacy of BAF312 via determination of hemorrhage and edema volumes, as described elsewhere in this document. The effective radiation dose per scan is expected to be

approximately 2 mSv, amounting to a total of 8 mSv including the two standard-of-care scans (V1 and V2) (McCollough et al 2015 and Smith-Bindman et al 2009). This is considered to be a minor to intermediate risk level corresponding to the benefit to the patient (category IIb based on ICRP 62 1992) and is balanced against the possible substantial societal benefit gained from the trial (European Commission Radiation Protection 1998 and ICRP 62 1992). The radiation dose from CT scans will be in accordance with local clinical practice and regulations.

The investigators must regularly review the degree of burden and the risk threshold for the patients enrolled in this study.

There may be unknown risks with BAF312 which may be serious and unforeseen in the ICH patient population.

The treatment with BAF312 may benefit ICH patients. In a pilot study with another $S1P_1$ modulator (fingolimod), treated patients showed a reduction of neurologic impairment compared to placebo, regained a Glasgow Coma Scale score of 15 by Day 7; and had a NIHSS score reduction of 7.5 vs 0.5 in the placebo group (Fu et al 2014a).

Taking into account the nature of the known risks, the short duration of treatment, and the lack of alternative specific therapies for ICH, it is considered that the overall risk-benefit is favorable to study the therapeutic effect of BAF321 in ICH patients.

3.7.1 Blood sample volumes

A maximum of 300 mL of blood is planned to be collected over a period of 3 months from each patient as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule (Section 8.1).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and Central Laboratory Manual.

See Section 8.9 regarding the potential use of residual samples.

4 Population

The study population consists of adult patients with stroke due to ICH fulfilling the eligibility criteria listed below at screening.

Approximately 33 patients per treatment group (~65 patients in total) will be randomized to obtain at least 60 completed study subjects (Day 14).

4.1 Inclusion criteria

ICH patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Male or female patients aged 18 to 85 years (inclusive).
2. Written informed consent obtained before any study assessment is performed.
   If the patient is not able to give the informed consent personally, consent by a relative or legal representative is acceptable.

3. Spontaneous, supratentorial intracerebral hemorrhage in cerebral cortex or deep brain structures (putamen, thalamus, caudate, and associated deep white matter tracts) with a volume ≥ 10 mL but ≤ 60 mL (calculated by the ABC/2 method, after Kothari et al 1996) determined by routine clinical MRI or CT.
4. Patients with the onset of ICH witnessed and/or last seen healthy no longer than 24 hrs previously.
5. Patients with Glasgow Coma Scale (GCS) best motor score no less than 5 (brings hands above clavicle on stimulus to head or neck).

4.2 Exclusion criteria

ICH patients fulfilling **any** of the following criteria are **not** eligible for inclusion in this study:

1. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline (for biologics), whichever is longer.
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (e.g., fingolimod).
3. Current use of concomitant medications with potent CYP2C9/3A4 inhibitory or induction potential.
4. *Intentionally blank – removed with protocol amendment #2.*
5. Infratentorial (midbrain, pons, medulla, or cerebellum) ICH.
6. Candidates for surgical hematoma evacuation or other urgent surgical intervention (i.e., surgical relief of increased intracranial pressure) on initial presentation. If during the treatment period surgical hematoma evacuation or surgical intervention to lower intracranial pressure becomes indicated, the investigational treatment should be stopped.
7. Patients with intraventricular hemorrhage (IVH) having a Graeb score (oGS) of >3 on initial presentation. Patients **must not** have blood in the 4th ventricle (0 points max), and may only have blood in the 3rd ventricle in the absence of ventricular expansion (≤1 point max). Trace or mild hemorrhage in either or both lateral ventricles (≤1 point each) is permitted. Patients with hydrocephalus determined radiographically on initial presentation are excluded regardless of oGS (see Section 8.8).
8. Secondary ICH due to:
   - aneurysm
   - brain tumor
   - arteriovenous malformation
   - thrombocytopenia, defined as platelet count of <150,000/µl
   - known history of coagulopathy
   - acute sepsis
   - traumatic brain injury (TBI)
   - disseminated intravascular coagulation (DIC)
9. Prior disability due to other disease compromising mRS evaluation, thereby interfering with the primary outcome, operationally defined as an estimated mRS score (by history) of ≥ 3 before ICH for patients ≤ 80 years of age. For ICH patients 81-85 years of age, estimated mRS by history prior to ICH **must** be ≤1 (no significant disability despite symptoms).

10. Preexisting unstable epilepsy.
11. Patients with active systemic bacterial, viral or fungal infections.
12. Concomitant drug-related exclusion criteria:
    - Intravenous immunoglobulin, immunosuppressive and/or chemotherapeutic medications.
    - Moderate immunosuppressives (e.g. azathioprine, methotrexate) and/or fingolimod within 2 months prior to randomization.
    - Stronger immunosuppressives (e.g. cyclophosphamide, immunosuppressive mAb) within (minimally) 6 months prior to randomization, or longer with long-lasting immunosuppressive medications as determined by the investigator.
13. Cardiovascular exclusion criteria:
    - Cardiac conduction or rhythm disorders including sinus arrest or sino-atrial block, heart rate <50 bpm, sick-sinus syndrome, Mobitz Type II second degree AV block or higher grade AV block, or preexisting atrial fibrillation (either by history or observed at screening).
    - PR interval >220 msec. Long QT syndrome or QTcF prolongation >450 msec in males or >470 msec in females on screening electrocardiogram (ECG).
    - Patients receiving treatment with QT-prolonging drugs having a long half-life (e.g., amiodarone).
14. Any of the following abnormal laboratory values prior to randomization:
    - White blood cell (WBC) count < 2,000/µl (< 2.0 x 10^9/L)
    - Lymphocyte count < 800/µl (< 0.8 x 10^9/L)
15. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
16. Patients with any other medically unstable condition or serious laboratory abnormality as determined by the investigator.

The Investigator must ensure that all patients being considered for the study meet the inclusion criteria, above.

Patient selection is to be established by checking through all eligibility criteria at screening. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a patient from enrollment into the study.

5 Restrictions for Study Subjects

For the duration of the study, patients should be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Women of child bearing potential must be informed that taking BAF312 may involve unknown risks to the fetus if pregnancy were to occur during the study; and agree that in order to participate in the study they must use highly effective methods of contraception during study. Highly Effective contraception methods include:

- Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **NOT** acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
- Other forms of contraception that have comparable efficacy (failure rate <1%), for example placement of a non-hormonal intrauterine device (IUD) or intrauterine system (IUS).

Study CBAF312X2207 will enroll only ICH patients with basal ganglia (putamen, caudate, thalamus) primary hemorrhages. This population consists mainly of older patients with long histories of smoking, hypertension, and/or diabetes. The study specifically excludes patients with secondary ICH (i.e., due to malignancy, vascular malformation, aneurysm, trauma, etc.), which is more often the underlying cause in younger patients. As such, with these Inclusion/Exclusion Criteria, it is very unlikely that our study will enroll women of child-bearing potential. Furthermore, given the significant short-term disability of our ICH patients, it is highly unlikely that they will be sexually active during the treatment phase of our study, consisting of the first 14 days after their stroke; or immediately thereafter, when they will very likely be in an inpatient rehabilitation hospital.

In the unlikely event that a female ICH patient with child-bearing potential enrolled in our study choses to become sexually active immediately after the treatment phase, but while still in the follow-up phase of the study, all female ICH patients of child-bearing potential should not use hormone-containing methods of systemic contraception, oral or injectable, for the duration of the study. Alternative methods of contraception should be discussed between these patients and their personal physicians, and be decided upon by the patient with the counsel of her doctor.

Contraception requirements start at the Screening/Baseline Visit, and are to be maintained until at least 30 days after the last administration of study drug.

If there is any question that the patient will not reliably comply, the patient should not be entered or continue in the study. Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

5.2 Prohibited treatment

Use of medications displayed in Table 5-1 are **NOT** allowed during treatment with BAF312 due to increased risk of immunosuppression, confounding of efficacy and/or potential interaction with study treatment (***NB***: CYP2C9 and CYP3A4 are the major metabolizing enzymes for BAF312).

Table 5-1 Prohibited Medications

Medication	Action to be taken
Immunosuppressive/chemotherapeutic medications or procedures, including cyclosporine, azathioprine, methotrexate, and immunomodulatory mABs	Stop taking. If not possible, consider discontinuation of study treatment
Medication that suppress AV conduction (e.g. carbamazepine, non-dihydropyridine calcium-channel blockers, or cardiac glycosides) with the exception of beta-blockers	Stop taking. If not possible, consider discontinuation of study treatment
Strong inhibitors of CYP2C9 or CYP3A4 (Table 21-1)	Stop taking. If not possible, consider discontinuation of study treatment Assess ECG and monitor lymphocyte counts
Potent inducers of CYP2C9 (Table 21-2)	Stop taking. If not possible, consider discontinuation of study treatment

5.3 Dietary restrictions

- No grapefruit or grapefruit juice is to be consumed during the study until 7 days following the last dose (i.e., Day 21 after ICH).

5.4 Other restrictions

- No strenuous physical exercise (e.g. weight training, aerobics), not including formal rehabilitation therapy, until after Study Completion evaluation.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for patient numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual.

6.1.1 Investigational treatment and control drug(s)

Table 6-1 Overview of study medication

Study drug name	Formulation	Unit dose	Packaging	Provided by
BAF312/placebo	Film-coated Tablet	2 mg / 0 mg	Double blind kits	Novartis
BAF312/placebo	Concentrate for Solution for Infusion	4.5 mg /4.5 mL for BAF312; 0 mg/4.5mL for placebo	Double blind kits	Novartis

6.1.2 Additional study treatment

All patients will receive standard of treatment and care for patients with ICH according to the AHA/ASA (Hemphill et al 2015) and ESO Guidelines (Steiner et al 2014). No additional treatment beyond investigational treatment is required for this trial.

General Stroke Unit/Intensive Care Unit management throughout the study needs to be recorded on the Concomitant Medication eCRF. Post ICH rehabilitation, dates and therapy sessions should also be recorded on the same CRF.

6.2 Treatment arms

Patients will be assigned to one of the following 2 treatment arms in a ratio of 1:1.

Study treatments are defined as:

BAF312

Commercially Confidential Information

-OR-

Placebo

- Days 1 through 7: matching i.v. placebo
- Days 8 through 14; matching p.o. placebo QD

6.3 Treatment assignment and randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced using a validated system that automates the random

assignment of patients to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for patients will be reviewed and approved by a member of the sponsor Randomization Office.

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of patients.

6.4 Treatment blinding

This is a patient and investigator-blinded study. Patients and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

All site staff (including study investigators, coordinators, and nurses) will be blinded to study treatment throughout the study.

In this study, blinded, third-party Independent Raters will rate perihematoma edema (PHE) on CT images and mRS Scores from video-recorded interviews.

Unblinding a single patient at a site for safety reasons (i.e., necessary for patient management) will occur via an emergency system in place at the site (see Section 6.7).

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study:

- Unblinded clinical staff managing drug re-supply to site.
- Unblinded PK sample analyst(s)

The independent statistician(s) and independent programmer(s) will be able to access the randomization list and treatment assignment information

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All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-2 Blinding levels

Role	Time or Event			
	Randomization list generated	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**	**Interim Analysis & dose escalation**
Subjects/Patients	B	B	B	B
Site staff	B	B	B	B
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff (see text for details)	B	UI	UI	UI
Independent statistician/statistical programmer/data analysts	B	UI	UI	UI
Independent DMC used for assessing interim safety results*	B	UI	UI	UI
All other sponsor staff not identified above	B	B	B	B

B - Remains blinded

UI - Allowed to be unblinded on individual patient level

* Semi-blinded by treatment group (Group A, Group B, etc.) unless and until a between-group safety imbalance is seen by DMC (see Section 11.9 Interim analyses).

6.5 Treating the subject

Once a patient meets all eligibility criteria and is randomized to a treatment arm, the treatment should start as soon as possible, CCI after the time of the ICH, defined as the time the patient was last witnessed to be healthy.

The total treatment lasts 14 days: 7 days of BAF312 with i.v. up-titration Commercially Confidential Information CCI (see Figure 3-1) followed by 7 days of CCI BAF312 p.o. once daily.

Commercially Confidential Information

As described in the accompanying Pharmacy Manual, syringe pump changes must occur every 6 hours, with a window of -15/+30 minutes.

During the i.v. up-titration period patients must be closely monitored. Special attention should be given to monitoring the HR and cardiac rhythm, with continuous CV telemetry in the Stroke Unit/Neurointensive Care Unit (Stroke/NICU) setting for at least the first 48 hours of the i.v. treatment phase. In case of symptomatic bradycardia or cardiac rhythm abnormalities (e.g. atrioventricular blocks or sinus pauses), the Investigator should follow the guidance given in

Section 6.6. Under those predefined conditions a dose may be postponed or skipped, but not more than 2 times in a row.

During the 7 days of i.v. infusion treatment, all patients must undergo a swallowing safety evaluation. Those ICH patients who do not successfully pass a swallowing safety evaluation per the treating hospital's institutional guidelines and practices will not be transitioned to the p.o. phase of treatment, and BAF312 must be discontinued after Day 7. Failure to pass a swallowing safety evaluation should be recorded in the source documentation, and patients who are unable to safely swallow oral medications should continue to be followed for the remainder of the Assessment schedule; they should **not** be terminated from the study. The p.o. phase of treatment consists of five tablets to be taken whole, with or without food, in the morning.

Because the first i.v. treatment must begin Commercially Confidential Information following the time the patient was last witnessed to be normal, and may occur at any time during the day or night, the transition from i.v. to p.o. BAF312 must also transition from CCI hospital days to calendar days. Operationally, if the last syringe infusion ends between 12:00 AM (midnight) and 8:00 AM, the subject should be administered their first oral dose **on that calendar morning** (i.e., between 8:00 AM-12:00 PM). If the last syringe infusion ends after 8:00 AM, but before 12:00 AM (midnight) the following night, the subject should be administered their first oral dose **on the following calendar morning** on awakening.

Once patients have completed the 7-day i.v. phase of treatment, passed a swallowing safety evaluation per the treating institution, and successfully transitioned to p.o. BAF312 administration, they may be discharged to home or transferred to a rehabilitation facility at the Investigator and/or treating physician's discretion. If the patient is discharged or transferred, handling and tracking of investigational drug should occur as detailed below in Section 6.8.

During the Treatment Epoch, patients must undergo study-specific assessments according to the Assessment schedule.

Detailed instruction for i.v. solution preparation and infusion will be provided in a separate manual.

Sponsor-qualified personnel will be readily available to advise on trial-related medical questions or problems.

6.6 Permitted dose adjustments and interruptions of study treatment

Continuous cardiac monitoring will be implemented in the Stroke Unit/Neurointensive Care Unit setting (telemetry or bedside monitoring) in all patients during days indicated in the Assessment schedule. Monitoring will start from 1 hour before first dose and will continue up to at least 48 hours after the first drug administration. Continuous cardiac monitoring may be done for a longer duration on a case-by-case basis at the discretion of the Investigator and/or treating intensivist.

Cardiac safety monitoring data will be used for cardiac rhythm evaluation (mainly bradyarrhythmias, such as atrioventricular blocks and sinus pauses) and for HR assessment (bradycardia). Bradycardia and/or bradyarrhythmias with BAF312 administration typically occur within the first 48 hours of dosing, and are almost completely eliminated with BAF312 up-titration as proposed.

Management of Bradycardia or Bradyarrhythmia

The Investigator should be guided by the presence or absence of symptoms during bradycardic or bradyarrhythmic episodes (hemodynamic impact) and by the degree of atrioventricular block and/or duration of sinus pauses. Asymptomatic and minimally symptomatic patients do not necessarily require interruption of BAF312 dosing or taking any other action (Neumar et al 2010). In cases in which bradycardia is markedly symptomatic, or inappropriate for the clinical condition in the judgement of the treating intensivist, the BAF312 i.v. infusion will be interrupted.

Bradycardia with S1P modulators is usually benign, transient, and does not require treatment (Schmouder et al 2012). The patient should be assessed to determine if treatment continuation is acceptable to the treating physician and the Investigator (e.g., 1st or 2nd degree AV blocks) and if treatment will be continued once the patient recovers from symptomatic bradycardia. In the case of 3rd degree AV block and/or a hemodynamically-affected patient, the treatment should not be reinitiated (Section 7.2). The following AHA guidelines (Figure 6-1; Neumar et al 2010) should guide the Investigator: in the algorithm below, if the information from box 3 (persistent symptomatic bradycardia) leads to box 4 (monitor and observe) then:

1. The BAF312 infusion should be stopped for one hour,
2. The next dose escalation should be skipped
   Commercially Confidential Information and
3. The treatment infusion should be restarted only when the patient is hemodynamically stable.

If the information from box 3 leads to box 5 (therapeutic intervention), the investigational drug should be discontinued and not restarted (Section 7.2).

Any reduction in heart rate, which, in the opinion of the Investigator or treating intensivist, is clinically significant and requires intervention (e.g., acutely altered mental status, ongoing severe ischemic chest pain, congestive heart failure, hypotension, or other signs of shock) may be treated according to standard medical practice, and suggested treatment would include:

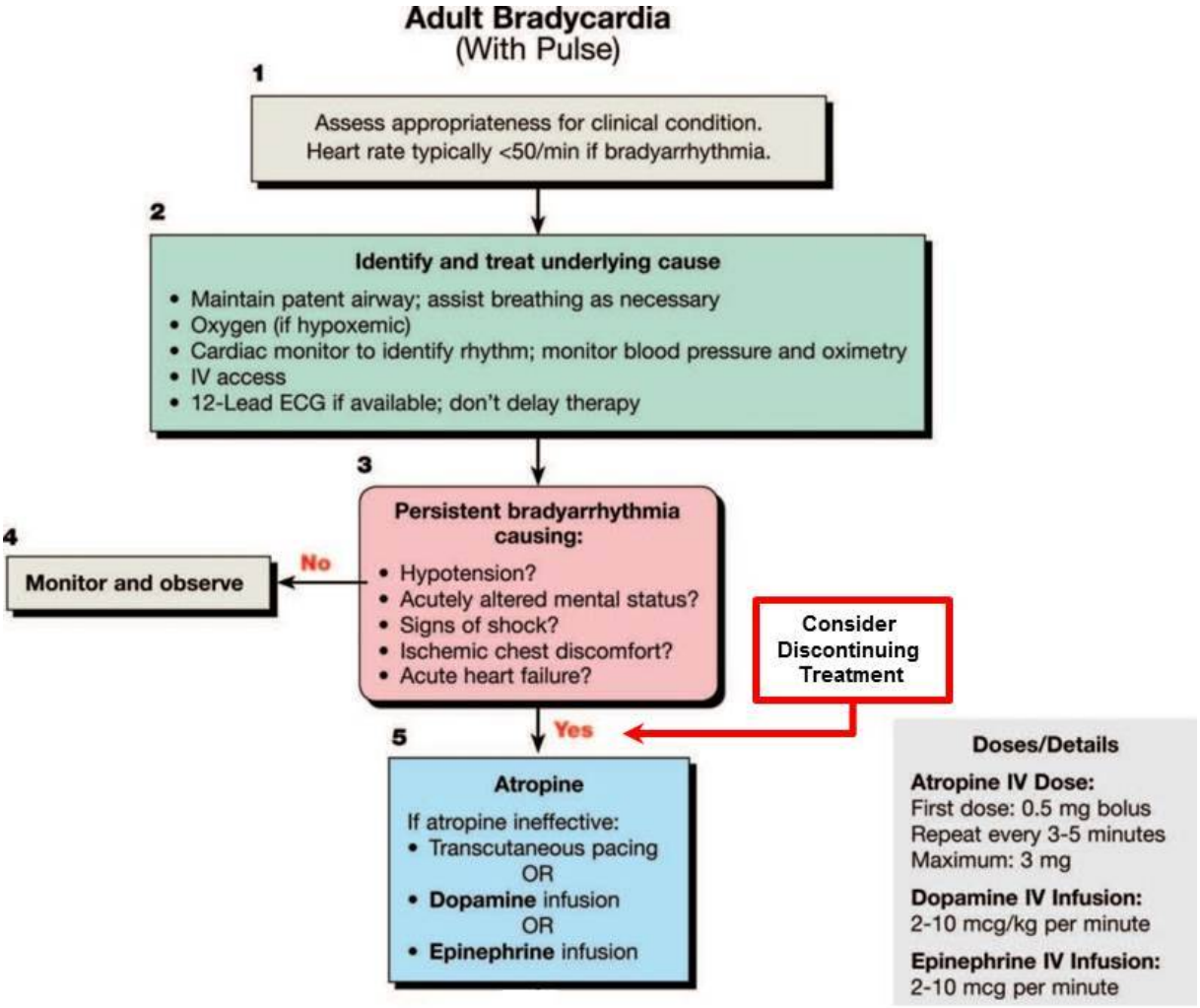
- Anticholinergics (e.g. atropine subcutaneous or i.v.)
- Beta-agonists/sympathomimetics (e.g. dopamine or epinephrine)

Dosing of these will be individualized with respect to the desired clinical effect by the treating intensivist.

This cardiovascular AE mitigation plan was deemed appropriate by the FDA on Type B Pre-IND review (September 2016) and approved by the Novartis CPRC (October 2016).

Any changes in administration of study medication must be recorded on the Dosage Administration Record CRF.

Figure 6-1 AHA Guidelines for Emergency Cardiovascular Care



6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a patient, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the patient. The Investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the Study Team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. In most cases, the Investigator will need to provide:

- Protocol Number
- Study Drug Name (if available)
- Patient Number

In addition, the Investigator must provide oral and written information to inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given patient.

6.8 Treatment exposure and compliance

BAF312 levels will be determined in patients' plasma samples, and population pharmacokinetic analysis will be done, as detailed in Section 8.7.

For the p.o. phase of the study (Days 8-14), if the patient is discharged from the hospital to home, the Investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed.

If the patient is transferred to an inpatient rehabilitation facility, the oral investigational drug should be transferred to the rehabilitation hospital pharmacy to be dispensed by the hospital pharmacist and administered by the nursing staff as five tablets to be given to the patient every morning, with or without food, through and including Day 14 after ICH. It is the responsibility of the Investigator to ensure appropriate tracking and document drug supply management for study drug provided to rehabilitation centers.

Compliance will be assessed by the Investigator and/or study personnel at each visit using pill counts and information provided by the patient. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.9 Recommended treatment of adverse events

Treatment of symptomatic bradycardia and/or bradyarrhythmias should be performed as outlined in Section 6.6.

Other AEs should be treated at the discretion of the Investigator.

Medication used to treat AEs must be recorded on the Concomitant Medications/Significant Non-Drug Therapies CRF.

6.10 Rescue medication

There is no rescue medication for patients with ICH.

6.11 Concomitant treatment

Per U.S. and European stroke care guidelines, corticosteroids should not be used for treatment of ICH because they are ineffective and increase complications (Hemphill et al 2015, Steiner et al 2014).

The Investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant Medications/Significant Non-Drug Therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact Novartis before randomizing a patient or, if the patient is already enrolled, to determine if the patient should continue participation in the study.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last patient completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All SAEs reported during the Follow-Up Period must be reported as described in Section 9.2 and the Site Operations Manual. Documentation of attempts to contact the patient should be recorded in the source documentation.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the patient or the Investigator.

Study treatment must be discontinued under the following circumstances or emergence of the following adverse events:

- Patient/guardian decision - patients may choose to discontinue study treatment for any reason at any time.
- The Investigator believes that continuation would negatively impact the safety of the patient or the risk/benefit ratio of trial participation.

- Severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension. Immediate interruption of the infusion to administer study treatment is required in such cases.
- Any protocol deviation that results in a significant risk to the patient's safety.
- Pregnancy (see Section 8.6 (Safety) and Section 9.6 (Pregnancy reporting))
- Use of prohibited treatment as per recommendations in Table 5-1.
- If a liver or renal event occurs, follow guidelines outlined in Appendix 1 and Appendix 2 regarding discontinuation of study treatment.
- Any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study.
- Expansion of initial ICH requiring surgical evacuation.
- Development of increased intracranial pressure requiring surgical intervention, including subsequent intraventricular expansion of the initial ICH leading to increased ventricular pressure requiring surgical management (e.g., EVD placement).
- Hemodynamically-significant bradycardia and/or 3rd degree AV block as described in Section 6.6.

The appropriate personnel from the site and Novartis will assess whether investigational drug treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

If discontinuation of study treatment occurs, the Investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the CRF.

Patients who discontinue study treatment, either by choice or due to adverse events as listed above, should **not** be considered withdrawn from the study **unless** they **also** withdraw their consent (see Section 7.3, Withdraw of Informed Consent). Patients who have discontinued BAF312 before Day 14 (V10) but have **not** withdrawn their consent to participate in the study should return for the assessments indicated by an asterisk (*) in the Assessment Table. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in Section 7.4 (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / Concomitant Treatments
- Adverse Events/Serious Adverse Events

The Investigator must also contact the IRT to register the patient's discontinuation from study treatment.

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

1. Does not want to participate in the study anymore, and
2. Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

7.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study stopping rules

Overall study stopping rules:

Enrollment in the study will be placed on hold if any of the following occurs:

- At least 2 or more patients present with hypersensitivity reactions and/or injection reactions of moderate-to-severe intensity that are considered related to study-drug.
- At least 2 or more patients experience a similar AE which is assessed as life-threatening or potentially life-threatening (CTCAE Grade 4-5) and is considered related to the study-drug; or
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

The study may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time. Should this be necessary, patients must be seen as soon as possible and treated as a prematurely discontinued patient. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study.
- Decision based on recommendations for applicable board(s) after review of safety and efficacy data.
- Discontinuation of study drug development.

8 Procedures and assessments

8.1 Assessment schedule

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment schedule

Study Phase	Screening/Baseline	Treatment									Follow-up	
Visit Numbers[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Days	-1	1	2	3	4	5	6	7	8	14 ± 1	30 ± 5	90 ± 10
Informed consent	X											
Glasgow Coma Scale	X											
Medical history/current medical conditions	X									X*	X*	X*
Routine Clinical Laboratory Tests	X	X	X	X				X		X*	X*	X*
ECG evaluation	X	X	X	X				X				
Pregnancy	X										X*	
Inclusion / Exclusion criteria	X											
Vital Signs	X	X	X	X	X	X	X	X	X	X*	X*	X*
Commercially Confidential Information												
Physical examination	X									X*	X*	X*
Neurological Examination	X									X*	X*	X*
Study drug dose-i.v. infusion		<----------										
Study drug dose -p.o. QD									<----------			
PK blood samples		X[2]							X[3]	X[3]		
Commercially Confidential Information												

Study Phase	Screening/Baseline	Treatment									Follow-up	
Visit Numbers[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Days	-1	1	2	3	4	5	6	7	8	14 ± 1	30 ± 5	90 ± 10
CT scan	X	X[4]								X*		
Modified Rankin Scale (mRS)	Estimate by history											X*
Commercially Confidential Information												
Study completion information												X*
Concomitant therapies	<---------->											
Adverse events	<---------->											
Serious adverse events	<---------->											

[1] Visit structure given for internal programming purpose only
[2] PK samples at 0.5hr, 2hr, and 6hr after start of first infusion; 2mL at each time point
[3] Before administration of oral dose. These samples should still be collected if the subject does not transition to the oral phase of the study.
[4] CT scan #2 to be performed between 24 and 48 hours after initial diagnostic scan.

* Assessments to be completed for patients who have discontinued BAF312 treatment before Day 14 **unless** they have **also** withdrawn consent.

8.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the patient's representative gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators a proposed informed consent form that complies with the International Conference on Harmonisation E6 GCP guideline and regulatory requirements and is considered appropriate for this study.

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The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the patient.

Ensure patients are informed of the contraception requirements outlined in Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

Refer to the Site Operations Manual for a complete list of Informed Consent Forms included in this study.

8.3 Subject screening

It is permissible to re-screen a patient if s/he fails the initial screening and **if re-screening occurs within 24 hours of the patient last seen normal**; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.4 Subject demographics/other baseline characteristics

Demographic and baseline characteristic data will be collected on all patients. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the Site Operations Manual.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.5 Efficacy / Pharmacodynamics

8.5.1 Clinical Outcome Assessments (COAs)

CT Imaging

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. Studies of the trajectory of perihematoma edema (PHE) assessed with either MR (Venkatasubramanian et al 2011) or CT imaging (Staykov et al 2011) largely agree on the average time course of its development, which increases to a plateau between days 7-14 after ICH. In a study of fingolimod in ICH (Fu et al 2014a), the authors showed that while there were no differences in hematoma volume between active drug- and placebo-treated patients, absolute PHE volume (aPHE) was lower in fingolimod-treated patients at Day 7 but not at Day 14; and relative PHE (rPHE; aPHE/hematoma volume) was significantly lower in fingolimod-treated patients at both Day 7 and Day 14 after ICH. Analyzing data from the VISTA-ICH archive, Murthy et al (2015) showed an association between early PHE expansion within 72 hours after ICH and poorer 90 day functional outcomes in basal ganglia hemorrhages ≤ 30 cc in volume. Recently (Volbers et al 2018) it has also been shown that peak PHE is an independent predictor of 90 day functional outcome after supratentorial ICH.

Although the presence of intraventricular hemorrhage (IVH) has been shown to worsen outcomes to some extent in ICH patients (Steiner et al 2006; Mayer et al 2009), the larger the initial hematoma is, the greater is the likelihood that the ICH patient will present with some degree of IVH on initial presentation, while on the other hand much smaller ICH volumes (e.g., < 10 ml) do not generate significant PHE. To balance the presence of IVH with ICH volumes capable of generating PHE, we have elected to set the following subject exclusion criteria based on the original Graeb score (oGS; Graeb et al 1982), which grades IVH severity on a scale of 0-12. The third and fourth ventricles are each scored as 0 (no blood present), 1 (blood present, ventricle size normal), or 2 (ventricle filled with blood and expanded); and the two lateral ventricles are each scored as 0 (no blood), 1 (trace of blood or mild bleeding), 2 (< 50% of ventricle filled with blood), 3 (>50% of ventricle filled with blood), or 4 (ventricle filled with blood and expanded), for a total maximum score of 2 + 2 + 4 + 4 = 12. Blood within the 4th ventricle, and to some extent in the 3rd ventricle is a risk factor for hydrocephalus requiring surgical intervention, which would eliminate ICH patients from our study. As such, patients presenting with any 4th ventricular blood (max = 0), any evidence of 3rd ventricular expansion (max = 1), and more than trace or mild blood in either or both lateral ventricles (max = 1 each), thereby having an oGS > 3 will be excluded from participating in this study.

Following the initial diagnostic CT, repeat CT images will be obtained between 24-48 hours after the diagnostic scan, and on Days CCI 14 Commercially Confidential Information Only non-contrast study CT scans will be obtained on Days CCI 14. The non-contrast scan acquired on each patient at first follow-up (i.e., 24-48 hours after the diagnostic scan) will serve as the baseline for our analysis. All CT scans will be uploaded through a secure server,

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Additional CT or MRI scans may be performed, in particular in the event of changes in the patient's clinical course, according the site's local standard of care for ICH patients.

Modified Rankin Scale (mRS)

The modified Rankin Scale (mRS), attached as Appendix 4-Section 18 is a widely-used, clinician-assessed instrument, and is considered the current standard assessment for stroke outcomes by most Health Authorities. It consists of 6 grades of disability, higher scores indicating more severe disability (0 = asymptomatic, 6 = dead). The strength of the mRS is that it captures the full spectrum of limitations in activity and participation after stroke with reasonable inter-rater reliability (Banks and Marotta 2007). The mRS can be administered by investigators, study nurses, and research assistants. Training in administration of the mRS interview will be provided to site personnel as necessary, and proficiency certification will be monitored and centrally recorded. In this study, mRS interviews will be video recorded, then securely transferred to and rated by a Central Independent Adjudication Panel. Individual (rater) mRS scores (and the panel average) as well as the panel consensus score for each interview will be recorded.

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8.6 Safety

The methods, assessment, specification, and recording for each assessment will be detailed in the Site Operations Manual.

8.6.1 Physical examination

A complete physical examination will be performed at the visits indicated in the Assessments schedule (Table 8-1) and will include an assessment of skin, head and neck, lymph nodes, heart, lungs, abdomen, back, neurological function and comments on general appearance. All significant findings that are present prior to signing informed consent must be reported on the relevant medical history/current medical conditions eCRF. Significant findings made after signing the informed consent that meet the definition of an AE and must be recorded on the adverse events eCRF. Due to the seriousness of the illness at baseline it might not be possible to assess all aspects of physical examination.

8.6.2 Vital signs

Vital signs will include pulse rate, systolic and diastolic blood pressure in supine position, respiratory rate, and temperature which will be assessed at the visits indicated in Table 8-1.

8.6.3 Clinical laboratory evaluations

Due to the emergency setting of the patient, screening/baseline laboratory evaluation can be performed locally. A central laboratory will be used for all other time points for the analysis of all specimens collected. Timings of blood sample collection are outlined in the Table 8-1. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Abnormal laboratory parameters, inconsistent with clinical presentation of stroke or which cause suspicion of an underlying medical condition, should be repeated for confirmation. Additional local lab samples will be taken according the site's local practice to adhere to local standard of care for ICH patients.

8.6.3.1 Hematology

Blood samples will be collected at the scheduled visits indicated in Table 8-1. The parameters assessed will include: red blood cell count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, neutrophils), platelet count, hemoglobin, hematocrit,

mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and red blood cell morphology.

Due to the seriousness of the condition, local lab blood sampling needed for the routine medical care will have to be taken as well. **The Treating Physician will take special care that after the initiation of study treatment absolute total WBC count and lymphocyte counts are only communicated to persons on the treatment team who need to know this result for clinical decision making**. It is imperative that this information is not communicated more broadly: the Treating Physician must under no circumstances communicate this information to ward personnel, and particularly not to local Independent Raters, those study team members who will be conducting follow-up mRS assessments on ICH patients.

For study blinding purposes after the baseline visit only the absolute counts for eosinophils, basophils, neutrophils and monocytes will be communicated to sites by the central laboratory. The absolute total WBC, and lymphocyte counts will be measured at each visit by the central laboratory, will be blinded from the sponsor and the Investigator; and will **only** be communicated to the site Principal Investigator in case of an abnormality which might require an AE evaluation and/or could result in a change in patient treatment.

8.6.3.2 Clinical chemistry

Blood samples will be collected at the scheduled visits indicated in Table 8-1 and the parameters assessed will include: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, P), non-fasting glucose, albumin, alkaline phosphatase, creatinine, ALT, AST, GGT, amylase, total bilirubin, conjugated bilirubin, and CRP. After the initial screening chemistry, total cholesterol, triglycerides, HDL, and LDL may or may not be repeated at the discretion of the Investigator.

8.6.4 Electrocardiogram (ECG)

Continuous cardiac monitoring must be implemented via bedside monitoring or telemetry in all patients during days when the patient is in the Stroke Unit/Neurointensive Care Unit. Cardiac monitoring must be performed from 1 hour before dosing to 48 hours after the first drug administration. Continuous cardiac monitoring may be done for a longer duration on a case-by-case basis at the discretion of the Investigator and the treating physician.

Standard twelve-lead ECGs will be performed for all patients at the time points as indicated in Table 8-1. All ECG data must be stored and made available to the sponsor upon request.

For telemetry, in the event of clinical significant abnormalities, rhythm strips should be captured and printed, or annotated by the Investigator/treating physician, and kept with the source documents. In the case of no CV abnormalities, source notes confirming review of telemetry data are sufficient. Cardiac safety monitoring data will used for cardiac rhythm evaluation (mainly bradyarrhythmias, such as atrioventricular blocks and sinus pauses) and for HR assessments.

Clinically significant abnormalities should be recorded on the Medical History/Adverse event eCRF page.

Symptomatic events, particularly when requiring medical intervention may lead to patient discontinuation. Treatment interruption or omitting a dose of BAF312 should be guided by the considerations outlined in Section 6.6.

8.6.5 Pregnancy test and assessments of fertility

Urine pregnancy testing will be done for all female study subjects of childbearing potential at baseline and Day 30 (V11). Positive urine pregnancy tests will be confirmed with serum pregnancy testing.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms, etc.) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks prior to ICH. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up FSH level assessment is she considered not of child-bearing potential.

8.7 Pharmacokinetics

Pharmacokinetic (PK) samples will be collected at the time points defined in the Assessment schedule (Section 8.1). Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing and shipment.

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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 (see Section 11.5.3).

8.8 Other assessments

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8.9 Use of residual biological samples

Residual blood samples may be used for another protocol-specified endpoint.

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9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient after **providing written informed consent** for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant, or
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

Adverse events should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. CTCAE severity grade (1-5)

   If CTCAE grading does not exist for an adverse event, use: 1=mild, 2=moderate, 3=severe 4=life threatening* (see Section 9.2 for definition of a serious adverse event (SAE))

   *Note: There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria).

   CTCAE grade 5 (death) is not used, but is collected as a seriousness criteria and also collected in other CRFs (e.g. Study Completion, Death/Survival).

2. Its relationship to the study treatment (no/yes).
3. Its duration (start and end dates); or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding investigational treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)
6. Its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the

form of Investigator Notifications. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

*Refer to the Site Operations Manual for data capture methodology regarding AE collection for patients that fail screening.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, **unless hospitalization is for**:
    1. routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    2. elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study) and has not worsened since the start of study drug
    3. treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    4. social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to International Conference on Harmonisation-E2D Guideline 2003).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to International Conference on Harmonisation-E2D Guideline 2003).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO&PS) as per Section 9.2.2.

9.2.2 SAE reporting

IMPORTANT: To comply with regulations, all suspected, unexpected, serious adverse reactions (SUSARs) occurring in a clinical trial must be reported in an expedited timeframe (7 or 15 days) to Competent Authorities.

However, regulations do allow that certain adverse experiences that would ordinarily fall under the SAE definition can be handled differently. These exemptions from reporting of SAEs are particularly relevant to studies in high morbidity and high mortality populations where study subjects are generally sicker, such as patients with ICH, and often carry significant concomitant disease burdens.

- **Event(s) common in the patient population under study**: The unblinding of single SAEs that are relatively common in the patient population under study, for SUSAR reporting, often does not increase the understanding of safety, and can damage the integrity of the blinded nature and analysis of a study. The following SAEs commonly seen in the ICH patient population will still be captured by the investigators as SAEs in the CRF and reported to Novartis, but they will not be unblinded during the course of the study, even if considered "related" to study treatment by the reporting investigator, nor reported on an expedited basis to regulatory authorities:
  1. **Ventricular extension of hemorrhage with increased ventricular pressure requiring surgical intervention (e.g., external ventricular drainage), and**
  2. **Expansion of initial intracerebral hemorrhage requiring surgical evacuation.**

Additionally, these safety data will be reviewed in an expedited timeframe of 15 days by the external DMC.

Screen Failures

Note the following requirement for Screen Failures: SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.

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To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until the study completion visit, must be reported to Novartis within 24 hours of learning of its occurrence as described below.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Chief Medical Office and Patient Safety (CMO& PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

9.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1-Appendix 1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 15-2-Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation within 48-72 hours.

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the patient. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the patient if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
- Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and GGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic. Retesting should be continued up to resolution.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 15-3.
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.4 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Chief Medical Office and Patient Safety (CMO& PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO& PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Guidance for capturing study treatment errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

This study enrolls women who are considered unlikely to be of child-bearing potential; thus pregnancy is not an expected outcome for any female study participant. However, in the case that a pregnancy in a female study participant should occur, please follow the below reporting guidelines.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO&PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy outcome information should continue to be collected from newborn infants and continue for up to one year from birth of the infant.

9.7 Prospective suicidality assessment

The ICH patients who will be enrolled in this study will have major, significant neurological impairment during and after dosing with BAF312 or placebo, which will confound the assessment of suicidality. This would make any such prospective suicidality assessment, such as the C-SSRS, of questionable value. Novartis, therefore, will not include a suicidality assessment as part of this Commercially Confidential Information study of BAF312 in ICH.

9.8 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (email) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. **[Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs.]** The investigator must also keep the original informed consent form signed by the patient (a signed copy is also given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the EDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

10.3 Database management and quality control

Novartis staff (or CRO working on behalf of Novartis) review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies, medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Blood samples for Pharmacokinetics will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient will be tracked using an Interactive Response Technology (IRT). The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

10.4 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) has been appointed and will be provided regularly with semi-blinded safety data. The DMC will 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 protocol that may be required to ensure patient safety and preserve trial integrity. The DMC may also advise to put the study on hold pending further data analysis, or to discontinue the trial.

10.5 Adjudication Committee

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11 Data analysis

The analysis will be conducted on all patient data at the time the trial ends. Any data analysis carried out independently by the Investigator must be submitted to Novartis before publication or presentation.

11.1 Analysis sets

The Full Analysis Set will include all patients who are randomized and received at least one dose of study drug after randomization.

The Safety Analysis Set will include all patients that received at least one dose of study drug.

The Per Protocol Set (PPS) will include all patients in the full analysis set (FAS) having received at least the first infusion on Day 1 and no protocol deviations with relevant impact on efficacy data.

The PK Analysis Set 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 with relevant impact on PK data.

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

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment arm and patient. Summary statistics will be provided by treatment arm.

Patient demographics will include age, sex, race, ethnicity, height, weight and BMI.

Other baseline disease characteristics include relevant medical history, current relevant medication, blood pressure, GCS score, CCI historically estimated pre-stroke mRS score, hematoma volume, location of hematoma, time from first symptoms of ICH or last seen neurologically normal, and any other relevant information.

11.3 Treatments

Data for study drug administration and concomitant therapies will be listed by treatment group and patient.

11.4 Analysis of the primary variable(s)

The primary aim of this study is 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.

11.4.1 Primary Variable(s)

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.

11.4.2 Statistical model, hypothesis, and method of analysis

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 90% CI will be calculated, and these estimates will be back-transformed to give a geometric mean ratio and 90% CI between BAF312 and placebo.

The primary analysis will be done on the PPS.

11.4.3 Handling of missing values/censoring/discontinuations

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

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11.4.4 Sensitivity analyses

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11.5 Analysis of secondary variable(s)

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

11.5.1 Efficacy / Pharmacodynamics

Not Applicable

11.5.2 Safety

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment group, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

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

11.5.3 Pharmacokinetics

BAF312 plasma concentration data will be listed by treatment, patient, and visit/sampling time point.

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11.5.4 Pharmacokinetic / pharmacodynamic interactions

Not applicable.

11.5.5 Other assessments

Not applicable.

11.6 Analysis of exploratory variables

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11.7 Sample size calculation

Based on the literature (Staykov et al 2011; Volbers et al 2011), the reported variability (Coefficient of Variation, CV) of absolute PHE volume in ICH patients within first 12 to 16 days of ICH is in the range 70% to 92%, and that of relative PHE is in the range 64% to 114%. Assuming a CV of 90%, the design with 60 evaluable patients expected to have data on aPHE at day 14 (30 on BAF312 and 30 Placebo) has 80% power to detect statistically significant treatment difference at 1-sided α=0.05, when the true mean percent reduction in PHE at a given time point (BAF312 over Placebo) is 40%.

11.8 Power for analysis of key secondary variables

Not applicable.

11.9 Interim analyses

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12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonisation Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g. advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs,

and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For this multi-center trial, a Coordinating Investigator will be selected by Novartis by the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

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15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance*
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance*

*Liver event guidance for CRF completion is available in the Site Operations Manual

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Ceruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase > 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.

17 Appendix 3: Clinically notable laboratory values and vital signs

Table 17-1 Notable Vital Signs And Body Weight

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

18 Appendix 4: Modified Rankin Scale

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____
Rater Name: _____
Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

References

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20 Appendix 6: Glasgow Coma Scale (GCS)

From: www.glasgowcomascale.org

GLASGOW COMA SCALE : Do it this way

GCS at 40 EYES VERBAL MOTOR

Institute of Neurological Sciences NHS Greater Glasgow and Clyde

CHECK	OBSERVE	STIMULATE	RATE
For factors Interfering with communication, ability to respond and other injuries	Eye opening , content of speech and movements of right and left sides	Sound: spoken or shouted request Physical: Pressure on finger tip, trapezius or supraorbital notch	Assign according to highest response observed

Eye opening

Criterion	Observed	Rating	Score
Open before stimulus	✔	Spontaneous	4
After spoken or shouted request	✔	To sound	3
After finger tip stimulus	✔	To pressure	2
No opening at any time, no interfering factor	✔	None	1
Closed by local factor	✔	Non testable	NT

Verbal response

Criterion	Observed	Rating	Score
Correctly gives name, place and date	✔	Orientated	5
Not orientated but communication coherently	✔	Confused	4
Intelligible single words	✔	Words	3
Only moans / groans	✔	Sounds	2
No audible response, no interfering factor	✔	None	1
Factor interfering with communication	✔	Non testable	NT

Best motor response

Criterion	Observed	Rating	Score
Obey 2-part request	✔	Obeys commands	6
Brings hand above clavicle to stimulus on head neck	✔	Localising	5
Bends arm at elbow rapidly but features not predominantly abnormal	✔	Normal flexion	4
Bends arm at elbow, features clearly predominantly abnormal	✔	Abnormal flexion	3
Extends arm at elbow	✔	Extension	2
No movement in arms / legs, no interfering factor	✔	None	1
Paralysed or other limiting factor	✔	Non testable	NT

Sites For Physical Stimulation

Finger tip pressure | Trapezius Pinch | Supraorbital notch

Features of Flexion Responses

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For further information and video demonstration visit www.glasgowcomascale.org

21 Appendix 7: List of prohibited medications

The aim of this document is to provide a specific list of drugs that should not be co-administered with BAF312 because of their CYP2C9/3A4 inhibitory or induction potential.

Due to the constant information arising on drugs, these lists are by no mean exhaustive and medical judgment should always prevail. These lists are adapted to the patient population and the exclusion criteria of the study CBAF312X2207 only.

Only potent CYP2C9 and CYP3A4 inhibitors may have a significant effect on BAF312 exposure and should not be co-administered with BAF312 (Table 21-1).

Potent CYP2C9 and/or CYP3A4 inducers (Table 21-2) should not be coadministered with BAF312 to avoid a potential decrease of efficacy of BAF312 in case of under-exposure due to CYP2C9/CYP3A4 induction (note that topical use is permitted).

Table 21-1 Typical inhibitors of CYP2C9 or CYP3A4

Antibiotics:	**Antivirals:**
Clarithromycin	Boceprevir
Sulfaphenazole	Telaprevir
Telithromycin	
Troleandomycin	
Protease Inhibitors:	**Others**:
Indinavir	Amiodarone
Lopinavir	Ataciguat
Nelfinavir	Azapropazone
Ritonavir	Benzbromarone
Saquinavir	Bucolome
Tipranavir	Cobicistat
Antifungals:	Conivaptan
Fluconazole	Elvitegravir
Itraconazole	Mibefradil
Ketoconazole	Nefazodone
Miconazole	Oxandrolone
Posaconazole	Tielinic Acid
Voriconazole	

Table 21-2 Typical inducers of CYP2C9 and/or CYP3A4

Aprepitant	Ginkgo	Rifabutin
Avasamide	Lersivirine	Rifampin
Bosentan	Lopinavir	Ritonavir
Carbamazepine	Mitotane	Secobarbital
Dalcetrapid	Modafinil	Semagacestat
Efavirenz	Nafcillin	St. John's wort
Enzalutamide	Nelfinavir	Talviraline
Escalicarbazepine	Nevirapine	Thioridazine
Etravirin	Phenobarbital	Tipranavir
Genistein	Phenytoin	Vigabatrin