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Official Title:	A multicenter, international, randomized, placebo controlled, double-blind, parallel group and event driven Phase 3 study of the oral FXIa inhibitor asundexian (BAY 2433334) for the prevention of ischemic stroke in male and female participants aged 18 years and older after an acute non-cardioembolic ischemic stroke or high-risk TIA
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Title Page

Protocol Title:

A multicenter, international, randomized, placebo controlled, double-blind, parallel group and event driven Phase 3 study of the oral FXIa inhibitor asundexian (BAY 2433334) for the prevention of ischemic stroke in male and female participants aged 18 years and older after an acute non-cardioembolic ischemic stroke or high-risk TIA

Protocol Number: 20604

Protocol Version: 3.0

Amendment Number: Amendment 2

Compound Number: Asundexian (BAY 2433334)

Short Title: Phase 3 study to investigate the efficacy and safety of the oral FXIa inhibitor asundexian (BAY 2433334) compared with placebo in participants after an acute non-cardioembolic ischemic stroke or high-risk TIA

Study Phase: 3

Acronym: OCEANIC-STROKE (Phase 3 program of the **O**ral fa**C**tor **E**leven **A** i**N**hibitor asundex**I**an as novel anti-thromboti**C** –**STROKE** study)

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Protocol Date: 18 APR 2024

Name: PPD Role: PPD

Medical Monitor name and contact information can be found in the Trial Master File.

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List of Abbreviations and Definitions of Terms

AC	Anticoagulant
ADL	Activities of daily living
AE	Adverse Event
AF	Atrial fibrillation
AG	Joint stock company*, Aktiengesellschaft*
AHA	American Heart Association
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AXIA	Activated Factor XIa activity
BARC	Bleeding Academic Research Consortium
BCRP	Breast Cancer Resistance Protein
BfArM	Das Bundesinstitut für Arzneimittel und Medizinprodukte, Federal Institute for Drugs and Medical Devices
BID	Twice a day*, Bis in die*
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CEC	Clinical Events Committee
CEOT	Common End of Treatment
CES1	Carboxylesterase 1
CFR	Code of Federal Regulations
CI	Confidence interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CSR	Clinical study report
csHR	Cause-specific hazard ratio
CT	Computed tomography
CTA	Computed tomography angiography
CV	Cardiovascular
CYP2C8	Cytochrome P450, family 2, subfamily C, polypeptide 8
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
D	Day
DNA	Desoxyribonucleic acid
DRE	Disease-related event
DSA	Digital subtraction angiography
DWI	Diffusion-weighted imaging
e.g.	For example, *exempli gratia*
EC	Executive Committee
ECG	Electrocardiogram
eCRF	Electronic case report form

eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	European Quality of Life group 5-Dimension questionnaire
ESO	European Stroke Organization
ESUS	Embolic stroke of undetermined source
ET	Early termination
EU	European Union
EudraCT	European Clinical Trials Database
EVT	Endovascular thrombectomy
F	Factor
FAS	Full Analysis Set
FDA	Food and Drug Administration
$FeCl_2$	Ferric chloride
FSH	Follicle stimulating hormone
γGT	Gamma glutamyl transpeptidase
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
HR	Hazard ratio
HRT	Hormonal replacement therapy
i.e.	That is, *id est*
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISTH	International Society on Thrombosis and Hemostasis
LDH	Lactate dehydrogenase
LMWH	Low molecular weight heparin
LOC	Level of consciousness
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MI	Myocardial infarction
MRA	Magnetic resonance angiogram
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NJ	New Jersey
NOAC	Non-Vitamin K oral anticoagulant
NSAID	Nonsteroidal anti-inflammatory drug
OD	Once a day
$P2Y_{12}$	G_i-coupled platelet receptor for adenosine diphosphate
PAD	Peripheral artery disease

PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
P-gp	Permeability glycoprotein
PH	Parenchymatous hematoma
PK	Pharmacokinetic(s)
PLC	Program Leadership Committee
popPK-PD	Population PK-PD
QC	Quality control
RBC	Red blood cell (count)
RND	Randomization
ROTEM	Rotational thromboelastometry
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical analysis software
SC	Steering Committee
SCR	Screening
SFU	Safety follow-up
SI	Study intervention
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
TAVI	Transcatheter Aortic Valve Implantation
TEAE	Treatment Emergent Adverse Event
TIA	Transient ischemic attack
TKA	Total knee arthroplasty
TM	Trademark
TMF	Trial Master File
U	Unit
ULN	Upper limit of normal
UN	Untestable
US / USA	United States / United States of America
VAS	Visual Analogue Scale
vs.	As compared to, *versus*
VKA	Vitamin K antagonist
W	Week
WBC	White blood cell (count)
WOCBP	Woman of Childbearing Potential
WONCBP	Woman of Nonchildbearing Potential

Index event	Stroke event or high-risk TIA qualifying the patient to participate in the study.

Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 2	3.0	18 APR 2024	Global amendment that includes changes applicable to all countries
Amendment 1	2.0	29 NOV 2023	Global amendment that includes changes applicable to all countries
DEU-1	DEU-1	13 FEB 2023	Updated to implement changes specific to Germany (DEU-1)
KOR-1	KOR-1	19 JAN 2023	Updated to implement changes specific to the Republic of Korea (KOR-1)
Clinical Study Protocol	1.0	12 SEP 2022	-

Note: A new naming and versioning approach was adopted after the local amendment for Germany (DEU-1, dated 13 FEB 2023) was prepared. According to the current naming and versioning approach, all amendments (both global and local) are sequentially numbered and versioned.

Protocol Amendment Summary of Changes Table

Amendment 2 (18 APR 2024)

This amendment/modification is considered to be substantial based on the relevant criteria of the European Union clinical trial legislation.

Overall Rationale for the Amendment:

This amendment is primarily prepared to increase the sample size of the study from 9300 to 12300 randomized participants, and to introduce an interim analysis for futility. The protocol assumptions for the sample size calculations were revised from the original calculations following review of blinded data. The increase in sample size is justified by a higher permanent discontinuation rate and lower incidence rate of ischemic stroke in the study that reduces the expected effect size for the primary efficacy endpoint and, thus, the HR used for the sample size estimate is changed to 0.80. In addition, the sample size increase allows a greater power for secondary efficacy endpoints and subgroups of interest. The interim analysis for futility is introduced to mitigate the risk of exposing participants to the study intervention if it is unlikely to be efficacious.

All changes made in this amendment are summarized below.

Section # and Name	Description of Change	Brief Rationale
Title Page	EudraCT number removed.	Superseded by EU-CT number.
	Statement regarding electronic signatures removed.	Process for electronic signature collection changed.
1.1 Synopsis	The planned number of participants screened, number of participants randomized, and target number of participants who experienced a primary efficacy event were revised.	The planning assumptions were reviewed and updated based on blinded data, and the sample size was increased.
1.2 Schema	The planned number of participants randomized was revised.	The planning assumptions were reviewed and updated based on blinded data, and the sample size was increased.
1.3 Schedule of Activities (SoA)	Footnote for timing of procedures and assessments at visit 2 revised.	Revised for clarity; procedures and assessments at visit 2 must be performed prior to randomization.
	Imaging collection of stroke outcome events revised.	Imaging required for all strokes (both ischemic and hemorrhagic) for completeness of exploratory analyses.
2 Introduction	Revised to include a statement on the early termination of OCEANIC-AF based on IDMC recommendation.	Revised to reflect the current development status.
4.1 Overall Design	Pre-screening data collection added.	Exploratory pre-screening data will be collected to investigate factors associated with participation in the OCEANIC-STROKE study.
6.1 Study Intervention(s) Administered	Administration of crushed tablets via feeding tube added.	Clarification added regarding administration of study intervention via feeding tube.
8.2.3.1 EuroQol Group 5-dimension questionnaire (EQ-5D)	Description of questionnaire completion revised.	Revised to clarify completion of questionnaire with assistance.
9.4 Interim Analysis	Interim analysis for futility added.	Interim analysis for futility added to mitigate the risk of exposing participants to study intervention if unlikely to be efficacious.
9.5 Sample Size Determination	The planned number of participants screened, number of participants randomized, and target number of participants who experienced a primary efficacy event were revised. Description of interim analysis added.	The planning assumptions were reviewed and updated based on blinded data, and the sample size was increased.
10.1.11 Publication Policy	Added a reference to the Publication Committee charter.	Added for completeness.

Section # and Name	Description of Change	Brief Rationale
10.1.3 Informed Consent Process	Instructions for re-consent revised.	Revised to incorporate flexibility in the re-consent process for minor changes to the ICF.
10.2.2 Liver Safety: Follow-up Assessments and Suggested Actions	Anti-herpes simplex virus IgM antibodies removed from list of central laboratory tests.	The test is no longer available at the central laboratory.
10.12 Appendix 12: Protocol Amendment History	Section added.	Summary of changes for Amendment 1 moved to this section.

1. Protocol Summary

1.1 Synopsis

Protocol Title: A multicenter, international, randomized, placebo controlled, double-blind, parallel group and event driven Phase 3 study of the oral FXIa inhibitor asundexian (BAY 2433334) for the prevention of ischemic stroke in male and female participants aged 18 years and older after an acute non-cardioembolic ischemic stroke or high-risk TIA

Short Title: Phase 3 study to investigate the efficacy and safety of the oral FXIa inhibitor asundexian (BAY 2433334) compared with placebo in participants after an acute non-cardioembolic ischemic stroke or high-risk TIA

Envisaged indications: Prevention of ischemic stroke in patients after an acute non-cardioembolic ischemic stroke or high-risk transient ischemic attack (TIA) in combination with antiplatelet therapy (non-cardioembolic ischemic stroke prevention).

Rationale: Asundexian, as an oral FXIa inhibitor, is expected to show a benefit in reducing the risk for stroke in patients after a non-cardioembolic ischemic stroke or high-risk TIA. At the same time, asundexian is expected to have a low risk of bleeding. This is supported by data from animal models as well as from the completed Phase 2 clinical studies.

Objectives, Endpoints, and Estimands

Table 1–1: Summary of primary and secondary objectives and endpoints

Objectives	Endpoints
Primary	
Efficacy	
To evaluate whether the oral FXIa inhibitor asundexian is superior to placebo on top of background antiplatelet therapy in reducing ischemic stroke in patients after an acute non-cardioembolic ischemic stroke or high-risk TIA	• Ischemic stroke*
Safety	
To compare the incidence of ISTH major bleeding for asundexian and placebo on top of antiplatelet therapy in patients after an acute non-cardioembolic ischemic stroke or high-risk TIA	• ISTH major bleeding*
Secondary	
Efficacy	
To evaluate whether asundexian is superior to placebo on top of antiplatelet therapy in reducing the occurrence of composite and individual efficacy endpoints	• All strokes (ischemic and hemorrhagic)* • Composite of CV death, MI or stroke* • Composite of all-cause mortality, MI or stroke* • Ischemic stroke in the first 90 days* • Disabling stroke (mRS ≥3 at 90 days)* • All-cause mortality* • Transient ischemic attack (TIA)*
Safety	
To compare asundexian and placebo on top of antiplatelet therapy with respect to individual bleeding endpoints	• Composite of ISTH major or clinically relevant non-major bleeding* • ISTH clinically relevant non-major bleeding* • Symptomatic intracranial hemorrhage* • Hemorrhagic stroke* • Fatal bleeding* • Minor bleeding*
Net clinical benefit	
To further compare the benefit and risk of asundexian and placebo with respect to a composite of efficacy and safety endpoints	• Composite of ischemic stroke or ISTH major bleeding* • Composite of CV death, all stroke, MI or ISTH major bleeding* • Composite of all-cause mortality, disabling stroke, fatal bleeding, symptomatic intracranial hemorrhage*

CV = cardiovascular, FXIa = Factor XIa, ISTH = International Society on Thrombosis and Hemostasis, MI = myocardial infarction, mRS = modified Rankin Scale, TIA = transient ischemic attack
* Time to first occurrence

Estimands are described in Section 3.

Overall Design Synopsis:

OCEANIC-STROKE (study 20604) is a multicenter, international, randomized, placebo controlled, double-blind, parallel group, event driven phase 3 study. The overall study design is depicted in Figure 1–1.

The purpose of this study is to investigate the efficacy of the oral FXIa inhibitor asundexian in prevention of ischemic stroke and its safety (bleeding) compared with placebo on top of background antiplatelet therapy in adult participants after an acute non-cardioembolic ischemic stroke or high-risk TIA.

Study details include:

- For individual participants the duration of the intervention period will depend on the timepoint of randomization and accrual of outcome events, and may be in the range of 3 to 31 months.
- There will be a screening visit followed by a randomization visit within 72 hours of the onset of symptoms of the index event (stroke or TIA). The visit frequency after randomization will be a first visit at 1 month (phone visit), the next visit at 3 months (site visit) and then every 3 months until the common end of treatment (CEOT) visit. After Month 6 visit, site and phone visits will be alternating, i.e. phone visit at Month 9, site visit at Month 12 etc. A safety follow-up visit via phone will take place 2 weeks after the CEOT visit.

Number of Participants:

Approximately 13000 participants will be screened to achieve +/- 12300 randomized participants (6150 randomized participants per intervention group). This is an event-driven study. The required target number of study participants who have experienced a primary efficacy event is estimated to be approximately 830. More details are available in Section 9.5.

Study Arms and Duration:

Asundexian is the sponsor's study intervention under investigation. The following intervention groups are included in the study:

- Asundexian 50 mg OD
- Placebo OD

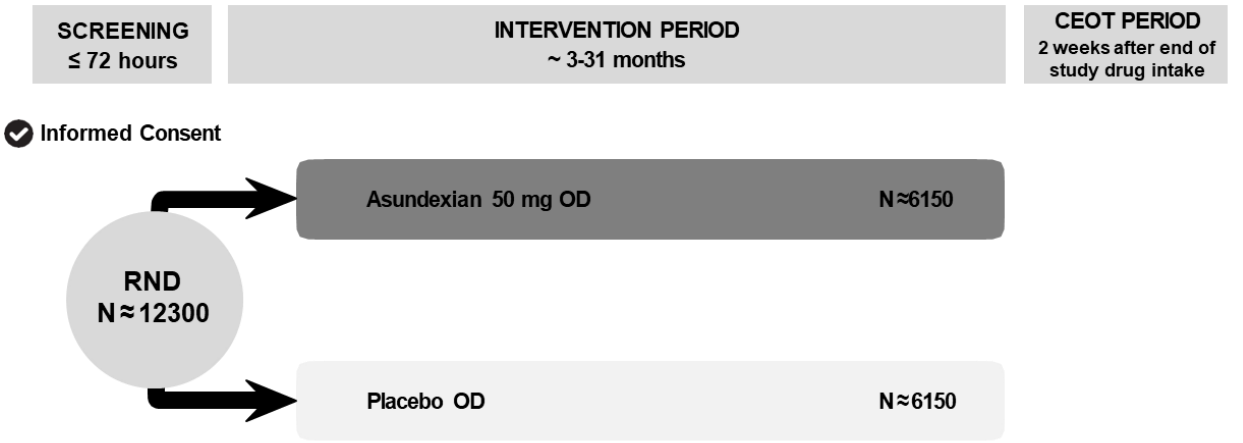
The total duration of study participation, along with the sequence and the duration of study periods, is provided under "Overall Design" in Section 4.1.

Independent Data Monitoring Committee:

An Independent Data Monitoring Committee (IDMC) will be involved in the review of safety data as well as efficacy data to determine the risk/benefit ratio (Section 10.1.6.4). Detailed information on the roles and responsibilities of the IDMC will be described in the IDMC Charter.

1.2 Schema

Figure 1–1: Study design overview



- phone visit

Abbreviations: CEOT = common end of treatment, M = month, N = number of participants, OD = once a day, RND = randomization, SFU = safety follow-up, W = weeks

* If applicable visits will continue after Month 30 in the same way as before until CEOT visit.

Day 1 is the day of randomization.

1.3 Schedule of Activities (SoA)

Study periods Duration	**Screening/RND** ≤72 hours before RND *		**Intervention period** ~3-~31 months **, from RND until Common End of Treatment (CEOT) visit / **Early Termination (ET)**										**Early Termination period***** ET until CEOT visit			**CEOT period** CEOT visit until 2 weeks thereafter	
Visit number	**1**	**2 ***	**3**	**4**	**5 ***	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ET visit**	**ET SFU visit**	**≥3→12**	**CEOT** visit	**CEOT SFU visit**
Visit type	site	site	☎	site	site	☎	site	☎	site	☎	site	☎	site	☎ (site)	☎ (site)	site (☎)	☎
Month [M] Study days [D] / weeks [W] and allowed windows	**SCR** D-3 → 1	**RND / M0** D1	**M1** D30 ±4D	**M3** W13 ±1W	**M6** W26 ±1W	**M9** W39 ±1W	**M12** W52 ±1W	**M15** W65 ±1W	**M18** W78 ±1W	**M21** W91 ±1W	**M24** W104 ±1W	**M27** W117 ±1W	**ET** **ET**	**ET+2W** +1W	**≥M1→ M27** ≥D30->W117 ±1W	**CEOT** CEOT ±~3W	**CEOT visit +2W** +1W
Administrative procedures																	
Informed consent	X																
Inclusion / exclusion criteria	X	X															
Demographics and biometrics	X																
Medical history	X																
Prior / concomitant medication	←========== continuously ==========→														AP/AC only	X(AP/AC only)	X
Clinical procedures / assessments																	
mRS (+ on D7 after index event)			X	X	X	X	X	X	X	X	X	X	X		X	X†	
NIHSS (D7 after index event)	X	X															
12-lead ECG	X																
Vital signs (BP and heart rate)	X	X		X	X		X		X		X		X			X†	
Adverse events	procedure-related	←========== continuously ==========→														X†	X
Outcome events		←========== continuously ==========→															
Healthcare Resource Utilization	←========== continuously ==========→																
EQ-5D		X			X		X		X		X		X			X†	
IRT																	
Randomization		X															
Visit registration	X			X	X		X		X		X		X			X	
Study intervention (SI) administration																	
SI dispensation		X		X	X		X		X		X						
SI collection / accountability				X	X		X		X		X		X			X†	
Laboratory assessments																	
Safety Blood sampling		X		X	X		X				X		X			X†	
Pregnancy test (if WOCBP)	X												X			X†	
PK				X			X										
At selected sites																	
PD (a) / Biomarker (b)		a, b		a			a, b										
MRI (see Section 10.10)		X			X												

Annotated Schedule of Activities (Annotated SoA)

Administrative procedures	
Informed consent	Informed consent must be obtained before initiation of any study-specific procedure.
Inclusion / exclusion criteria	In case screening and randomization are performed on the same calendar day, these criteria need to be assessed only once.
Demographics and biometrics	Biometrics refers to measurement of height and weight and will only be performed and recorded at screening.
Prior / concomitant medication	if SI is *permanently* discontinued ≥ 2W before CEOT visit, only AP/AC need to be reported at scheduled visits, including CEOT visit; otherwise all meds need to be reported
Clinical procedures / assessments	
mRS / NIHSS	For mRS see Section 10.7; for NIHSS see Section 10.8. NIHSS is collected at presentation (hospital / ER) and at randomization. For eligibility, the score nearest to randomization needs to be used. mRS and NIHSS should be assessed on Day 7 after the index event or at hospital discharge, if it occurs before Day 7. mRS should additionally be assessed at all time points indicated in the SoA. For recurrent stroke events: maximum score during hospitalization (NIHSS), Day 7 after the event (or at hospital discharge, if this occurs before Day 7: NIHSS and mRS).
12-lead ECG	At least one ECG (either done as part of routine management or part of the study) should be done before randomization, as close as possible to randomization to rule out atrial fibrillation (Section 8.3.6).
Vital signs (BP and heart rate)	Can also be used if done as part of routine assessment of the index event; BP needs to be re-assessed before randomization as specified in exclusion criterion 5 (Section 5.2). Description is in Section 8.3.5.
Adverse events	(S)AEs will be collected from start of SI intake until SFU visit; (CEOT SFU or ET SFU); only study procedure related events will be reported from signing of ICF (8.4.1).
Outcome events****	Outcome events including all bleeding, death, myocardial infarction, and stroke, as well as events indicative of a potential outcome (Section 10.9) need to be reported in the CRF continuously from randomization until CEOT SFU or death. See Section 7 and 8 for more details.
Healthcare Resource Utilization	Healthcare Resource Utilization (within hospitals) in conjunction with AEs and outcome events needs to be documented, e.g. time points or periods affected
EQ-5D	At visits where the questionnaire is required, participants should complete it (or with assistance if required) before any other study procedures or assessments.
IRT	
Randomization Visit registration	Screening and randomization can take place on the same calendar day if all information is available (visits 1 and 2 are combined); SI intake will start as soon as possible after randomization (Day 1), i.e. within 4 hours of randomization
Study intervention (SI) administration	
SI dispensation	At each contact the participants should be instructed regarding SI compliance. SI is taken once a day (see Section 6.1)
SI collection / accountability	At the CEOT visit the final SI collection occurs: no SI intake should take place on the day of this visit anymore; the last intake of SI occurs on the previous day.
Laboratory assessments	
Safety Blood sampling	The full set of safety laboratory tests is provided in Table 10–1. *For country-specific requirements for the Republic of Korea (KOR-1), see Section 10.11.3.1.*
Pregnancy test (if WOCBP)	A WOCBP must have a negative serum or urine pregnancy test before randomization. *For country-specific requirements for the Republic of Korea (KOR-1), see Section 10.11.3.1.*
PK	Refer to Table 1–2 regarding further details.
At selected sites	
PD (a) / Biomarker (b)	Refer to Table 1–2 regarding further details. Pharmacogenetics will be collected in a subset of participants.

Abbreviations: AE = adverse event, AP/AC = antiplatelets/anticoagulants, BP = blood pressure, CEOT = common end of treatment, CRF = case report form, ECG = electrocardiogram, EQ-5D = European Quality of Life group 5-Dimension questionnaire, ET = early termination, ICF = informed consent form, IRT = interactive response technology, MRI = magnetic resonance imaging, mRS = modified Rankin Scale, NIHSS = National Institute of Health Stroke Scale, PD, PK = pharmacodynamic(s), -kinetic(s), SCR = screening, SFU = safety follow-up, SI = study intervention, SoA = Schedule of Activities, W = week(s), WOCBP = woman of childbearing potential

* Randomization needs to take place within 72 h after symptom onset of the index event. Procedures and assessments at visit 2 should be conducted prior to randomization; SI dispensation / intake will usually be concluding the visit. Month 6 visit should be scheduled ≤ 14 weeks after the Month 3 visit (even though in theory up to 15 weeks could lie between Visit 4 and Visit 5 due to the allowed visit windows), to prevent that the participant runs out of SI.
** If applicable (if the number of efficacy outcome events does not accrue until Month 31 as expected) the visit schedule will continue after Month 27 with the respective labelling, e.g. visit 13, 14, etc. The duration of the intervention period depends on when a participant joins during the course of the study. Displayed timepoints might therefore not be applicable to all participants.
*** An **ET visit** is only applicable to participants who prematurely discontinue intake of SI *permanently*; those should undergo an ET visit as soon as possible after discontinuation of SI. An **ET SFU visit** will occur 2 weeks (+7 days window) after the day of the discontinuation of SI (Section 7.1), unless *permanent* discontinuation occurred < 2 W prior to CEOT visit, in which case a **CEOT SFU** will be performed instead. After permanent discontinuation of SI participants will take part in the remaining visits (via phone) as scheduled, including the CEOT visit (or CEOT SFU).
****If available, imaging related to stroke will be centrally collected.
† if SI *permanently* discontinued: item not applicable; only if discontinued < 2 weeks before CEOT visit, CEOT SFU will replace ET SFU; if SI is *permanently* discontinued a phone call CEOT visit is expected.

An overview of the PK, PD, and biomarker sampling is shown in Table 1–2. Refer to Sections 8.5 and 8.6 for details.

Table 1–2: PK, PD and Biomarker sampling

	Day 1 (Visit 2)	Month 3 (Visit 4)	Month 12 (Visit 7)
Sample timing *	Pre-dose	Pre-dose	Pre-dose
PK **	-	X	X
At selected sites only			
PD **	X	X	X
Biomarker plasma **	X	-	X
Biomarker serum **	X		X
Biomarker blood for pharmacogenetics	X	-	-

Abbreviations: PD, PK = Pharmacodynamic(s), -kinetic(s)

* At all visits: in order to collect pre-dose samples for PK and PD, participants should take their study intervention at the site only after blood sampling. The investigator must record the time when the study intervention is taken at the site. A phone call to remind the participants not to take the study intervention at home is recommended prior to study visit.

** If study intervention is temporarily discontinued, PK / PD blood samples should only be obtained if the study intervention has been restarted and sustained for at least 4 days, see Section 7.1.

PD and biomarkers will be collected in a subset of participants if approved by local IECs / IRBs and competent authorities (refer to Sections 8.5, 8.6 and 8.8). Biomarker blood for pharmacogenetics is generally planned to be collected at the randomization visit (Day 1), however, it can also be collected at a later visit in case it has not yet been taken and can be collected at any time in relation to study intervention intake at the respective visit.

The second biomarker sample should be taken at Month 12 or at CEOT, whichever occurs sooner.

The exact time of PK, PD and biomarker sampling needs to be recorded, as well as the time of the most recent / associated study intervention intake (i.e. on the PK / PD sampling day, as well as on the day before that).

2. Introduction

Asundexian is a direct, potent inhibitor of activated coagulation factor XI (FXIa) developed for 2 indications:

1. Prevention of ischemic stroke in patients after an acute non-cardioembolic stroke or high risk transient ischemic attack (TIA) in combination with antiplatelet therapy (non-cardioembolic ischemic stroke prevention)
2. Prevention of stroke and systemic embolism in patients with AF (cardioembolic stroke prevention)

OCEANIC-STROKE (study 20604) will be an event-driven Phase 3 study and will test asundexian against placebo on top of background antiplatelet therapy in participants after an acute non-cardioembolic ischemic stroke or high-risk TIA.

The clinical development of asundexian (FXIa inhibitor) included 1 additional Phase 3 study in participants with atrial fibrillation (OCEANIC-AF, study 19767). This study was testing asundexian against apixaban. After reviewing unblinded data on 19 NOV 2023, the IDMC recommended early termination of the OCEANIC-AF study because of inferior efficacy of asundexian compared to apixaban. The Sponsor concurred with the recommendation. The IDMC recommended continuation of the OCEANIC-STROKE study as planned.

Each individual study has its own study objectives to further characterize safety and efficacy of asundexian in the respective indications.

2.1 Study Rationale

OCEANIC-STROKE will explore asundexian 50 mg once daily in order to determine superiority to placebo on top of background antiplatelet therapy in reducing ischemic stroke in patients after an acute non-cardioembolic ischemic stroke or high-risk TIA. In addition, it will compare the bleeding profile between asundexian and placebo on top of background antiplatelet therapy.

Despite available treatments addressing risk factors for ischemic stroke, including antiplatelet therapy for secondary prevention, the recurrence of stroke is considerable (see Section 2.2.1). Anticoagulation therapy is currently not used in this indication.

It has been shown that patients with a stroke have increased levels of FXI, whilst patients with FXI deficiency have a lower risk for stroke (Schumacher et al. 2010).

Rivaroxaban was tested against acetylsalicylic acid [ASA] in patients with embolic stroke of undetermined source (ESUS) in the NAVIGATE ESUS study, which showed comparable efficacy, but led to an increase in bleeding (Hart et al. 2018). In the planned Phase 3 study, asundexian will be tested against placebo, added on top of contemporary background antiplatelet therapy. This approach of combining an anticoagulant and an antiplatelet therapy is supported by data from a post-hoc analysis of the COMPASS study in patients with stable atherosclerotic disease affecting the coronary and/or peripheral arteries. Patients who received the combination of 2.5 mg BID rivaroxaban plus ASA had fewer ischemic/uncertain strokes when compared to those who received ASA alone (HR 0.51, 95% CI 0.38–0.69). In addition, in the subgroup of patients with prior stroke the HR was 0.42 (95% CI 0.19-0.92) (Sharma M et al. 2019).

Additionally, exploratory analysis of an atherosclerosis subgroup in THALES identified a higher absolute risk and a greater absolute risk reduction of stroke or death at 30 days in patients with ipsilateral atherosclerosis stenosis than in those without (Amarenco et al. 2020).

The study will include patients with a non-cardioembolic ischemic stroke as well as high-risk TIA. Patients with a high-risk TIA have a relevant risk for a subsequent occurrence of a stroke. These patients were also included in earlier acute stroke studies such as SOCRATES, POINT and THALES.

Based on data from the completed dose-finding Phase 2 PACIFIC-STROKE study (see Section 2.2.4), participants to be included into the study need to have either evidence of cerebrovascular or systemic atherosclerosis (based on medical history or vascular imaging) or documented non-small vessel (non-lacunar) stroke (based on brain imaging). Participants can be enrolled if at least one of the three criteria is fulfilled. These criteria are intended to increase the number of patients with atherosclerotic disease into the study and also to reduce the number of participants with a small vessel (lacunar) stroke. In PACIFIC-STROKE participants with a small vessel (lacunar) stroke were over-represented (45% of patients). This phenomenon has been seen in earlier stroke studies (Chaturvedi 2004), as these patients typically have smaller strokes and milder symptoms and thus, are more easily enrolled. In OCEANIC-STROKE patients with small vessel (lacunar) stroke can be included, but only if there is evidence of atherosclerosis or if brain imaging of the index events shows a larger and/or cortical stroke. The intention is to reduce the number of these to at least what is seen in the normal stroke population (~25%).

Asundexian, as an oral FXIa inhibitor, is expected to show a benefit in reducing the risk for stroke in patients after a non-cardioembolic ischemic stroke or high-risk TIA. Animal models with asundexian had shown a reduction in thrombus formation beyond what has been shown with a therapeutic dose of NOACs. In addition, this is supported by data from the completed dose-finding Phase 2 PACIFIC-STROKE study (see Section 2.2.4).

At the same time asundexian is expected to have a low risk of bleeding. This is based on the available preclinical data, and clinical data from four Phase 2 proof-of-concept studies in participants undergoing total knee replacement (see Section 2.3.2), as well as data from the completed dose-finding Phase 2 studies (see Section 2.2.4).

Asundexian is therefore an attractive candidate to evaluate as a potential treatment for prevention of ischemic stroke in patients with non-cardioembolic ischemic strokes or high-risk TIA.

2.2 Background

2.2.1 Disease Background

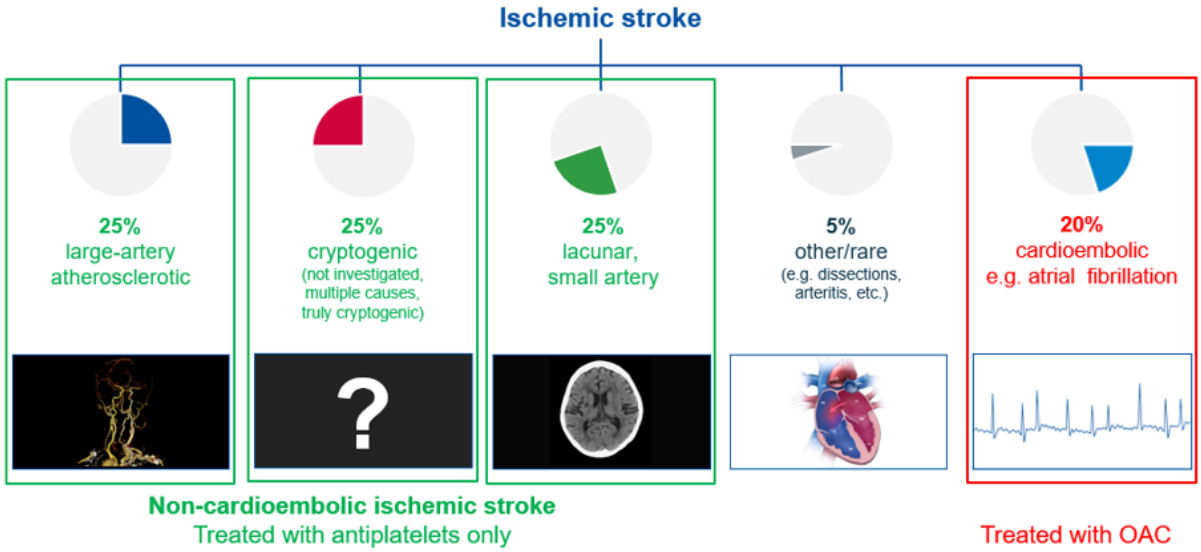
Based on the Global Stroke Fact Sheet worldwide, 12.2 million people suffer a first ever stroke annually and > 101 million people currently living have experienced a stroke. 6.5 million people die from a stroke annually. Over 143 million years of healthy life is lost each year due to stroke-related death and disability (WSO 2021).

25% of all ischemic stroke patients will have another stroke within 5 years. The ischemic stroke recurrence rate is substantial and remains at 3 to 6% per year. Overall, 58% of ischemic strokes happen in patients under 70 years of age. Also, the TIAregistry.org project found that patients with TIA or minor stroke had a 1 year risk of the composite outcome of major fatal or nonfatal cardiovascular events of 6.2%, and a 5.1% estimate for the risk of stroke (Amarenco et al. 2016).

85% of all strokes are ischemic strokes and 15% are hemorrhagic strokes. Non-cardioembolic ischemic stroke is a subset of ischemic stroke and accounts for around 75% of all ischemic strokes. It includes lacunar stroke, large artery arteriosclerotic strokes and cryptogenic stroke/embolic stroke of undetermined source [ESUS] and excludes cardioembolic strokes e.g. related to atrial fibrillation. See also Figure 2–1.

The study population will include ischemic stroke and high-risk TIA patients with evidence of cerebrovascular or systemic atherosclerosis based on the medical history and/or vascular imaging. In addition, patients qualify if brain imaging shows a lesion that is not a single small subcortical (lacunar) stroke, suggesting a small vessel etiology. This population is expected to include approximately 75% of patients with a non-cardioembolic ischemic stroke.

Figure 2–1: Ischemic Stroke Subtypes (TOAST criteria)



Abbreviations: OAC = oral anticoagulant, TOAST = Trial of ORG 10172 in Acute Stroke Treatment

2.2.2 Treatment Guidelines

Patients with non-cardioembolic ischemic stroke are treated with antiplatelet therapy, which represents current standard of care for secondary prevention according to available guidelines, AHA/ASA 2021 (Kleindorfer et al. 2021), 2018 guidelines for the early management of patients with acute ischemic stroke (Powers et al. 2018), CHEST 2012 (Lansberg et al. 2012), ESO 2008 (Ringleb et al. 2008) and ESO expedited recommendation for use of short-term dual antiplatelet therapy (Dawson et al. 2021). Preference for standard of care antiplatelet therapy varies by region and by country. Stroke management guidelines recommend a range of single antiplatelet therapies that include acetylsalicylic acid (ASA), clopidogrel, cilostazol, prasugrel and the combination of ASA and dipyridamole or ASA and cilostazol. Based on data from the CHANCE and POINT studies (Johnston et al. 2018, Wang et al. 2013), dual antiplatelet therapy with ASA and clopidogrel for 21 or 90 days is used in patients after a high-risk TIA or minor acute ischemic stroke. In addition, the THALES study showed that the combination of ASA and ticagrelor also led to a benefit when compared to ASA alone (Johnston et al. 2020). This combination has been approved by US FDA but the application was withdrawn from EMA.

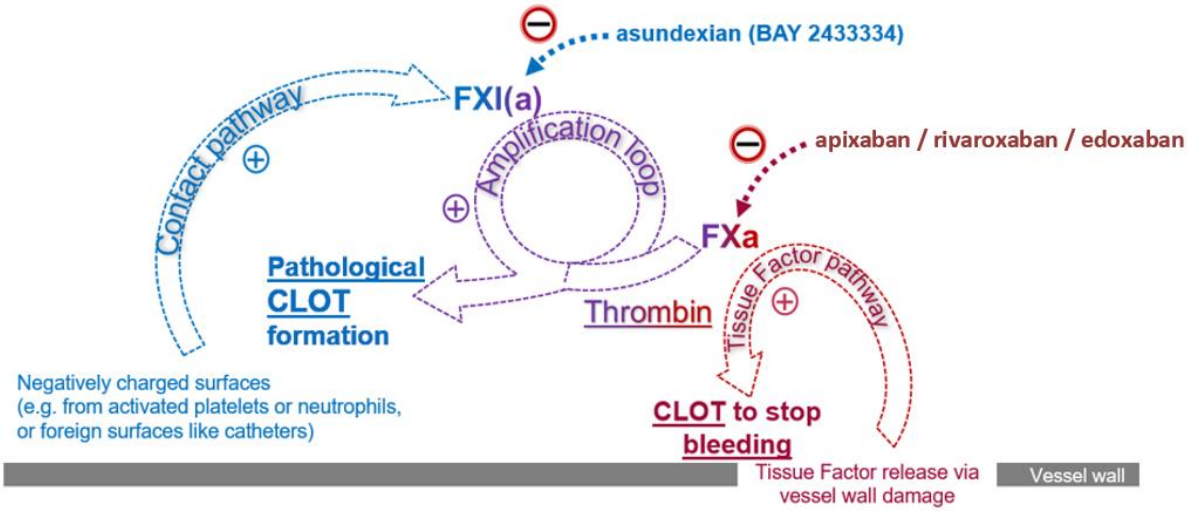
2.2.3 FXIa Inhibition: Mode of Action

Asundexian is an oral direct, potent inhibitor of activated coagulation factor XI (FXIa).

The plasma serine protease zymogen factor XI (FXI) is activated after initiation of the contact activation pathway via factor XIIa (FXIIa) and during the amplification phase as part of a positive feedback loop through activation by thrombin (Figure 2–2). FXIa is thought to contribute strongly to clot progression, which may potentially lead to vessel occlusion and pathological manifestations of thrombosis but has minor impact on hemostasis due to its limited role in the initiation phase of the extrinsic (tissue factor) pathway.

FXIa inhibition by asundexian may offer the opportunity to prevent thrombosis without interference with hemostasis and to thereby set a paradigm shift compared to Vitamin K antagonists and Non-Vitamin K oral anticoagulants (NOACs).

Figure 2–2: FXI(a) in the coagulation cascade



The Tissue Factor pathway is activated after vascular damage, forming a small amount of thrombin to build a clot at the site of injury and thereby stop any bleeding. The Contact pathway is activated by negatively charged surfaces from e.g. activated cells, leading to FXI activation and clot formation within the vessel. Thrombin itself activates FXI via the Amplification loop to generate a secondary burst of thrombin, allowing an initial clot to grow and obstruct the vessel lumen. While both pathways of thrombus formation are inhibited by apixaban, inhibiting FXI(a) maintains the ability to form a clot at the site of vessel wall injury.
Drafted by Heitmeier S and van Giezen JJJ, 2021.

2.2.4 Asundexian (BAY 2433334)

Preclinical / Toxicology Data

Preclinical data using FXI-deficient mice or studies using pharmacological inhibition of FXIa in different animal models, for example a $FeCl_2$-induced thrombosis model, have shown a benefit in reduced thrombus formation. The data indicate that higher efficacy might be possible to achieve when compared with the therapeutic doses of NOACs.

The benefit in these animal models was not associated with an increase in bleeding time as is seen for NOACs in these models. Importantly, no further increase in bleeding time was seen even when asundexian was given on top of dual antiplatelet therapy.

Data regarding toxicology studies as well as more preclinical data can be found in the Investigator's Brochure but are also partly described in the benefit / risk section (see Section 2.3).

Clinical Data

As of June 2022 the sponsor conducted 20 Phase 1 studies in more than 550 subjects which investigated the safety, tolerability, PK and pharmacodynamic (PD) properties of asundexian.

Two additional clinical Phase 1 studies are currently ongoing. Doses of asundexian that were tested in these studies ranged from 5 mg to 150 mg as single doses, and multiple doses up to 100 mg once daily.

These studies support further development of asundexian including the planned Phase 3 studies.

The dose finding Phase 2 PACIFIC-studies for 3 selected indications, i.e. AF, acute non-cardioembolic ischemic stroke, and AMI, in a total of 4164 randomized patients have been completed. They allowed for collection of information on the safety and efficacy of asundexian in different indications using different comparators (placebo / NOAC), and on top of different standard of care (i.e. single or dual antiplatelet therapy).

The objective of the Phase 2 study in patients with AF was to evaluate whether the incidence of bleeding with asundexian is lower when compared with a NOAC (apixaban), whereas for acute non-cardioembolic ischemic stroke and AMI the aim was to evaluate whether the bleeding profile is similar to placebo and there is a benefit in prevention of cerebro- and cardiovascular thromboembolic events when testing asundexian against placebo and on top of standard of care (single or dual antiplatelet therapy).

In addition to the individual study objectives, each of the Phase 2 studies supported each other for the evaluation of safety (bleeding) and efficacy in patients who were at risk for arterial thromboembolic events. Since the same dose levels were studied in all 3 studies (with the exception of the lowest dose, that was not tested in PACIFIC-AF), this allowed for pooling the data across all studies.

To secure an integrated evaluation of the emerging safety and benefit of asundexian in the 3 Phase 2 studies, one IDMC was set up for the program. In addition, an adjudication committee was in place for the adjudication of primary and secondary efficacy and bleeding endpoints.

Hence, at the end of the Phase 2 a large and robust data package from 4164 patients with exposure up to 12 months was available, which provided a solid ground for dose selection and further supported the development of asundexian in Phase 3 clinical studies.

An overview of the completed and ongoing studies can be found in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

The FXIa inhibitor asundexian is an oral anticoagulant that is planned to be developed for patients with AF as well as non-cardioembolic ischemic stroke or high-risk TIA. Phase 2 studies have been initiated in 2020 in all 3 indications and have been completed (AF in October 2021, AMI and non-cardioembolic stroke in February 2022).

The Phase 2 PACIFIC-Stroke study was the first study investigating asundexian in patients with non-cardioembolic ischemic stroke. Once daily doses of 10 mg, 20 mg and 50 mg were tested in the study. Based on analysis of the overall data from the Phase 2 studies a decision was made to take the 50 mg dosage into Phase 3 across the indications sought. More details on the justification for this can be found under Section 4.3.

Asundexian as an FXIa inhibitor is expected to have a lower risk for clinically significant bleeding when compared with other oral anticoagulants (VKAs and NOACs), while leading to an efficacy benefit.

The expected clinical profile of asundexian is based on preclinical data as well as epidemiological and clinical data from FXI-deficient individuals, other FXI-targeting compounds and the Phase 2 results from the PACIFIC program. The separation of bleeding and efficacy might be explained by the fact that inhibition of FXIa affects the intrinsic and propagation pathways, but keeps the extrinsic pathway unaffected, which is activated in case of vessel injury.

Patients after an acute ischemic stroke are at risk for hemorrhagic transformation of the infarcted area and as well as for intracranial hemorrhages (including hemorrhagic stroke). Therefore, in patients with acute ischemic stroke, anticoagulants are initiated with delay depending on stroke severity (Kleindorfer et al. 2021, Powers et al. 2018). The Phase 2 program, and specifically the PACIFIC-STROKE study, addressed this issue. Available results did not show an increased risk of hemorrhagic transformation or intracranial bleeding after early intervention and inclusion of mild and moderate stroke (NIHSS ≤ 15) and in post-thrombolysis and/or thrombectomy participants. MRI data after study intervention showed similar incidence of hemorrhagic transformation between asundexian and placebo treated participants. Primary treatment-emergent intracranial bleeding were few, 3 cases in the asundexian arms vs one in the placebo arm.

Based on the comprehensive available data from the Phase 2 program and early development, a lower risk for bleeding with FXIa inhibition is expected and therefore, early initiation of treatment on the study population is justified.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of asundexian can be found in the IB.

2.3.1 Risk Assessment

The following information related to safety as well as potential risks for patients is available:

1. Bleeding is the main safety concern with antithrombotic therapies. Inhibition of FXIa is expected to have a lower risk of bleeding compared with currently available NOAC and VKA therapies. Data supporting this are listed below:

FXI and risk for bleeding:

- Patients with inherited FXI deficiency are typically identified when presenting with a prolonged activated partial thromboplastin time (aPTT) in routine clinical testing. There is no direct association between FXI activity levels and bleeding risk, though historically and predominantly in the Ashkenazi Jewish population, FXI deficiency has been categorized as having a mild bleeding phenotype that generally only manifests following injury or trauma in tissues with high fibrinolytic activity.

Nonclinical evidence:

- FXI-deficient knockout mice do not show a bleeding phenotype. In addition, in the thrombosis animal models no increase in bleeding time (gum and ear) was reported. Importantly, no further increase in bleeding time was seen when asundexian was given on top of dual antiplatelet. In addition, in the toxicology studies no relevant bleeding was reported for up to 37-fold the expected human exposure of the planned 50 mg multiple dose in patients.

Clinical evidence:

- In the completed and ongoing Phase 1 studies conducted with asundexian, no relevant bleeding events were reported.

- An integrated (pooled) safety analysis of the completed Phase 2 studies showed lower bleeding in participants treated with asundexian compared to the active comparator apixaban (PACIFIC-AF), and no relevant increase in bleeding in participants treated with asundexian compared to placebo (PACIFIC-STROKE and PACIFIC-AMI). However, risk for bleeding cannot be completely excluded in participants after an acute non-cardioembolic ischemic stroke or high-risk TIA included in the Phase 3 study. Specific eligibility criteria have been implemented to exclude patients with a higher risk for bleeding (e.g. with a known bleeding disorder; refer to Section 5.2). Bleeding will be closely monitored in the study and will be adjudicated by an independent and blinded clinical event committee.

2. In toxicology studies, the liver was identified as a target organ in the rat but not in the dog. This included dose dependent spontaneous, mostly transient increases in liver enzymes in single animals without clear correlation to histopathological findings in the hepatic tissue at MoE (multiples of exposure) of 5 compared to systemic exposure observed in patients receiving 50 mg asundexian OD. Based on this, patients with a > 2.5-fold ALT or AST increase were excluded from the PACIFIC Phase 2 studies and liver findings during the studies were defined as AE of special interest. In the PACIFIC studies, with over 3000 asundexian exposed subjects reassuringly low incidences of AEs of special interest and elevations of liver transaminases were observed. Nevertheless, patients with known significant liver disease or known hepatic insufficiency classified as Child-Pugh B or C will be excluded in Phase 3, liver parameters are part of the safety laboratory panel and follow-up will be required for certain liver events (refer to Section 10.2.2). Data from preclinical and clinical studies regarding liver-related AEs do not indicate an unfavorable risk profile for asundexian.
3. In all completed Phase 1 and 2 studies asundexian was well tolerated and no additional safety signal was identified regarding general safety, laboratory parameters or vital signs and ECGs. A dedicated thorough QT study did not reveal any general issues relating to QT prolongation. The completed Phase 2 PACIFIC program showed no specific safety concerns regarding laboratory parameters or vital signs. Furthermore, no new or unexpected safety topic has been identified in the Phase 2 studies. In these studies, the characteristics of SAEs (including life-threatening and fatal SAEs) in general are consistent with the corresponding clinical populations.

In order to ensure the safety of the patients enrolled in each of the Phase 3 studies an IDMC will monitor the safety with a focus on bleeding and general safety during the study conduct for each of the Phase 3 indications. Furthermore, there will be an overarching IDMC assessing the data from all studies together.

In conclusion, asundexian is believed to represent a potentially improved new therapeutic option for thrombosis prevention in life-threatening thrombotic diseases with superior bleeding safety compared to oral anticoagulants and without a significant increase in bleeding risk on top of available background antiplatelet therapy. This also will enable treatment of patients at higher risk for bleeding events than current standards of care allow. Moreover, the dose selection was not limited by bleeding in Phase 2, thus enabling the use of 50 mg once daily as the highest dose investigated in Phase 2 for further investigation in Phase 3. The overall risk is currently anticipated to be acceptable in the context of the anticipated benefit. Taken all together, the current results show a favorable safety profile of asundexian and support its further development in Phase 3.

Table 2–1: Risk assessment

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Study Intervention asundexian		
A risk for bleeding cannot be excluded in participants randomized to asundexian or placebo on top of antiplatelet therapy.	Bleeding is the main safety concern related to antithrombotic therapies.	Exclusion criteria are phrased to exclude patients with a higher risk for bleeding (e.g. recent major surgery / active bleeding at randomization). Bleeding will be closely monitored in the study and will be adjudicated by an independent clinical event committee. Furthermore, an IDMC will monitor unblinded study data on an ongoing basis.
A specific risk of intracranial bleeds cannot be excluded in participants after an acute non-cardioembolic stroke randomized to asundexian or placebo on top of antiplatelet therapy.		Additionally to the general risk of bleeding, inclusion of participants with NIHSS classification > 15 is not allowed. Randomization after thrombolysis and thrombectomy is only allowed after > 24 hours and for thrombolysis after available follow-up clinical imaging. Active bleeding (including PH1 or PH2 hemorrhagic transformation, if known before randomization) and known vascular malformation of the brain with high risk for bleeding (except isolated cavernoma, aneurysm treated and secured, or aneurysm with diameter <5 mm) are excluded.
Liver-related adverse effects	The findings regarding liver-related adverse events were reassuring during the PACIFIC Phase 2 studies. Liver-related adverse effects will continue to be monitored to further characterize the clinical profile of asundexian.	Patients with known significant liver disease or known hepatic insufficiency classified as Child-Pugh B or C will be excluded from Phase 3, liver parameters are part of the safety laboratory panel and follow-up will be required for certain liver events Furthermore, an IDMC will monitor unblinded study data on an ongoing basis.
Study Procedures		
Clinical procedures or assessments mandated by the protocol (see SoA) are routine measures from everyday practice. They do not carry a risk of clinical significance to the safety of the participants.	Procedures or assessments do not pose more than minimal additional risk or burden compared with normal clinical practice.	No mitigation strategy is required.
Participation in this study presents minimal risk for SARS-CoV-2 infection during study participation	As long as the COVID-19 pandemic situation is ongoing, there is a risk of SARS-CoV-2 infections for study participants as for the general population. However, this risk during study participation is not increased compared to the general population.	In order to minimize their infection risk during study participation, the investigators / sites will follow all recommendations issued by local authorities and guidelines aiming to reduce the risk of disease spreading. Details on the measures are specified by the site and agreed with the sponsor. Measures which prioritize participant safety and data validity are implemented. In case these two objectives conflict, participant safety always prevails. During the pandemic situation, further measures according to recommendations and requirements from local health authorities may become necessary. These will be followed within the context of this study as far as applicable.

Abbreviations: IDMC = independent data monitoring committee, NIHSS = National Institutes of Health Stroke Scale, PH = parenchymatous hematoma, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2, SoA = Schedule of Activities.

2.3.2 Benefit Assessment

At this stage of development there is clinical evidence available suggesting the efficacy benefit of asundexian in patients with non-cardioembolic-stroke. The data supporting that asundexian is expected to lead to prevention of thrombosis events in the intended indications are the following:

FXI and risk for thrombotic events:

- In people with inherited Factor XI deficiency, a rare coagulation deficiency caused by either reduced production of factor XI or by production of a loss-of-function factor XI molecule, a lower risk for venous thromboembolic events as well as cardiovascular events and especially stroke has been reported. The lower stroke risk was evident for all stroke subtypes (Georgi et al. 2019).
- Increased levels of FXI are reported in patients with an acute stroke and are a risk factor for venous thromboembolism and myocardial ischemia or stroke. Whether there is a causal relationship is unclear.

Nonclinical experience:

- FXI-deficient knockout mice are protected from thrombosis. In addition, in various thrombosis models in rabbits, asundexian demonstrated reduced thrombus weight, and this was seen when given with or without antiplatelets. While therapeutic doses of NOACs lead to a 20-30% reduction in thrombus formation in the same animal models, asundexian was able to reduce the thrombus formation by up to ~90%.

Clinical evidence from asundexian:

- Phase 2b Clinical Pharmacodynamics:

  In the PACIFIC studies, concentration-dependent, near-complete inhibition of FXIa, measured with the AXIA assay (Heitmeier et al. 2022), was observed across the program. 50 mg OD asundexian led to rapid, sustained and near-complete inhibition of FXIa with 10% activity left at trough and 6% at peak in PACIFIC-STROKE, and this observation was consistent across all three Phase 2 studies.

  At the same time, the trough mean aPTT prolongation ratio predicted by the current popPK-PD model is 1.55 (for PACIFIC-AF) and 1.6 (for PACIFIC-Stroke and PACIFIC-AMI) for the 50 mg OD asundexian dose.

- Phase 2b Clinical Efficacy:

  In PACIFIC-STROKE, the primary analysis showed no significant difference in the occurrence of symptomatic ischemic stroke and/or covert brain infarcts detected by MRI with asundexian 10 mg, 20 mg or 50 mg doses compared to placebo. Despite the primary objective not being met, the analysis of other secondary efficacy endpoints showed a trend of a numerically lower number of participants in the asundexian treatment groups compared to placebo reporting the endpoints i) **composite of symptomatic ischemic stroke, CV death and MI**, ii) **symptomatic ischemic stroke**, iii) **symptomatic ischemic and hemorrhagic stroke,** and thus symptomatic events only. Additional post-hoc analysis identified the following groups as responders to asundexian: participants who have evidence of cerebrovascular, or systemic atherosclerosis as well as non-lacunar (small subcortical) strokes.

Clinical evidence from other FXI(a)- targeting compounds:

- A first proof-of-concept targeting FXI as anticoagulant has been shown by a FXI Antisense Oligonucleotide (Büller et al. 2015), as well as a FXIa antibody (osocimab) (Weitz et al. 2020). Reducing FXI levels in patients undergoing total knee arthroplasty (TKA) led to an improved prevention of postoperative venous thromboembolism (VTE), when compared with enoxaparin. This was confirmed by two more recent studies with a further antibody compound (abelacimab) (Verhamme et al. 2021), as well as a small molecule compound (milvexian) (Weitz et al. 2021), both also tested in TKA patients.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with asundexian are justified by the anticipated benefits that may be afforded to participants after an acute non-cardioembolic ischemic stroke or high-risk TIA.

More detailed information about the known and expected benefits and risks and commonly reported adverse events of asundexian may be found in the IB.

3. Objectives, Endpoints, and Estimands

Objectives and endpoints (primary, secondary and exploratory) and **estimands** of the study are reported below.

Table 3–1: Study objectives and endpoints

Objectives	Endpoints
Primary	
Efficacy	
To evaluate whether the oral FXIa inhibitor asundexian is superior to placebo on top of background antiplatelet therapy in reducing ischemic stroke in patients after an acute non-cardioembolic ischemic stroke or high-risk TIA	• Ischemic stroke*
Safety	
To compare the incidence of ISTH major bleeding for asundexian and placebo on top of antiplatelet therapy in patients after an acute non-cardioembolic ischemic stroke or high-risk TIA	• ISTH major bleeding*
Secondary	
Efficacy	
To evaluate whether asundexian is superior to placebo on top of antiplatelet therapy in reducing the occurrence of composite and individual efficacy endpoints	• All strokes (ischemic and hemorrhagic)* • Composite of CV death, MI or stroke* • Composite of all-cause mortality, MI or stroke* • Ischemic stroke in the first 90 days* • Disabling stroke (mRS ≥3 at 90 days)* • All-cause mortality* • Transient ischemic attack (TIA)*
Safety	
To compare asundexian and placebo on top of antiplatelet therapy with respect to individual bleeding endpoints	• Composite of ISTH major or clinically relevant non-major bleeding* • ISTH clinically relevant non-major bleeding* • Symptomatic intracranial hemorrhage* • Hemorrhagic stroke* • Fatal bleeding* • Minor bleeding*
Net clinical benefit	
To further compare the benefit and risk of asundexian and placebo with respect to a composite of efficacy and safety endpoints	• Composite of ischemic stroke or ISTH major bleeding* • Composite of CV death, all stroke, MI or ISTH major bleeding* • Composite of all-cause mortality, disabling stroke, fatal bleeding, symptomatic intracranial hemorrhage*
Exploratory	
Efficacy	
To further investigate the efficacy of the study intervention	• Modified Rankin Scale • Ischemic stroke after the first 90 days*
To investigate the effect of the study interventions on quality of life	• EQ-5D questionnaire
Safety	
To further investigate the safety of the study intervention	• Gastrointestinal bleeding * • BARC type 3 and 5 bleeding* • BARC type 2, 3 and 5 bleeding* • BARC type 1 and 2 bleeding*
Net clinical benefit	
To further compare the benefit and risk of asundexian and placebo with respect to hospitalizations	• Total number of hospitalizations due to efficacy or safety outcome events
Other exploratory	
To further investigate the study intervention and drugs with similar, e.g. mode-of-action-related effects, and to further investigate pathomechanisms deemed relevant to cardiovascular diseases and associated health problems	• PK and various biomarkers (e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

Abbreviations: BARC = Bleeding Academic Research Consortium, CV = cardiovascular, EQ-5D = European Quality of Life Group 5 Dimension questionnaire, FXIa = Factor XIa, ISTH = International Society on Thrombosis and Hemostasis, MI = myocardial infarction, mRS = modified Rankin Scale, PK = pharmacokinetic(s), TIA = transient ischemic attack

* Time to first occurrence

The estimands for the primary efficacy and safety objectives are described as follows:

For the primary efficacy objective:

To evaluate whether the oral FXIa inhibitor asundexian is superior to placebo on top of background antiplatelet therapy in reducing ischemic stroke in patients after an acute non-cardioembolic ischemic stroke or high-risk TIA

the primary efficacy estimand is described by the following attributes:

- **Population:** Adult patients with an initial diagnosis of acute non-cardioembolic ischemic stroke or high-risk TIA, assigned to treatment within 72 hours of the onset of symptoms and with the intention to be treated with antiplatelet therapy.
- **Treatment condition:**
    - Experimental: once daily oral administration of 50 mg of asundexian
    - Control: once daily oral administration of matching placebo

  Both experimental and control treatment are given on top of standard of care, which includes single and dual antiplatelet therapy. The choice is left to the discretion of the treating physician.
- **Endpoint:** Time from treatment assignment to first occurrence of ischemic stroke
- **Population-level summary**: Cause-specific hazard ratio (i.e. ratio of cause-specific hazard rates of the endpoint of interest) comparing the two treatment conditions
- **Intercurrent events and strategies:**
    - The treatment effect including effects of discontinuation of assigned treatment is of interest. Observation time and primary efficacy events will be used regardless of treatment discontinuation (*treatment policy strategy* for the intercurrent event *discontinuation of assigned treatment*)
    - The treatment effect irrespective of any change in background therapy is of interest. Observation time and primary efficacy events will be used regardless of changes in background therapy (*treatment policy* strategy for the intercurrent event *change in background therapy*)
    - The treatment effect irrespective of any changes in therapy (i.e. discontinuation of assigned treatment and initiation of indicated therapy) due to a diagnosis atrial fibrillation is of interest. Observation time and primary efficacy events will be used regardless of changes in study or background therapy (*treatment policy* strategy for the intercurrent event *change of treatment due to atrial fibrillation*)
    - In case of death, observation time up until death will be used (*while alive* strategy for the intercurrent event *death*)
    - Other intercurrent events related to a significant trial-continuity issue (e.g. caused by Covid-19 pandemic) will be addressed by *treatment policy* strategy
    - Other relevant intercurrent events are not anticipated.

Rationale for the primary efficacy estimands:

The key clinical question related to the primary efficacy endpoint is to show that assigning asundexian versus placebo to patients after an acute non-cardioembolic ischemic stroke or high-risk TIA on top of standard of care antiplatelet therapy is superior in reducing ischemic stroke.

The probability of experiencing a subsequent ischemic stroke in the target population is highest during the first weeks and months after the index event and then decline thereafter. Relative to standard of care antiplatelet therapy alone it is expected that adding asundexian will reduce the risk of experiencing an ischemic stroke when added to standard acute and chronic therapies. To summarize the relative effect of the two treatment conditions over time, the ratio of cause-specific hazard rates of the primary efficacy outcome is considered an appropriate summary measure. It will be supplemented with estimates of the cumulative incidence over time.

The primary clinical question is about the difference between assigning asundexian versus placebo including effects of treatment discontinuation, implicitly including potential open-label treatment with an anticoagulant and including potential changes in the standard of care, i.e. antiplatelet therapy. This reflects treatment effects that are going to be observed on average in a large population in clinical practice with diverse patient journeys where treatments are not necessarily taken as prescribed. Assuming a beneficial effect of asundexian, using the proposed treatment policy strategy is considered conservative.

The strategy for the primary efficacy estimand is similar to what has been called the intent-to-treat principle in the past.

In terms of observing the primary efficacy outcome, death of patients after treatment initiation is considered a competing risk because it would preclude the primary efficacy outcome from occurring. Therefore, it is of interest to characterize the treatment effect prior to the death of a study participant, using the “while alive” strategy. The estimate of the treatment effect on the primary efficacy outcome will be presented together with estimates of the treatment effect on the competing event “death” itself, to complement its understanding and interpretation.

For the primary safety objective:

To compare the incidence of ISTH major bleeding for asundexian and placebo on top of antiplatelet therapy in patients after an acute non-cardioembolic ischemic stroke or high-risk TIA

the primary estimand for **safety assessment** is described by the following attributes:

- **Population**: Adult individuals assigned to treatment within 72 hours of the onset of symptoms and with an initial diagnosis of an acute non-cardioembolic ischemic stroke or high-risk TIA, taking at least a single dose of the assigned treatment, and with intention to be treated with antiplatelet therapy.
- **Treatment condition:**
    - Experimental: once daily oral administration of 50 mg of asundexian
    - Control: once daily oral administration of matching placebo

  Both experimental and control treatment are given on top of standard of care, which includes single and dual antiplatelet therapy. The choice is left to the discretion of the treating physician.

- **Endpoint:** Time from first treatment intake to first occurrence of ISTH major bleeding
- **Population-level summary:** Cause-specific hazard ratio (i.e. ratio of cause-specific hazard rates of the endpoint of interest) comparing the two treatment conditions
- **Intercurrent events and strategies**:
    - In case of early discontinuation of the assigned study treatment, observation time and safety events up to two days after the last intake of study treatment will be used (*while exposed to treatment* strategy for the intercurrent event *discontinuation of assigned treatment*)
    - The treatment effect irrespective of any change in background therapy is of interest. Observation time and primary safety events will be used regardless of changes in background therapy (*treatment policy* strategy for the intercurrent event *change in background therapy*)
    - In case of death, observation time up until death will be used (*while alive* strategy for the intercurrent event *death*)
    - Other intercurrent events related to a significant trial-continuity issue (e.g. caused by Covid-19 pandemic) will be addressed by *treatment policy* strategy
    - Other relevant intercurrent events are not anticipated.

Rationale for primary safety estimand:

The key clinical question related to the primary safety endpoint is about the risk for ISTH major bleeding when treating patients with asundexian versus placebo control on top of standard of care antiplatelet therapy in a population of patients after an acute non-cardioembolic ischemic stroke. In contrast to other anticoagulants, it is expected that asundexian as a FXIa inhibitor does not lead to a relevant increase in bleeding.

The ratio of cause-specific hazard rates of the primary safety outcome is expected to summarize the relative effect of the two treatment conditions over time. Assuming that asundexian does not lead to an increase in ISTH major bleeding, the hazard ratio is assumed to be constant over time.

Similar to what was described for the efficacy estimand, in terms of observing a primary safety outcome, death (unrelated to bleeding) of patients after treatment initiation is considered a competing risk because it would preclude the primary safety outcome from occurring. Therefore, it is of interest to characterize the treatment effect prior to the death of a study participant, using the “while alive” strategy. In this setting, information on the treatment effect on the competing event “death” itself will complement the understanding of the treatment effects on safety outcome events.

It cannot be precluded that early discontinuation of asundexian (or the underlying reasons leading to treatment discontinuation) could change the probability of the occurrence of a primary safety outcome event. It is of interest to quantify the risk associated with the intake of asundexian, i.e. while patients are exposed to the treatment, and not the risk related to other medication that are given after discontinuation. Therefore, the proposed estimand for the safety question addresses early treatment discontinuation using a "while exposed to randomized treatment" strategy (in the past: "on-treatment effect"). This decision implies that early treatment discontinuation is considered a "soft" competing risk in the sense that thereafter the safety event in principle still could occur. Estimates of the treatment effect on the competing event "early treatment discontinuation" itself will complement the understanding of the treatment effects on safety outcome events.

Further secondary estimand(s)

Estimands for the further secondary efficacy and safety endpoints are defined following the same approach as done for the respective primary estimands, considering the appropriate competing risks, respectively.

The estimand for the exploratory net clinical benefit objective is defined following the same approach as done for the primary safety estimand.

Please refer to Section 9 for a description how data is handled in the statistical analysis to estimate the defined estimands.

4. Study Design

4.1 Overall Design

Study 20604 is a multicenter, international, randomized, placebo controlled, double-blind, parallel group, event driven Phase 3 study. The overall study design is depicted in Figure 1–1.

Participants ≥ 18 years of age, will be randomized in a 1:1 fashion to the 2 arms, as follows:

- 1 investigational study intervention arm asundexian 50 mg OD or
- 1 placebo arm OD

in addition to their background therapy (see Section 5.1, inclusion criterion 6).

The randomization will be stratified by whether participants will receive dual antiplatelet therapy with ASA and a $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor or prasugrel) or not.

The study will consist of the following study periods:

- **Screening period (from visit 1 until visit 2)**: up to 72 hours. Participants will be screened and have to be randomized within 72 hours after the onset of symptoms of the index event. If all information is available, a participant can be randomized on the day of screening (visits 1 and 2 are combined).
- **Intervention period (from visit 2 until the common end of treatment [CEOT] visit)**: approximately 3-31 months: For individual participants the duration of the intervention period will vary, depending on the timepoint of randomization and accrual of outcome events.

The first dose of study intervention should be given as soon as possible after randomization (i.e. within 4 hours of randomization), and then once daily at a regular schedule (preferably in the morning).

In person clinic visits take place at 3 months, 6 months and then every 6 months until the common end of treatment visit (CEOT) (see below).

Telemedicine (phone or video) visits will take place at 1 month, 9 months and then every 6 months in between site visits.

If an in person clinic visit is not possible a site staff member can visit the participant`s home, rehabilitation clinic or hospital, or perform a telemedicine visit. Local safety labs are allowed if onsite and / or central lab determinations are not possible (special circumstances e.g. COVID-19 restrictions, hospitalization outside of the study site). In exceptional situations study intervention might be sent directly to patients, if allowed by local laws.

The last day of intake of study intervention will be on the day before the CEOT visit.

For an individual participant the CEOT visit marks the end of the intervention period (for participants permanently discontinuing study intervention, refer to "Early Termination period").

The sponsor will notify the sites of the CEOT date when sufficient outcome events are expected to have been accrued. The sites will be informed of the visit window (approximately +/- 3 weeks of the CEOT date), during which the CEOT visits should be performed.

- **Common End of treatment period (from CEOT visit until CEOT SFU visit)**: 2-week period that will end upon completion of the CEOT SFU visit for participants who did continue intake of study intervention as expected.
- A participant only *temporarily* interrupting study intervention intake and taking the last dose within less than 2 weeks before the CEOT visit will complete the study upon completion of the CEOT SFU visit. A participant temporarily interrupting study intervention with a final dose taken 2 or more weeks before the CEOT will complete the study upon completion of the CEOT, and in such a case no additional SFU telephone call will be required thereafter, as follow up of the participant has been already 2 or more weeks after the last study intervention intake.

Only in case participants *permanently* discontinue study intervention earlier than planned:

- **Early termination (ET) period (from ET until CEOT visit)**

  If the study intervention is *permanently* discontinued earlier than expected, the participant will enter the ET period and an ET visit has to be performed as soon as possible. In addition, a SFU visit will also need to be conducted 2 (+1) weeks after permanent discontinuation.

  All living participants who permanently discontinued study intervention prior to the CEOT visit are still part of the study and will participate in their visits as scheduled as part of their ET period. Those visits are foreseen to take place via telephone calls, unless participant or investigator prefers on-site visits. In those participants also the

above-mentioned CEOT visit will need to be performed, that marks the end of the ET period.

For participants who permanently discontinue study intervention 2 or more weeks prior to the CEOT visit, an ET SFU visit will also be conducted 2 weeks after permanent discontinuation of study intervention. If the ET visit is delayed and is 2 or more weeks after permanent discontinuation of study intervention, an additional ET SFU visit will not be performed. In any of these participants the CEOT is supposed to be the last study visit.

For participants who permanently discontinue study intervention less than 2 weeks prior to the CEOT visit, the ET SFU visit will be replaced by the CEOT SFU visit, that is to be conducted after the CEOT visit and is the last study visit for those participants.

Further details on premature discontinuation of the study intervention are reported in Section 7.1.

Details of study procedures and their timing are summarized in the SoA (Section 1.3).

MRI sub-study

An MRI sub-study will be conducted at selected sites in +/- 1000 participants and involve acquiring a baseline and one follow-up MRI that will be submitted to a central MRI core lab for interpretation. The required study MRI sequences to detect e.g. covert brain infarcts, hemorrhagic transformation and microbleeds are based on brain MRIs done for routine clinical care of acute stroke patients. Further detailed procedures and sequences can be found in Appendix 10.10 and MRI manual.

Pre-screening data collection

Exploratory pre-screening data will be collected by Population Health Research Institute (PHRI, Hamilton, Canada) to investigate factors influencing participation in the OCEANIC-STROKE study. This will be conducted at selected sites in approximately 1000 participants. The purpose is to identify correlations in willingness to participate in the OCEANIC-STROKE study by collecting basic demographic, sociodemographic and hospital/process factors associated with participation. Upon consent, participant data will be collected via a questionnaire. Subsequent participation in the OCEANIC-STROKE study is not required. Participant information will be stored on a high-security computer system at Population Health Research Institute and kept strictly [redacted]

More detailed information on the data collection, associated consent, and questionnaire is provided separately. The analysis will not be part of the main study and will be reported separately.

4.2 Scientific Rationale for Study Design

This is a pivotal Phase 3 study. It will apply the principles of randomization and double-blinding in order to prevent bias in the inclusion of participants or reporting of safety or efficacy events.

There is no requirement for a dose escalation or reduction approach for asundexian, because based on the available preclinical and clinical data for asundexian there are no safety concerns related to the selected dose of 50 mg once daily tested in the study (see section 6.1).

The study design is based on contemporary trials on similar study populations (CHANCE, POINT, THALES and SOCRATES) and on studies with major cardiovascular events

outcomes (e.g. COMPASS). The prevention of ischemic strokes is considered a meaningful measure of efficacy due to its clinical significance, associated morbi-mortality and disability.

The study will include participants after an acute non-cardioembolic stroke or high-risk TIA, who will be treated with standard of care single or dual antiplatelet therapy for prevention of ischemic stroke. Study intervention with asundexian or placebo will be given on top of background antiplatelet therapy in order to show that the addition of a FXIa inhibitor to antiplatelet therapy will lead to additional benefit in prevention of recurrent ischemic strokes. It is not expected that the replacement of an antiplatelet would lead to a higher benefit and that rather the combination of an anticoagulant and antiplatelet therapy is required to achieve maximum efficacy as observed in COMPASS.

4.2.1 Patient Input into Design

Not applicable.

4.3 Justification for Dose

The study will test 50 mg of asundexian once daily.

The selection of the dose in this study was based on the safety and tolerability data from toxicology studies, the results of the human Phase 1 studies conducted in healthy volunteers, as well as the results of the Phase 2 PACIFIC program conducted in participants with AF, non-cardioembolic stroke and acute myocardial infarction.

The dose of 50 mg was widely tested among the 3 different indications of the Phase 2 PACIFIC program and demonstrated favorable bleeding safety against apixaban (in PACIFIC-AF study), as well as no relevant increase in bleeding in participants treated with asundexian compared to placebo (PACIFIC-STROKE and PACIFIC-AMI). Across the Phase 2 studies, the evaluation of the AEs, laboratory parameters, vital signs and ECG did not show any unfavorable safety signals for asundexian. The dose selection was not limited by bleeding in Phase 2, thus enabling the use of 50 mg once daily as the highest dose investigated in Phase 2 for further investigation in Phase 3.

In PACIFIC-STROKE a favorable trend in benefit for symptomatic ischemic stroke in participants taking asundexian could be seen particularly in participants with evidence of cerebrovascular, or systemic atherosclerosis as well as non-lacunar (small subcortical) strokes (Section 2.3.2). Based on the available data, asundexian 50 mg leads to a near complete inhibition of FXIa, showing a favorable benefit-risk profile.

Taken all together, the current results support further development of asundexian in Phase 3 in patients with a non-cardioembolic ischemic stroke. More detailed information may be found in the Investigator's Brochure as well as in Sections 2.2.4 and 2.3.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study globally. The date of the last visit of the last participant in the study globally will also be regarded as primary completion date according to the FDA Amendment Act.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The study will enroll adult participants after an acute non-cardioembolic ischemic stroke or high-risk TIA on background antiplatelet therapy.

In order to have a balanced study population across the eligibility criteria, and to avoid overrepresentation of any single entry criterion, recruitment of participants will be monitored on an ongoing basis. If an imbalance is observed (e.g. overrepresentation of TIA or medical history of atherosclerosis), enrolment based on the affected criterion may be restricted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. 18 years of age or older (at legal age of consent according to local legislation) at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who have an acute onset of neurological deficit attributed to non-cardioembolic focal brain ischemia due to either:
   - Non-cardioembolic ischemic stroke with NIHSS ≤ 15 at randomization and either of the following:
     - Persistent signs and symptoms of stroke lasting for ≥ 24 hours OR
     - Acute ischemic brain infarction documented by magnetic resonance imaging (MRI; diffusion weight imaging), standard computed tomography (CT) or perfusion CT[1] that could account for the clinical presentation.

     OR
   - High-risk TIA with complete resolution of symptoms within < 24 hours and an ABCD[2] score ≥ 6 with negative neuroimaging (CT or MRI) for acute ischemia.
3. All participants must have *at least one* of the following criteria a - c:
   a. Cerebrovascular atherosclerosis defined as vascular imaging (CTA, MRA, ultrasound, DSA) showing atherosclerotic plaque involving intracranial or extracranial cerebral arteries or the aortic arch[2],
   OR
   b. Medical history of atherosclerosis:

[1] CT perfusion with deficits that resolve after EVT and/or thrombolysis are eligible and will be considered as imaging evidence of ischemic stroke. Also participants who undergo EVT and have all symptoms/signs resolve within 24 hours of onset and without imaging evidence of infarction are eligible and will be considered to have (aborted) brain infarction.
[2] Qualifying plaques are those that clearly protrude into the vessel lumen as interpreted by the local investigator

i. CAD or AMI with documented coronary atherosclerotic disease, prior CABG, or prior PCI

ii. PAD requiring previous bypass surgery, or percutaneous transluminal angioplasty revascularization, limb or foot amputation for arterial vascular disease (i.e., excludes trauma), OR history of intermittent claudication and one or more of the following: 1) an ankle/arm blood pressure (BP) ratio < 0.90, or 2) documented peripheral artery stenosis

iii. Carotid stenosis ≥ 50% or previous carotid revascularization

iv. Documented aortic plaque,

OR

c. Brain imaging demonstrating an acute non-lacunar infarct (CT, CT perfusion or DWI MRI) defined as cortical location and/or size >20 mm for DWI and >15 mm for CT.

4. If no brain infarct is documented prior to randomization (i.e. clinical diagnosis of stroke or TIA with negative imaging) at least one of the following needs to be present that is not otherwise explainable and is related to the acute ischemic stroke/TIA event: motor deficits, speech deficits (aphasia/dysarthria), visual deficits (hemianopsia) and/or neglect. Thus, patients with isolated dizziness/vertigo or isolated numbness are not eligible.
5. Imaging of brain (CT or MRI) prior to randomization ruling out hemorrhagic stroke or another pathology that could explain symptoms (e.g. brain tumor, abscess)
6. Plan for secondary prevention of stroke/TIA with single or dual antiplatelet therapy including ASA, clopidogrel, ticagrelor, prasugrel, cilostazol and dipyridamole and in line with local guidelines.

Other Inclusions

7. Able to be randomized within 72 hours after the onset of symptoms of the index event (or after patients were last known to be without symptoms in case of wake-up stroke).
   NOTE: In case of endovascular therapy (mechanical thrombectomy) and / or thrombolysis, randomization can only occur > 24 hours after endovascular therapy and in case of thrombolysis only after 24 hours and standard clinical imaging has been performed post thrombolysis to exclude hemorrhage.

Sex and Contraceptive/Barrier Requirements

8. Male or female

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- **Male participants**: there are no measures required for the study
- **Female participants**: a female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 4

OR

- is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 during the study intervention period and for at least 4 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g. noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) before randomization, see Section 8.3.8. If a urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. *See country-specific requirements for the Republic of Korea (KOR-1) in Section 10.11.3.1*
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.8. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

9. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Recent ischemic stroke within 7 days before index event
2. Strokes (index event) following procedures (e.g. TAVI, CABG) or strokes due to other rare causes (e.g. bacterial endocarditis, vertebral artery dissections)
3. Known premorbid (before index event) mRS ≥ 4
4. History of atrial fibrillation / flutter, left ventricular thrombus, mechanical valve or other cardioembolic source of stroke requiring anticoagulation
5. Sustained uncontrolled hypertension after index stroke/TIA event[3]
6. Known vascular malformation of the brain with high risk for bleeding (except isolated cavernoma, aneurysm treated and secured, or aneurysm with diameter <5 mm)
7. Active non-trivial bleeding (including PH1 or PH2 hemorrhagic transformation of the index stroke event, if known before randomization[4]); known chronic bleeding disorder (e.g. von Willebrand disease); history of non-traumatic intracranial hemorrhage (does not include cerebral microbleeds or asymptomatic hemorrhagic transformation of an ischemic stroke); other non-traumatic major bleeding or clinically significant gastrointestinal bleeding within last 6 months before randomization

[3] Based on investigator judgement e.g. persistent (>1 out of 3) consecutive measurements of blood pressure ≥ 180/100 mmHg prior to randomization
[4] Heidelberg HI 1 and HI 2 are allowed (Larrue et al. 2001)

8. Known significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis, or signs of coagulopathy) or known hepatic insufficiency classified as Child-Pugh B or C at randomization[5] *See country-specific requirements for the Republic of Korea (KOR-1) in Section 10.11.3.1.*
9. End stage renal disease requiring dialysis or expected to be started on dialysis within the next 12 months[5]
10. Major surgery during the last 30 days prior to randomization
11. Known allergy, intolerance or hypersensitivity to the study intervention (asundexian or excipients)

Prior / Concomitant Therapy

12. Concomitant use, planned use or anticipated need for
    - Oral anticoagulation
    - Full dose and/or long-term anticoagulation therapy with heparin/LMWH during study conduct[6]
    - Chronic (more than 4 weeks continuous) therapy with NSAIDs during the study conduct
    - Concomitant use of combined P-gp and strong CYP3A4 inducers, e.g. carbamazepine, St John's wort[7], as well as within 14 days (or at least five half-lives of the active substance, whichever is longer) before randomization
    - Concomitant use of combined P-gp and strong CYP3A4 inhibitors e.g. human immunodeficiency virus protease inhibitors, systemically used azole antimycotic agents (e.g. ketoconazole), clarithromycin, nefazodone[7], as well as within 14 days (or at least five half-lives of the active substance, whichever is longer) before randomization
    - Herbal or traditional medicine, and / or supplements with known anticoagulant and / or antiplatelet effect (a list of the most commonly used ones will be provided separately).

Prior/Concurrent Clinical Study Experience

13. Previous (within 30 days of randomization or 5 half-lives of the investigational drug, whichever is longer) or concomitant participation in another clinical study with investigational medicinal product(s) or device(s). Registries and observational studies are allowed.

Other Exclusions

14. Unable to start study intervention within 4 hours from randomization
15. Known current alcohol and / or illicit drug abuse that may interfere with the participant's safety and / or compliance at the discretion of the investigator

[5] Assessment of relevant laboratory parameters is only required if there is a clinical suspicion (e.g. hepatic insufficiency or end stage renal disease)
[6] Venous thromboembolism prophylaxis with LMWH or unfractionated heparin for short periods of time (e.g., 14 days, according to hospital routine) is allowed.
[7] A list will be provided to the investigators

16. Close affiliation with the investigational site; e.g. a close relative of the investigator or a dependent person (e.g. employee or student of the investigational site or the sponsor)
17. Any other history, condition or therapy, or uncontrolled intercurrent illness which would make the participant unsuitable for the study (e.g. non-compliance) or otherwise vulnerable (e.g. participant in custody by order of an authority or a court), or life expectancy < 12 months.

For country-specific requirements for the Republic of Korea (KOR-1), please see Section 10.11.3.1.

5.3 Lifestyle Considerations

No restrictions during any of the study periods pertaining to lifestyle (except for the above-mentioned substance abuse) and / or diet apply.

5.4 Screen Failures

A screen failure occurs when a participant consents to participate in the clinical study but is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Re-screening of participants who failed initial screening is not allowed.

5.5 Criteria for Temporarily Delaying Enrollment or Randomization

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study interventions are all pre-specified investigational and non-investigational medicinal products, devices and other interventions (e.g. surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

The following study interventions will be administered in the study:

- Asundexian: sponsor's study intervention under investigation
- Placebo to asundexian

Asundexian is taken orally once a day, if possible in the morning, preferably around the same time each day. The immediate-release tablets will be provided as pink, oval, film-coated tablets containing 50 mg of asundexian (see Table 6–1).

The study interventions should be swallowed whole with a glass of water. The study interventions can be taken irrespective of food intake. If required, the study interventions can be crushed. It is recommended to use a tablet crusher. After resuspending (e.g., in water or apple sauce), the crushed tablet can be administered orally. Administration via feeding tube (e.g., nasogastric or gastric tube) is also permitted.

Matching placebo for asundexian is supplied in the same way.

At Visits 4 and 7 participants should not take study intervention as usual in the morning at home, as a PK / PD sample will be drawn at the site before intake of study intervention. Study intervention at those visits should be taken out of the respective bottle that participants receive at their dispensation visit (i.e. at Visit 4 and Visit 7).

Missed study intervention dose

If a dose is missed, the participant should take a dose immediately on the same day, up until 12 hours after the scheduled intake. After this time point, the dose should be skipped, and the next scheduled dose should be taken.

The dose of study intervention should not be doubled to make up for a missed dose.

Table 6–1: Study Intervention(s) Administered

Intervention Arm Label	Asundexian	Placebo
Intervention Name	Asundexian	Placebo to asundexian
Dose Formulation	tablet	tablet
Unit Dose Strength(s)	50 mg	NA
Dosage Level(s)	50 mg	NA
Frequency	Once a day, preferably in the morning	Once a day, preferably in the morning
Route of Administration	oral	oral
Use	Experimental	Placebo (experimental)
Packaging and Labeling	HDPE bottles. Each bottle will be labeled as per country requirement	HDPE bottles. Each bottle will be labeled as per country requirement

Abbreviations: HDPE = high-density polyethylene, NA = not applicable

Table 6–2: Study Arms

Arm Title	Asundexian	Placebo
Arm Type	Experimental	Placebo
Arm Description	Participants will receive asundexian	Participants will receive placebo
Associated Intervention Labels	Asundexian	Placebo to asundexian

6.2 Preparation, Handling, Storage, and Accountability

All study interventions will be stored at the investigational site in accordance with Good Clinical Practice (GCP) requirements and the instructions given by the clinical supplies department of the sponsor or its affiliates.

1. The investigator or designee must confirm study intervention has been received and, if a temperature data logger has been included, appropriate temperature conditions have been maintained during transit. Any discrepancies are to be reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff, where local regulations permit, may supply or administer study intervention.

3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, institution, the head of the institution (where applicable) or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records). Drug returns, reconciliation and destruction return information will be captured in IRT.
5. Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Site File.

6.3 Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention using an Interactive Response Technology (IRT). To accomplish random assignments, computer-generated randomization lists specified by the sponsor's responsible statistician will be prepared by the study sponsor or delegate. The randomization lists are provided to an IRT vendor. Before the study is initiated, the log-in information and directions for the IRT will be provided to each site.

The randomization will be stratified by whether participants are receiving dual antiplatelet therapy with ASA and a $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor or prasugrel) or not.

Study intervention will be dispensed at the study visit 2 (randomization), as summarized in the SoA, and again at the next visit after 3 months.

Subsequently, the Month 6 visit follows, marking the start of 6-monthly on-site visit intervals. From this visit onward, participants will receive study intervention at on-site visits which will last them until the next 6-monthly visit. The Month 6 visit should be scheduled ≤ 14 weeks after the Month 3 visit (even though in theory up to 15 weeks could lie between Visit 4 and Visit 5). Otherwise, participants will need to get equipped with additional bottles of each of the study intervention to prevent insufficient supply until the Month 6 visit. At each contact, hence also at the intermittent telephone visits, the participants should be instructed regarding study intervention compliance (refer to Section 6.5).

From the Month 3 visit onward, unused study intervention will get returned to the site and should not be re-dispensed to the participants.

6.4 Blinding

Participants will be randomly assigned in a 1:1 ratio to receive study intervention. Investigators, participants and study personnel will remain blinded to each participant's assigned study intervention throughout the course of the study. Sponsor personnel responsible for bioanalytics will be unblinded and will have access to the randomization list.

Tablets containing 50 mg of asundexian and matching placebo are identical in appearance and packed in bottles labeled with a unique number which will be pre-printed on each bottle.

6.4.1 Unblinding

Unblinding unnecessarily should be avoided and should only be undertaken by the investigator when it is essential for the participant's safety and needed for treatment decision. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a participant's treatment assignment is warranted. If the investigator is unavailable, and a treating physician not

associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the study-specific emergency medical advice 24 hours / 7-day service. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should attempt to contact the sponsor prior to unblinding a participant's treatment assignment, unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor should be notified preferably within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Asundexian is known to prolong the activated partial thromboplastin time (aPTT) in a dose dependent manner. aPTT is a commonly used functional coagulation test widely used in clinical practice in participants using anticoagulants and is as well commonly used during acute hospitalizations, and as pre-procedural screening test. Thus, inadvertent unblinding of the participant or investigator might take place in cases where aPTT test results are known. Therefore, the measurement of aPTT during the study conduct is strongly discouraged and should only be done in case of (emergency) situations where aPTT may help to guide treatment decision. Determinations of aPTT that might be obtained as part of the study protocol will therefore not be reported to investigators during the study in order to maintain the blinding.

Pharmacokinetic and exposure-response analysis may be performed using population approaches. Such evaluations will be described in a separate analysis plan and will be reported separately and may be started prior to database lock. If this is applicable, appropriate measures will be taken to maintain blinding of the sponsor's study team, e.g. data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

6.5 Study Intervention Compliance

Study intervention will be dispensed according to the schedule provided in the SoA (Section 1.3). The date of dispensing the study intervention to the participant will be documented.

Participants will be instructed to take study intervention as scheduled, and to return all unused study intervention and empty packages at the on-site visits for accountability purposes. Participant compliance with study intervention will be assessed at each visit by direct questioning. At the regular on-site visits, compliance will be assessed by counting returned tablets. The need for compliance assessment applies also to participants prematurely and permanently discontinuing study intervention who will undergo that assessment at the early termination visit. For participants taking study intervention until the regular end of the intervention period this assessment will occur for the last time at the CEOT visit. Tablets not returned will be considered to have been taken unless otherwise specified.

To monitor compliance, the investigator will be required to document drug dispensing and return for each participant in the source documents and this record must be reconciled with study intervention and compliance records.

An adequate record of receipt, distribution, and return/destruction of all study intervention must be captured on the dispensing log and/or the IRT.

Intervention start and stop dates will also be recorded.

Any discrepancies between actual and expected amount of returned study medication must be discussed with the participant at the time of the visit and any deviation as well as explanation for deviation(s) from the prescribed dose regimen should be recorded in the CRF.

Overall compliance with study intervention intake should be between 80% and 120% of the scheduled dose at the end of treatment with study intervention.

6.6 Dose Modification

This protocol does not allow any alteration from the currently outlined dosing schedule of asundexian (Section 6.1).

6.7 Continued Access to Study Intervention after the End of the Study

No further study intervention is planned following the End of the Study. For the definition of "End of Study" please refer to Section 4.4.

Any further therapy at the end of the study is at the discretion of investigator / treating physician.

6.8 Treatment of Overdose

For this study, any dose of asundexian greater than 3 assigned daily dosages (i.e. more than 3 tablets) within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose of asundexian, as a specific antidote for the study intervention is not available. The use of activated charcoal to reduce absorption may be considered.

Due to the mechanism of action, an overdose of the study intervention could potentially result in hemorrhage. In case of bleeding linked to overdose the guidance on bleeding management as found in section 6.9.1 should be followed.

In the event of an overdose, the investigator should:

1. Evaluate the participant to determine in consultation with the medical monitor, if possible, whether study intervention should be interrupted.
2. Closely monitor the participant for any AE / SAE and laboratory abnormalities as medically appropriate and until the study intervention can no longer be detected systemically (at least 5 days).
3. Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Prior and Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or vaccine that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor (sponsor's Study Medical Expert) should be contacted if there are any questions regarding prior or concomitant therapy.

Participants are expected to receive antiplatelet therapy as background therapy during the study conduct. Special focus needs to be on antiplatelet and anticoagulant medications, for which any change in 30 days before screening and concomitant use from study entry until the last scheduled study visit of the participant, needs to be captured on the specified concomitant medication page.

The concomitant use of NSAID therapy during the study is strongly discouraged since this has been shown to increase the risk of gastrointestinal (GI) bleeding. However, if a NSAID must be temporarily used, it is recommended that the lowest possible dosage for the shortest duration possible is selected, not to exceed 4 consecutive weeks. Should analgesics be needed, use of paracetamol / acetaminophen is recommended.

Proton pump inhibitors (PPIs) may be considered to reduce the risk for gastrointestinal bleeding and accompanying hospitalizations, especially in those with a history of GI bleeding or ulcer.

Potential for drug-drug interactions

At supratherapeutic doses asundexian is a weak inhibitor of the cytochrome P450 isoenzyme 2C8 (CYP2C8) and two transporter proteins, i.e. breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp). The risk of clinically relevant drug-drug interactions at a dose of 50 mg asundexian due to inhibition of the respective proteins is regarded as low but cannot be excluded.

If sensitive substrates of the mentioned proteins are taken concomitantly, the pertinent medication labels should be consulted, especially for:

- **rosuvastatin 20 mg daily or higher**, for which additional monitoring may be warranted
- **digoxin** or **paclitaxel**, which should be used with caution and for which additional monitoring may be warranted
- **repaglinide** or **pioglitazone**, for which additional blood glucose monitoring might be warranted.

Furthermore, the respective drug labels should be consulted, if asundexian is given concomitantly with other medication that may increase the exposure of BCRP, P-gp, and CYP2C8 substrates (a list of relevant substances will be provided to the investigators separately).

Prohibited concomitant medications are listed in exclusion criterion 12. Concomitant therapy with combined P-gp and strong CYP3A4 inhibitors, or combined P-gp and strong CYP3A4 inducers is prohibited from 14 days (or at least five half-lives of the active substance, whichever is longer) before randomization and until at least 48 hours after the last study intervention administration. A separate, more detailed list with prohibited medications will be provided to the investigator.

For participants who have *permanently* discontinued study intervention only information on concomitant antiplatelet and anticoagulant medications needs to be collected after completing their applicable early termination safety follow-up visit.

6.9.1 Guidance for Management of Participants who Have Bleeding During the Study

In general, the management of bleeding is under the discretion of the treating physician and should follow local practice.

Participant's bleeding events should be assessed in relation to the last intake of the study intervention, considering that asundexian has a total clearance of about 2.1 L/h and a half-life of approximately 21.5 hours.

If a participant has a clinically relevant bleeding or serious bleeding during the study intervention period that requires hospitalization, the following routine measures should be considered:

- Consider supportive treatments for bleeding, including local control of bleeding through standard procedures based upon the bleeding location, fluid replacement, blood transfusion, and fresh frozen plasma (FFP) transfusion. Consideration may also be given to the use of an antifibrinolytic agent (according to the package insert/label), such as tranexamic acid or ε-amino caproic acid (Tomaselli et al. 2017).
- Temporarily or permanently discontinue the study intervention. The decision to discontinue study intervention, temporarily or permanently, will be at the discretion of the treating physician and must be documented.
- Temporarily discontinue antiplatelet therapies until the bleeding event is sufficiently controlled, based upon the discretion of the treating physician.
- Investigate other causes of serious bleeding such as coagulopathies, thrombocytopenia, kidney / liver dysfunction, or other concomitant medications.

If bleeding cannot be controlled by the above measures, consider urgent surgical or non-surgical procedures to stop the bleeding (emergency surgery, arterial embolization, endoscopic cauterization, etc.) and unblinding of the randomized treatment assignment.

For those participants treated with asundexian, administration of the following procoagulants should also be considered (according to the package insert/label of the respective procoagulant) (Salomon and Gailani 2022), but there are no definite data in support of use of these agents:

- Recombinant FVIIa (NovoSeven) or activated prothrombin complex concentrate (aPCC) / factor 8 inhibitor bypass activity (FEIBA), based on *in vitro* data showing that these can fully reverse the prolongation of aPTT and ROTEM clotting time induced by asundexian.
- FXI concentrate (FXI).

6.9.2 Guidance for Management of Participants who Have Surgery or Percutaneous / Endoscopic Procedures

When possible, surgery and percutaneous / endoscopic procedures should be planned and delayed for at least 24 hours to allow for a 24-hour washout period after temporary discontinuation of study intervention to mitigate risks of bleeding.

For urgent or emergent surgery or percutaneous / endoscopic procedures, when waiting for 24 hours is not an option to allow for study intervention washout after temporary discontinuation, the increased risks of procedural bleeding should be assessed against the

urgency of the procedure based upon the clinical situation. Peri-procedure management may in part depend on the randomized treatment assignment (asundexian or placebo) and unblinding of treatment assignment may be necessary. In general, the treatment recommendations should follow the Guidelines for Severe Perioperative Bleeding Management (Kozek-Langenecker et al. 2013). The procedure should be conducted in such a way to minimize the risk of bleeding.

Treatment of participants receiving asundexian during urgent or emergency procedures may be guided by published data regarding patients with an inherited FXI deficiency. Apart from giving FXI concentrate as replacement therapy to cover a surgical bleeding event (Ling et al. 2016), there have been reports in the literature about the successful use of tranexamic acid or ε-amino caproic acid for the management of these patients with a FXI deficiency when undergoing surgery (Duga and Salomon 2013).

More detailed information can be found in the Investigator's Brochure.

6.9.3 Guidance for Management of Participants who Experience Ischemic Stroke During the Study

For participants who experience an ischemic stroke during the study, a complete diagnostic work-up including brain imaging, vascular imaging, at least 24-hour cardiac rhythm monitoring, and echocardiography is encouraged.

The treatment assignment may have to be emergently unblinded if necessary (see Section 6.4.1), to facilitate management decisions (e.g. intravenous thrombolysis or intra-arterial thrombolysis in case of mechanical clot removal).

Mechanical clot removal (thrombectomy), if indicated and available, may be performed in any case but without preceding thrombolysis. In case thrombolysis is considered, the following should be taken into account:

- For participants after an acute ischemic stroke who are receiving asundexian, the risk of bleeding with concomitant use of intravenous thrombolysis is unknown and has not been studied; hence a clear recommendation in this situation cannot be given. However, it is not recommended that a thrombolytic agent be given unless it is known that the study intervention (asundexian) has not been taken in the previous 48 hours, and the aPTT is normal. In this case, the risk of bleeding associated with thrombolysis is not expected to be increased (and unblinding may not be necessary).
- For participants who undergo thrombolysis; study intervention should be withheld until at least 24 hours after thrombolysis.

Regarding hemorrhagic stroke and other intracranial bleeding the experience with asundexian is limited due to the low number of events observed during Phase 2 across the 3 trials, please follow the current recommendations as per guidelines (Greenberg et al. 2022) and previous sections.

6.9.4 Guidance for Management of Participants who Experience an Acute Coronary Syndrome During the Study

For participants who experience a suspected new, acute coronary syndrome requiring hospitalization (unstable angina or AMI), standard of care medications should be administered according to local practice guidelines and based upon the chosen invasive procedure (dual antiplatelet therapy, intravenous / subcutaneous anticoagulants, or intravenous antiplatelet therapies such as glycoprotein IIb/IIIa inhibitors or cangrelor).

Cardiac ischemic event (AMI) endpoint reporting guidelines and processes should be followed for these situations.

For participants who undergo urgent or emergent coronary angiography (with or without PCI) as treatment for the new ischemic event, the interventional procedure can usually be conducted while on study intervention, similar to common practice with NOACs such as apixaban (Lane et al. 2019), unless bleeding risk exceeds the expected benefits. Radial access is preferable in such situations. If interruption of study intervention for PCI is desired by the local study team, the study intervention may be restarted as early as considered safe, e.g. no earlier than 24 hours after the arterial sheath has been removed and / or no earlier than 24 hours after the last dose of intravenous / subcutaneous anticoagulant or intravenous antiplatelet agent has been administered; the temporary pause of study intervention might be reduced if the radial route is used for PCI. For participants who are treated with urgent or emergent CABG surgery for the new ischemic event after coronary angiography, study intervention should be restarted no earlier than 24 hours after the post-surgical drains (chest tubes) have been removed.

For participants who are receiving asundexian, the risk of bleeding related to the concomitant use of an intravenous fibrinolytic is unknown and has not been studied. For participants treated with intravenous fibrinolytics, study intervention should be restarted no earlier than 24 hours after receiving fibrinolytics.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

7.1.1 Permanent Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy outcome events until the common end of treatment visit (CEOT visit). Thus, a permanent study intervention discontinuation should not lead to a stop of participation in the study and further study assessments. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed up to the CEOT visit.

At the time of informed consent, participants will be informed of all the options to continue in the study after permanent discontinuation of study intervention. This will be re-discussed at the time of permanent discontinuation of study intervention and the participant's specific agreement will be documented.

Study intervention will not be routinely permanently discontinued in participants reaching a potential outcome event or in case of unblinding, unless there is a safety concern or a clear indication for an alternative antithrombotic therapy as determined by the local investigator.

Before making a decision on permanent discontinuation of the study intervention, it is recommended to consider whether a temporary interruption is an option.

An early termination (ET) visit is only applicable to participants who prematurely discontinue intake of study intervention *permanently*; such participants should undergo the ET visit as soon as possible, after permanent discontinuation of study intervention. A safety follow-up

visit (telephone call) will occur 14 days after the day of the premature discontinuation (early termination) of study intervention (+7 days window). If the ET visit is conducted ≥ 2 weeks after permanent discontinuation of study intervention, an additional safety follow-up visit will not be performed.

In this study vital status data, outcome events and information on antiplatelet and anticoagulant medications are crucial to the analysis and must be collected until the end of the study, as participants will still be part of the study even if they are no longer taking study medication. Therefore, all efforts shall be taken to motivate participants to participate in the remaining study visits, usually by phone, and to continue to be followed until the CEOT visit.

Specifically, a permanent discontinuation of study intervention will be required if any of the following occurs and will last throughout the expected remaining intervention period. Otherwise, an interruption of study intervention could be considered for the duration:

- Pregnancy and breastfeeding of the study participant (see also Section 8.4.5)
- Concomitant treatment with any of the medications excluded per exclusion criterion 12 that has to be taken continuously for the remaining duration of the study e.g anticoagulation for atrial fibrillation, valvular disease, etc.
- Abnormal liver function if a participant meets one of the conditions outlined in Section 10.2.2 (and no other explanation is available) or if the investigator believes that it is in best interest of the participant

See country-specific requirements for the Republic of Korea (KOR-1) in Section 10.11.3.1.

See the SoA for data to be collected at the time of premature intervention discontinuation and for any further evaluations that need to be completed.

After permanent discontinuation of the study intervention, the participant is expected to continue the study visits as outlined in the protocol by telephone and will therefore be contacted by the study site at the regular follow-up intervals. The remaining outlined visits may also be done as site visits if preferred by investigator or participant. Ad hoc additional telephone contacts may also be requested and made to the participant themselves or to other contact as provided by the participant.

If it is not possible for any reason to continue the visits, the investigator and participant must discuss and determine further follow-up options, as listed below, in descending order of preference:

1. Participant allows his / her treating physician, e.g. general practitioner or a family member, to be contacted or his medical file checked at the regular follow-up interval, or at least once at study end (if allowed in respective country)
2. Participant will be contacted only once at the common end of treatment visit (at least this visit should be performed in all living participants)

After permanent discontinuation of the study intervention, the following information will need to be collected at the regular study visits and up to the last scheduled study visit (CEOT visit or CEOT SFU visit, as specified under section 4.1), preferentially directly from the participant and as agreed to by the participant during the initial informed consent process:

- Vital Status
- Outcome events (MI, stroke, death, bleeding)
- Antiplatelet and anticoagulant medications

It is of utmost importance for the final study results to make every effort to determine if relevant outcome events (e.g. an ischemic stroke) have occurred, regardless of the continued intake of study intervention. Based on the participant's respective consent, information on outcome events and vital status may be obtained by reviewing the participant's medical and pharmacy records and health insurance information.

If a participant does not wish to have direct follow-up contacts, sites shall explain to the participant why follow-up information on the health status is critical for the evaluation of the study results. It should be clarified and documented whether the participant upholds consent to collect the above listed follow-up visit information or would at least permit that sites contact the participant's representative, family member or treating physician by telephone or by mail to collect the specified follow-up information.

In the event that the participant has explicitly withdrawn consent to collect further non-public health information, the participant's vital status may be obtained from consulting public information or public sources (e.g. social media, health insurance, public [death] registry), unless this process is not allowed by local regulations.

7.1.2 Temporary Discontinuation of Study Intervention

In the event of a temporary interruption of study intervention for any reason, study intervention will be restarted as soon as medically justified in the opinion of the investigator. An example would be continuous concomitant treatment with any of the prohibited medications mentioned above (in Section 7.1), that has to be taken only for a limited, foreseeable timeframe, that is expected to be considerably less than the expected remaining intervention period of the study. In such a case, based on medical judgement, a temporary interruption of study intervention should be considered instead of permanent discontinuation. The need for a temporary interruption might also arise from an adverse event, for instance relating to liver dysfunction (refer to Section 10.2.2). There is no predefined maximum limit for temporary treatment interruption.

In the event of a trial-continuity issue (e.g. caused by a pandemic), the sponsor may provide additional guidance in study-specific communication.

If study intervention is temporarily discontinued, PK / PD blood samples should only be obtained if study intervention has been restarted and sustained for at least 4 days before PK / PD blood sampling.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request, for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- When a participant withdraws consent from study participation before completing the study, meaning that the participant does not agree to any kind of follow-up and specifically refuses any further contact with the investigator, the reason for consent withdrawal (if disclosed by the participant) is to be documented in the source document. Public information can be used to obtain vital status for these participants where allowed by local regulations.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if the participant repeatedly fails (at least 3 times) to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- In order to reduce risk for lost to follow-up the site should collect 2 alternative means of contact for each participant e.g. contact information of family members, caretaker, legal representative, or treating physician. The correctness of these contact details should be checked regularly at the study visits.
- A patient locator service may be used (where allowed by local regulations) to re-establish contact with a participant in case the site has exhausted all means of regaining contact.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Results from procedures conducted as part of the participant's routine clinical management and as part of the hospitalization for the index event (e.g. ECG, vital sign measurement) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3). Monitoring of the absence of atrial fibrillation as part of routine ECG monitoring before randomization is especially important to prevent early discontinuation of study intervention after randomization.
- Laboratory / analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- In the event of a significant trial-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority / ethics requirements.
- The maximum blood draw volume for each participant over the duration of the study is provided in a separate document (e.g. ICF and laboratory manual).
- If a participant requires an unscheduled visit to perform additional procedures / assessments other than regularly scheduled (e.g. for lab sampling), this should be documented in the CRF accordingly. Unscheduled visits may occur any time during the study conduct.

8.1 Administrative and Baseline Procedures

Administrative and baseline procedures are summarized in the SoA (Section 1.3).

8.2 Efficacy Assessments

The efficacy assessments include primary, secondary and exploratory endpoints of the study (refer to Section 3). Planned timepoints for all efficacy assessments are provided in the SoA.

8.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is time to ischemic stroke.

The definition of the primary efficacy outcome event is provided as follows. Details on the time periods for collecting Outcome Events information are reported in Section 10.9.

8.2.1.1 Ischemic Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by an injury of the brain, spinal cord, or retina as a result of hemorrhage or infarction.

Either of the following is considered to be an ischemic stroke:

- Rapid onset (or present on awakening) of a new focal neurological deficit with clinical signs and symptoms (≥ 24 hours) that is not attributable to a non-ischemic cause (i.e. not associated with infection, tumor, seizure, severe metabolic disease) or imaging evidence of infarction.
- Acute worsening of an existing focal neurological deficit (e.g. the qualifying stroke) that is judged to be attributable to a new infarction or extension of the previous infarction in the same vascular territory, based on persisting symptoms / signs or imaging evidence of infarction and no evidence of a non-ischemic etiology. If imaging is inconclusive,

persistent symptoms / signs must be significant (worsening of NIHSS score of 4 or more) and sustained (duration of ≥ 24 hours or until death).

The term undetermined stroke will apply when sudden focal neurological deficits persist for 24 hours (or if death occurs before 24 hours) but without neuroimaging or autopsy. For the purpose of analyzing the endpoints undetermined strokes will be counted as ischemic strokes.

8.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are listed in Table 3–1.

Definitions of the secondary efficacy outcome events are provided as follows.

8.2.2.1 Cardiovascular Death

Cardiovascular (CV) death includes death due to stroke, myocardial infarction, heart failure or cardiogenic shock, sudden death or any other death due to other cardiovascular causes or CV procedures. In addition, death due to non-traumatic cardiovascular hemorrhage will be included, e.g. non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g. aortic aneurysm), or hemorrhage causing cardiac tamponade (Hicks et al. 2015).

Death for which the cause cannot be determined, so called “undetermined death”, will be included in the analysis as cardiovascular death (yet will not be excluded from SAE reporting).

8.2.2.2 Myocardial Infarction

The term acute MI is used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. According to the 4th Universal Definition of MI from 2018 (Thygesen et al. 2018) the diagnosis of MI requires the combination of:

- Presence of acute myocardial injury (changes in cardiac biomarkers) **and**
- Evidence of acute myocardial ischemia derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging, or in case of post-mortem pathological findings irrespective of biomarker values

8.2.2.3 Disabling Stroke

A disabling stroke is defined as a stroke of any type during the trial associated with a modified Rankin Scale (mRS) of ≥ 3 at 90 days after the recurrent stroke or an increase of 1 point if the last available mRS before the recurrent stroke event was ≥ 3.

Participants should be assessed for their resulting disability by mRS (Section 10.7) as follows:

7 days after the recurrent stroke event (or at hospital discharge / death, if this occurs before that date), and

at any subsequent visit as specified in the SoA. For the 90 days assessment the mRS determined at the visit closest to 90 days after the stroke event will be taken, if assessed at least 30 days after the stroke event.

8.2.2.4 Transient Ischemic Attack (TIA)

In contrast to a stroke, a TIA is defined as transient episode of neurologic dysfunction caused by focal brain, spinal cord or retinal ischemia with all symptoms and signs resolving within 24 hours of onset and without evidence of acute infarction on neuroimaging or autopsy (Easton et al. 2009). Differentiating TIA from other mimicking conditions is important.

Symptoms of TIA usually start abruptly, followed by resolution, usually over minutes or several hours, and are typically associated with focal neurologic deficits and / or speech disturbance due to underlying cerebrovascular disease. Isolated dizziness / vertigo or isolated numbness do not qualify as classical TIA.

8.2.3 Exploratory Efficacy Assessments

Exploratory endpoints are listed in Table 3–1.

8.2.3.1 EuroQol Group 5-dimension questionnaire (EQ-5D)

A health-related quality of life assessment tool, the European Quality of life group 5-Dimension questionnaire (EQ-5D) will be administered at Day 1 (randomization), every 6 months, and at the CEOT visit. This is a standardized instrument for use as a measure of health outcomes primarily designed for self-completion by patients. The questionnaire is to be completed by the participant or with assistance, if required (questionnaires are provided in local languages). The participant will fill in a paper-based version of the questionnaire directly at the site, which is then entered by the study personnel into the CRF. If the participant has problems completing the questionnaire due to physical or visual limitation, an attempt can be made to repeat the questions in a neutral and unpersuasive manner. In this situation, participants may verbally indicate or point to their response, which is then entered by the study personnel.

Items and scores derived from EQ-5D are exploratory endpoints, and consist of 2 parts: the EQ-5D descriptive system and a Visual Analogue scale (VAS). The descriptive system asks questions across 5 dimensions of health (mobility, self-care, usual activities, pain / discomfort, anxiety / depression) with 5 response levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The health state index values derived from the descriptive system will be analyzed separately to support health economic evaluations (i.e. results will not be included in the CSR). The EQ-5D VAS records the participant's own assessment of his / her health status on a vertical graduated scale, anchored on 0 ('the worst health state you can image') to 100 ('the best health state you can imagine').

8.2.3.2 Modified Rankin Scale

The distribution of mRS scores at Day 7 after index event, at visit 3, 6, and 12, and at the CEOT visit will be included in exploratory efficacy assessment.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

The safety endpoints are primary, secondary and exploratory endpoints of the study. At each visit during the study as specified in the SoA, the investigator will evaluate the participant for the occurrence of bleeding events. All necessary information to classify bleeding events according to the ISTH, and the BARC criteria will be collected in the CRF.

8.3.1 Primary Safety Endpoint

The primary safety objective is to compare the incidence of ISTH major bleeding.

8.3.1.1 ISTH Major Bleeding

An event that meets at least one of the below criteria for a major bleeding event according to the definition given by the ISTH (Schulman and Kearon 2005):

- Fatal bleeding, and / or

- Symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular with compromised vision, pericardial, retroperitoneal, intra-articular, or intramuscular with compartment syndrome), and/or
- Clinically overt* bleeding associated with a recent (within 48 hours) decrease in the hemoglobin level of ≥ 2 g/dL (20 g/L; 1.24 mmol/L) compared with the most recent hemoglobin value available before the event, and/or
- Clinically overt* bleeding leading to transfusion of 2 or more units of packed red blood cells or whole blood

  * overt bleeding requires the identification of the bleeding location and the hemoglobin drop and / or transfusion needs to be related to the bleeding.

8.3.2 Secondary Safety Endpoints

Secondary safety endpoints are listed in Table 3–1.

8.3.2.1 ISTH Clinically Relevant Non-Major Bleeding

Clinically relevant non-major bleeding is considered any sign or symptom of acute or sub-acute clinically overt* bleeding that does not fit the criteria for the ISTH definition of major bleeding, but does meet at least one of the following criteria (based on criteria published by the EMA) (EMA 2014):

- requiring medical or surgical treatment by a healthcare professional for bleeding
- leading to hospitalization or increased level of care for bleeding
- a change in antithrombotic therapy (including study intervention) for bleeding

  * overt bleeding requires the identification of the bleeding location.

A visit alone at a healthcare professional (without fulfilling any of the above criteria) does not suffice. Also an assessment of bleeding as part of a healthcare encounter that is primarily for a different health issue does not qualify. Examples of clinically relevant non-major bleeding include, but are not limited to: multiple-source bleeding requiring treatment for bleeding; intramuscular hematoma documented by ultrasonography without compartment syndrome; macroscopic (gross, visible) hematuria (spontaneous or lasting > 24 hours if associated with an intervention) requiring increased medical care; epistaxis or gingival bleeding that requires tamponade or other medical intervention to stop the bleeding; hemoptysis, hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention.

8.3.2.2 Minor Bleeding

All other overt bleeding episodes not meeting the above criteria for ISTH major or clinically relevant non-major bleeding will be classified as minor bleeding (e.g. bleeding from a minor wound that does not prompt a face to face evaluation for a physical examination or laboratory testing, or epistaxis that does not require a medical treatment for bleeding or a change in antithrombotic therapy).

8.3.2.3 Hemorrhagic stroke

Hemorrhagic stroke is defined as symptomatic acute, atraumatic extravasation of blood into the brain parenchyma, intraventricular or subarachnoid space with associated neurological symptoms. This does not include microbleeds nor hemorrhagic transformation of an ischemic stroke.

8.3.2.4 Symptomatic intracranial hemorrhage

Intracranial hemorrhage is defined as any symptomatic intracranial hemorrhage (traumatic and not traumatic). It includes intracerebral bleeds (intraventricular bleeds and intraparenchymal bleeds), subarachnoid bleeds, epidural bleeds, and subdural bleeds.

It does not include any asymptomatic intracranial bleeding found by imaging alone (e.g. asymptomatic hemorrhagic transformation, microbleeds).

8.3.3 Exploratory Safety Endpoints

Exploratory safety endpoints are listed in Table 3–1.

8.3.3.1 BARC Bleeding

The BARC bleeding definition encompasses the following bleeding types (type 4: CABG-related bleeding is not applicable to this study):

- **Type 0:** no bleeding
- **Type 1:** bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
- **Type 2:** any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, or 5 but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
- **Type 3:**

  Type 3a

  - Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed)
  - Any transfusion with overt bleeding

  Type 3b

  - Overt bleeding plus hemoglobin drop ≥ 5 g/dL* (provided hemoglobin drop is related to bleed)
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
  - Bleeding requiring intravenous vasoactive agents

  Type 3c

  - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging or lumbar puncture
  - Intraocular bleed compromising vision
- **Type 5:** fatal bleeding

  Type 5a

- Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

- Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1g/dL hemoglobin)

8.3.4 Physical Examinations

Physical examination will only include height and weight (also referred to as biometrics in the SoA), which will be measured and recorded at screening (see Section 1.3).

8.3.5 Vital Signs

Vital signs will include systolic and diastolic blood pressure, and heart rate.

Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest in semi-supine position in a quiet setting and without distractions (e.g. television, cell phones).

8.3.6 Electrocardiograms

A single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3), preferably using an ECG machine that automatically calculates the heart rate.

The main purpose of the ECG is to confirm the absence of AF (exclusion criteria 4). It is encouraged to confirm the absence of AF just before randomization, even if the ECG required by the SoA has been completed. Also constant cardiac monitoring to detect arrythmias between screening and randomization is encouraged.

8.3.7 Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded.

8.3.8 Pregnancy Testing

A woman of childbearing potential must have a negative highly sensitive pregnancy test available before randomization. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or institutional review boards (IRB) / independent ethics committees (IEC). *For country-specific requirements for the Republic of Korea (KOR-1), please see Section 10.11.3.1.*

If a urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

In addition, a pregnancy test is required at the end of relevant systemic exposure, which is either at the early termination visit for participants that prematurely discontinue intake of study intervention (unless study intervention has been discontinued since more than 7 days) or at the CEOT visit for participants that end the study intervention period regularly.

Further serum or urine pregnancy tests should be performed in participants of childbearing potential as required by national / institutional regulations (e.g. at every site visit). At any time during study participation, additional pregnancy testing should be performed upon suspicion of pregnancy.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

Events that are deemed to be disease-related efficacy outcome events according to the study protocol will not be reported as (S)AEs and will only be reported on the dedicated outcome event CRFs. A description of these outcome events is covered in Section 8.4.6 and Section 10.9.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention and / or study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

(S)AEs will be collected from the start of study intervention until a participant's respective safety follow-up visit[8] at the timepoints specified in the SoA (Section 1.3). (S)AEs which are related to protocol-required study procedures (e.g. (S)AE related to invasive study procedures) will be recorded as (S)AEs from the signing of the ICF.

[8] For a participant with premature permanent discontinuation of study intervention, this is the early termination safety follow-up visit.

Any medical occurrences/conditions that begin in the period between signing ICF and the start of study intervention, and which are not related to a protocol-required study procedure, will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits / contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB / IEC, if appropriate according to local requirements.

For all studies except those using medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until 4 days after the last dose intake.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.

The female participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are part of the efficacy outcome events in participants after an acute non-cardioembolic ischemic stroke or high-risk TIA:

a. Ischemic stroke and TIA
b. Myocardial infarction
c. CV death
d. Events indicative of those outcome events listed under a) to c) (e.g. cardiac chest pain requiring hospitalization with increased cardiac enzymes).

Because the above mentioned DREs pertaining to efficacy endpoints are typically associated with the disease under study, they will be exempted from reporting as (S)AE by the investigator to the sponsor as well as from expedited SUSAR reporting.

Even though these events may meet the definition of an SAE (including life threatening or fatal events), they will not be reported according to the standard process for expedited reporting of SAEs to the sponsor. Consequently, they will not be subject to systematic unblinding and expedited SUSAR reporting to Health Authorities and Independent Ethics Committees / Institutional Review Boards (IECs / IRBs). Systematic unblinding of these expected efficacy events could compromise the integrity of the clinical study.

Instead, the above mentioned DREs and events indicative of those outcomes [a) to d)] will be recorded on the corresponding efficacy outcome / death CRF pages on an ongoing basis. Following documentation in the CRF, they will be adjudicated by the CEC and monitored on a routine basis by the IDMC as outlined in the respective charters (Section 10.1.6).

In case the diagnosis of a supposed DRE changes and the event no longer fulfills the criteria for a disease-related event as described above, the investigator is requested to proceed with reporting the event to the sponsor as (S)AE and – if serious – within the timelines required for an SAE (Sections 8.4 and 10.3), in addition to deleting the event from the outcome CRF.

In case efficacy outcome events listed above are adjudicated by the CEC as not meeting the outcome criteria specified in the CEC charter ("refuted"), these events will not be reported as SAEs, as the adjudication results will not be shared with the investigators during the study. Therefore, investigators will not be asked to change the reporting of these events.

This process will maintain the independence of the CEC. Refuted events will still be part of the review by the IDMC and later be summarized in final analyses.

However, if either of the following conditions applies, then the event may be recorded and reported as an (S)AE *in addition* to reporting on the efficacy outcome CRF:

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

  OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Safety outcome events (i.e. all bleeding) or efficacy outcome events with a symptomatic bleeding component (e.g. hemorrhagic stroke, ischemic stroke with symptomatic hemorrhagic transformation, cardiovascular death due to a ruptured aortic aneurysm) are not exempted and are therefore to be reported as (S)AE, in addition to reporting them on the respective outcome CRF pages.

Events that have already been reported as (S)AEs and eventually result in cardiovascular death will not be deleted from the adverse event CRF page (e.g. decompensated heart failure leading to death).

Irrespective of that, any death will need to be captured on the death CRF page and classified as either cardiovascular, non-cardiovascular or undetermined (refer to Section 8.2.2.1). The below Table 8–1 shows an overview of how different events are expected to be reported to the sponsor. Please also refer to Section 8.4.1 in relation to reporting of adverse events and Section 10.9 for more details on reporting in relation to the time of the occurrence of the respective outcome events.

Table 8–1: Reporting of events

Event type	Efficacy outcome / death CRF	Bleeding outcome CRF	(S)AE CRF *	Timing of reporting
Disease-related events # [detailed as a) to d) in beginning of this section]	X	–	–	Ongoing basis
Efficacy outcome events with symptomatic bleeding component	X	X	X**	SAE ≤ 24 hours†
Safety outcome events (all bleeding)	–	X	X**	SAE ≤ 24 hours†
Other (S)AE	–	–	X	SAE ≤ 24 hours†

Abbreviations: CV = cardiovascular, CRF = case report form, (S)AE = (serious) adverse event, SUSARs = suspected unexpected serious adverse reactions

* Reportable events (i.e. SUSARs) will be unblinded and reported to the competent authorities and Independent Ethics Committees / Institutional Review Boards (IECs / IRBs) according to legal requirements (Section 8.4.4).

** in case of premature permanent discontinuation of study intervention, (S)AE reporting is not required after the participant's early termination safety follow-up visit (Section 7)

Events leading to *non-CV* or *undetermined* death are not disease-related and will need to be reported as SAEs

† SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of the investigator learning of the SAE (Section 8.4.1 and Section 10.3).

8.4.7 Adverse Events of Special Interest

No AEs of special interest have been defined.

8.5 Pharmacokinetics

For the investigation of systemic exposure to asundexian and its relationship with treatment effects, the plasma concentrations of asundexian, M-10 (BAY 2826102), and optionally other metabolites will be determined at different time points using a sparse sampling approach. Details about the collection, processing, storage and shipment of samples will be provided separately (e.g. in the Laboratory Manual). Sponsor personnel responsible for bioanalytics will be unblinded and will have access to the randomization list. Analysis of samples from participants not treated with asundexian is optional.

Blood samples will be collected at the time points indicated in the SoA (Section 1.3). Deviations from the specified sampling intervals will be documented and taken into account for the PK analysis. Date and time of the PK sample collection and date and time of most recent study intervention intake (i.e. both timepoints on the PK/PD sampling day, and on the day before that) must be documented.

At visit 4 and visit 7 a trough sample for the determination of asundexian plasma concentrations will be collected before intake of study intervention. Study intervention at those visits should still be taken out of the respective bottle that participants receive, preferably at the study site. Ideally, the study personnel should contact the participants prior to visit 4 and visit 7 to remind them not to take the study intervention as usual in the morning at home. The PK data and the relationship of the asundexian exposure parameters with treatment effects might be evaluated using population approaches including potential influence of relevant participant co-variables. Analysis and report will be done under a separate cover. This evaluation might be started prior to database lock: if this is applicable,

appropriate measures will be taken to maintain blinding of the study team (refer to Section 6.4.1).

PK samples will be analyzed, using validated analytical methods. Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of calibration samples and QC samples will be reported in the Bioanalytical Report.

8.6 Pharmacodynamics

Blood sampling for PD parameters will be done only in a subset of countries / regions in approximately 2000 participants and is scheduled for the time points as given in Table 1–2. The actual date and time of study intervention intake and of blood sampling will be documented in the CRF. All PD parameters will be measured using validated methods.

Quality control and calibration samples will be analyzed concurrently with study samples. For selected PD parameters, the results of QC samples will be reported together with analyte concentrations in a Bioanalytical Report.

Results of the analysis are calculated according to the method description. Detailed method descriptions of all PD methods will be filed with the CSR. Results will be reported under separate cover.

The sampling will be done for an exploratory assessment of PD effects after administration of the investigational drug and may include but is not limited to baseline assessments of FXI levels (clotting assay), FXII levels (clotting assay), and von Willebrand factor activity, as well as aPTT at baseline and after study intervention intake. In addition, blood samples will be taken for exploratory biomarker analyses (see Section 8.8).

Detailed information about the collection, processing, storage and shipment of the samples will be provided separately (e.g. sample handling sheets and/or laboratory manual).

8.7 Genetics and/or Pharmacogenomics

Genetic as well as non-genetic analyses will be part of the biomarker investigations in this study, if approved by local ECs / IRBs and competent authorities. See Section 8.8 for details.

8.8 Biomarkers

Blood sampling for exploratory biomarker analyses will be done only in a subset of study sites in approximately 1000 participants (scheduled for the time points as given in Table 1–2). Biomarker plasma / serum samples should be collected before intake of study intervention at the respective visits. The exact biomarkers chosen will depend on the outcome of the Phase 2 biomarker analysis. Biomarkers related to the study intervention, its safety or drugs with similar, e.g. mode-of-action related effects may be examined. The same applies to further biomarkers deemed relevant to cardiovascular diseases and associated health problems. These investigations may include e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers.

Those additional analyses may include genetic as well as non-genetic biomarkers. Genetic investigations may be of any kind, except for whole genome sequencing. Results will be reported under separate cover, if the evaluations are performed.

Details on the collection, processing, storage, and shipment of biomarker samples will be provided in separate documents (e.g. sample handling sheets or lab manual). Samples may be

stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.

8.9 Immunogenicity Assessments

Not applicable.

8.10 Medical Resource Utilization and Health Economics

Participants will be asked to complete a quality of life questionnaire during the study conduct (see Section 8.2.3.1). In addition, the use of healthcare resources is going to be collected.

8.11 Healthcare Resource Utilization (HCRU)

The use of healthcare resources (hospitalizations) related to all SAEs and outcome events will be documented for all participants during the study. The total number of hospitalizations due to efficacy or safety outcome events will be assessed as exploratory net clinical benefit endpoint based on the investigator reported use of healthcare resources.

9. Statistical Considerations

The first version of the statistical analysis plan (SAP) will be finalized prior to study enrollment, with final updates made prior to database lock. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

As described in Section 3, the population-level summary to describe the treatment effects for the primary and secondary efficacy endpoints is the cause-specific hazard ratio comparing asundexian with placebo. Let $\lambda_{estimand}$ represent the (cause-specific) hazard ratio, i.e. the ratio of the cause-specific hazard for participants assigned to asundexian and the cause-specific hazard for participants assigned to placebo, for the respective estimand.

The study plans to test several efficacy null hypotheses.

The aim related to the primary efficacy objective is to show that asundexian is superior to placebo in preventing ischemic stroke in patients after an acute non-cardioembolic stroke. The two-sided test problem is

$$H_0: \lambda_{\text{primary efficacy}} = 1 \qquad \text{versus} \qquad H_a: \lambda_{\text{primary efficacy}} \neq 1$$

stating in the null hypothesis that “there is no difference between the cause-specific hazards of the two treatment arms for the primary efficacy outcome” and in the alternative that “there is a difference between the treatment arms in cause-specific hazards of the primary efficacy outcome”.

The two-sided test problems for the secondary efficacy endpoints

- All strokes (ischemic and hemorrhagic)
- Composite of CV death, MI or Stroke
- Composite of all-cause mortality, MI or Stroke

- Ischemic stroke in the first 90 days
- Disabling stroke (mRS ≥3)
- All-cause mortality
- Transient ischemic attack (TIA)

are defined analogously to the test problem for the primary efficacy endpoint. The cause-specific hazard ratio for all-cause mortality actually is the hazard ratio, since no competing risk is considered for this endpoint.

Assuming proportional cause-specific hazards for the time-to-event endpoints, the hypotheses will be tested using two-sided stratified logrank-tests.

For the primary and secondary safety endpoints, no formal testing is planned and no test problem is stated.

9.1.1 Multiplicity Adjustment

The type I error of $\alpha = 5\%$ will be controlled in the strong sense using a hierarchical testing procedure. The statistical testing of the null hypotheses for the primary and secondary efficacy endpoints will be carried out in the hierarchical order as follows:

- Ischemic stroke
- All strokes (ischemic and hemorrhagic)
- Composite of CV death, MI or stroke
- Composite of all-cause mortality, MI or stroke
- Ischemic stroke in the first 90 days
- Disabling stroke (mRS ≥3)
- All-cause mortality
- Transient ischemic attack (TIA).

Consequently, the second null hypothesis will only be tested if the first null hypothesis has been rejected in favor of asundexian and so on. Operationally the hypotheses will be evaluated by two-sided tests. The two-sided tests will be stratified logrank tests for the time-to-event endpoints.

9.2 Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full Analysis Set (FAS)	All participants randomized to study intervention.
Safety Set (SAF)	All participants randomized to study intervention and who take at least 1 dose of study intervention.

Unless otherwise specified, the FAS will be used for all analyses addressing efficacy estimands.

The SAF will be used for analyses addressing the primary safety estimand and other estimands relating to bleeding endpoints, as well as analyses of AEs.

9.3 Statistical Analyses

9.3.1 General Considerations

The statistical analyses will be performed using SAS and validated R; the version used will be specified in the statistical analysis plan (SAP).

Derivation of time-to-event endpoints, censoring and incomplete dates

For the key efficacy and safety events, see Section 3, the endpoint is the time to first occurrence of the outcome event of interest, which can be a single outcome or a composite. In general, time-to-event endpoints will be derived as the number of days from the individual participant's randomization date to the date of onset of the respective endpoint event. The time-to-event endpoint for participants who have not experienced the respective endpoint event will be censored on the date of the last follow-up in the following way:

- for participants who reach their CEOT visit without the event of interest, the censoring date will be the date of their CEOT visit,
- otherwise the censoring date will be based on latest date participants are known to be at risk for the event of interest

For analyses addressing the primary safety estimand and other estimands relating to bleeding endpoints, randomization date will be replaced by the date of first intake of study intervention when deriving the time-to-event endpoint.

Where the "while on-treatment" strategy is proposed to address the intercurrent event "early discontinuation of the assigned study treatment", see estimand definition in Section 3, the occurrence of this intercurrent event will be considered a "soft" competing risk in the analysis. I.e. in the analysis events of interest will only be counted up to the date of last intake of study intervention plus 2 days. Also in case the study intervention is taken up to the planned end date, the event of interest and time will be counted up to the date of last intake of study intervention plus 2 days. Similarly, if the "while alive" strategy is proposed to address the intercurrent event "death", the occurrence of death will be considered a competing risk in the analysis, resulting in "technical censoring" at the date of death.

If the date of a key endpoint or of censoring is incomplete following all attempts to get an approximate date by the investigator, a day will be imputed using the following algorithm:

If only the month of the event is known, then the 1st day of this month will be imputed.

If only the year of the event is known, then the 1st of January will be imputed.

If year, month and day are unknown, the randomization date will be imputed.

If this imputation rule leads to an implausible date, i.e. before the randomization date the date will be imputed as that date.

Descriptive statistics

Study data will be summarized using methods like frequency tables and other descriptive statistics. If not stated otherwise, confidence intervals will be presented as two-sided 95% confidence intervals.

For time-to-event endpoints, the numbers of participants with an event of interest in defined periods of patient follow-up will be presented. Incidence proportions and incidence rates for the event of interest as well as for potential competing risks will be shown.

Nelson–Aalen estimates of the cumulative hazard for the event of interest by treatment arm will be used to explore if the estimated hazards are reasonably constant over time as applicable. The cumulative incidence risk, i.e. the expected proportion of participants with an event of interest over the course of time taking competing risk into account, will be estimated for time to event endpoints using Aalen-Johansen estimators.

In addition, endpoint events after (administrative) censoring, will be summarized, as applicable.

Stratification

Regression models and statistical tests will be stratified (where applicable) by whether participants will receive dual antiplatelet therapy with ASA and a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor) or not.

Missing data

The aim is to minimize missing observation time as much as possible. Generally, all participants, including those who discontinue study intervention, will be followed until death or the end of the intervention period. Information of participants discontinuing study intervention or participation in study visits will be collected whenever possible and meaningful for the analysis. Data that would be meaningful for the analysis of a given estimand but were not collected are considered missing.

For participants who could not be followed up for outcome events on a regular basis, it is aimed to at least determine the participants' status at the end of the intervention period with respect to the occurrence and timing of key outcome events, including MI, stroke, death and bleeding. In general, sensitivity analyses will be performed to assess the robustness with respect to assumptions that need to be made to handle missing data. Details will be described in the SAP.

Handling of missing data for key time-to-event analyses

Regarding time-to-event endpoints censoring for administrative reasons will be assumed to be non-informative.

All efforts will be made to reduce incomplete follow-up with regard to the occurrence and timing of key outcome events at the end of the study to a minimum.

To keep the main analyses simple and in line with the estimation approaches commonly used, the observation time for event-free participants with incomplete follow-up time will be censored at the last available point in time for which data on the outcome has been obtained.

As a sensitivity analysis, the sponsor plans to apply statistical methods aligned with the targeted estimand in line with ICH E9(R1). When missing follow-up time occurs after the occurrence of an intercurrent event, the missing data will be addressed by methods aligned with the strategy proposed for the respective intercurrent event and estimand.

For example, it is assumed that after withdrawal of informed consent (or loss to follow-up) participants remain untreated if they have not already discontinued their randomized treatment earlier. Thus, when for a given estimand the intercurrent event "treatment discontinuation" is addressed by the treatment policy strategy, unobserved follow-up time will be modelled based on patient data observed after treatment discontinuation.

Unobserved follow-up time will be multiply imputed using hazard rates estimated from those participants who have observed data subsequent to the intercurrent event "treatment discontinuation" but who have not experienced the event of interest prior to "treatment

discontinuation". The constant hazard rate assumption will be assessed, and if not satisfied, a piece-wise exponential or other distribution will be used for imputing the missing follow-up time. The imputation will include the following steps:

1. Identify participants who have observed follow-up time subsequent to early discontinuation of randomized treatment and who have not experienced the event of interest prior treatment discontinuation. For these participants, estimate the hazard rate for the off-treatment period separately for each treatment group. The off-treatment period is defined as from the date of last intake of randomized treatment + 2 calendar days to either the outcome event of interest or the date of censoring due to study completion or death.
2. For each participant with incomplete follow-up for the event of interest who was censored without an outcome event of interest, simulate missing follow-up time as follows:
   - Draw (a) parameter(s) [Exponential, Weibull, or other] from the normal distribution using the estimates for the hazard rate in step 1 to incorporate variability in the estimated hazard rates.
   - Simulate a follow-up time from that resulting distribution and add it to the observed censoring date to get the imputed time to event for that participant.
3. If the imputed time to event is before a defined cut-off date, the participant "experienced" the outcome event at the imputed time; if not, the participant would be censored at the cut-off date. The cut-off date will be set to the last CEOT visit date over all participants, reflecting the maximal time under risk for these patients.
4. Analyze the time to the outcome event of interest based on the complete time to event data (observed + imputed).
5. Repeat steps 2, 3 and 4 multiple times and use Rubin's rule for combining analysis results from multiply imputed datasets using an approximate proper imputation.

9.3.2 Primary Endpoint(s)/Estimand(s) Analysis

The following subsections describe the planned statistical analyses addressing the primary efficacy and safety estimands.

9.3.2.1 Primary Efficacy Estimand

Definition of endpoint

The primary efficacy endpoint is the time from randomization to the first occurrence of ischemic stroke. The outcomes are defined in Section 3, the derivation of the time to event is described in Section 9.3.1.

Main Analytical Approach

In line with the while alive strategy applied to address the intercurrent event death for the primary efficacy estimand, see Section 3, death prior to the occurrence of a primary efficacy outcome will be considered a competing risk in the analysis. Addressing premature discontinuation of assigned treatment with the treatment policy strategy means that events occurring after treatment discontinuation are used in the analysis.

To estimate the relative change in the rate of the occurrence of the primary efficacy outcome in participants taking asundexian versus placebo according to the defined estimand, cause-

specific hazard ratios (csHRs) and their associated confidence intervals will be derived from a stratified cause-specific Cox proportional hazards regression model. The results will be presented together with estimates of the csHRs for the associated competing risks.

The primary efficacy null hypothesis will be tested using a two-sided stratified logrank test.

Missing follow-up time for the time to the primary efficacy outcome will be addressed as described for the main analysis in Section 9.3.1.

Sensitivity Analyses

If Nelson–Aalen estimates of the cumulative hazard for the primary efficacy outcome by treatment arm indicate that estimated hazards are not reasonably constant over time, piecewise incidence rates, with appropriately chosen cut-points, will be estimated and presented.

The plausibility of the proportional hazards assumption will be assessed by visually examining the plot of the log of the negative log of Aalen-Johansen estimates of the survival function versus the log time for evidence of non-parallelism. If there is strong evidence of non-proportionality, time-dependent cause-specific hazard ratios will be estimated with the model that includes the interaction term. Further details will be specified in SAP.

Missing follow-up time will be in general handled as described above. In addition, sensitivity analyses with regard to the missing follow-up time will be done as described in Section 9.3.1.

Supplementary Analyses

In a supplementary analysis the objective will be explored from a different angle, comparing the probability for the primary efficacy outcome as compared to the hazard rates. I.e. the supplementary estimand is the same as the primary efficacy estimand but the population-level summary is the sub distribution hazard ratio based on a Fine-Gray model. Gray's test is used to compare the cumulative incidences. Since the expected probability of the occurrence of a primary efficacy event is less than 20% over the whole duration of study follow-up, a sub distribution hazard ratio of x is associated with a x-fold decrease of the odds of the occurrence of the primary efficacy outcome when treated with asundexian versus placebo.

9.3.2.2 Primary Safety Estimand

Main Analytical Approach

In line with the "while on-treatment" strategy proposed to address intercurrent events for the primary safety estimand, see Section 3, both "death prior to the occurrence of a primary safety outcome" and "premature discontinuation of assigned treatment" will be considered competing risks in the analysis. This also implies that only participants who took at least one dose of study intervention will be included in the analysis, i.e. the analysis will be performed on the SAF.

To estimate the relative change in the rate of the occurrence of the primary safety outcome in participants taking asundexian versus placebo according to the defined estimand, csHRs and their associated confidence intervals will be derived from a stratified cause-specific Cox proportional hazards regression model. The results will be presented together with estimates of the csHRs for the associated competing risks.

The primary safety superiority null hypothesis, see Section 9.1, will be tested using a stratified log-rank test.

If applicable, incomplete follow-up for the time to the primary safety outcome will be addressed with statistical methods aligned with the targeted estimand.

Sensitivity Analyses

If Nelson–Aalen estimates of the cumulative hazard for the primary safety outcome by treatment arm indicate that estimated hazards are not reasonably constant over time, piecewise incidence rates, with appropriately chosen cut-points, will be estimated and presented.

The plausibility of the proportional hazards assumption will be assessed as described above for the primary efficacy outcome.

If applicable, the robustness of the main estimator to deviations from assumptions regarding incomplete follow-up for the time to the primary safety outcome will be addressed with statistical methods aligned with the targeted estimand.

Supplementary Analyses

In a supplementary analysis the objective will be explored from a different angle, comparing the probability for the primary safety outcome as compared to the hazard rates based on a Fine-Gray model and using Gray's test to compare the cumulative incidences.

9.3.3 Secondary Endpoints Analysis

The analysis of estimands associated with secondary endpoints will follow the principles as described for the respective primary efficacy and safety estimands.

For those efficacy composites that include CV death as a component of the endpoint, the competing risk death will be reduced to non-CV death and, obviously, death will not be a competing risk for the all-cause mortality endpoint, and fatal bleeding will not be a competing risk for the safety endpoints fatal bleeding and all bleeding.

Furthermore, the time-to-event net clinical benefit endpoints will be analyzed in line with the statistical approach described for the primary safety endpoint, considering "death prior to the occurrence of a net clinical benefit outcome" and "premature discontinuation of assigned treatment" as competing risks.

9.3.4 Exploratory Endpoints Analysis

Exploratory endpoints are listed in Table 3–1.

The analyses of exploratory time-to-event endpoints will follow the principles described above. Details will be specified in the SAP.

9.3.5 Other Safety Analysis

An overall summary of AEs will be generated by study intervention arm. The number and percentage of participants with treatment-emergent AEs (TEAEs; i.e. adverse events occurring until 2 days after last study intervention administration), post-treatment AEs (i.e. AEs occurring more than 2 days after last intake of study intervention), treatment-emergent SAEs, treatment-emergent study intervention-related AEs, treatment-emergent study intervention-related SAEs, TEAEs leading to premature and permanent discontinuation of study intervention, treatment-emergent non-serious AEs, TEAEs by maximum intensity, drug-related TEAEs by maximum intensity will be summarized by treatment group using Medical Dictionary for Regulatory Activities (MedDRA) terms grouped by Primary System Organ Class and Preferred Term.

Summary statistics including changes from or ratio to baseline will be calculated by study intervention group and visit for all quantitative laboratory parameters.

9.3.6 Other Analysis

Subgroup analyses of primary and secondary efficacy and safety outcomes will be performed to assess consistency of the investigational intervention effect across subgroups.

Key subgroups

The following subgroups are considered to be potentially prognostic and predictive:

- Stroke subtype of index event by TOAST (large artery atherosclerosis, lacunar stroke (small vessel occlusion), other determined etiology, undetermined etiology).
  Lower efficacy incidences but also lower benefit for asundexian is expected for participants with lacunar strokes.
- The criteria of inclusion criterion 3 related to atherosclerosis and non-lacunar stroke:
  - Medical history of atherosclerosis (Yes/No)
  - Vascular imaging evidence of atherosclerosis (Yes/No/not done)
  - Non-lacunar infarct in MRI (Yes/No/MRI not done)

  Higher efficacy incidences but also higher efficacy benefit is expected for subjects fulfilling any of these criteria.

The following factors that define subgroups are known or expected to possibly show different risks of either efficacy and/or safety events and are therefore considered potential prognostic factors:

- Stratification factor: dual antiplatelet therapy with ASA and a $P2Y_{12}$ inhibitor (yes/no)
  A higher bleeding risk and lower recurrent stroke risk might be expected for participants being treated with dual antiplatelet therapy.
- Age Group (<65 years, 65 – 75 years, >75 years)
- Weight (<60, 60-90, >90 kg)
- Body mass index (<25, ≥25 to <30, ≥30 kg/m^2)
- Race (White, Asian, Black, other)
  Focus is on the known differences in the risk profile for Asian and Black participants.
- eGFR (<30; 30-59; 60-90; >90 mL/min/1.73 m^2)
- History of stroke / TIA prior to index stroke (Yes/No)
- Index event (ischemic stroke, high risk TIA)
- NIHSS score of index event at randomization (≤3, 4-7, ≥8)
- mRS score of index stroke at Day 7 (0-2, ≥3)
- Thrombolysis and/or endovascular therapy (Yes/No)
- Hypertension (Yes/No)
- Diabetes (Yes/No)

List of subgroups that are determined in addition which are not expected to be predictive or prognostic:

- Sex (male/female)
- Region (North America, Western Europe and Australia, Eastern Europe, Asia)

If the number of participants is too small within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. For other factors there is no a priori rationale that the treatment effect could possibly be modulated.

Exploratory subgroups

Analyses of truly exploratory subgroups will be performed for a spectrum of demographic, disease and clinical characteristics, including but not be limited to additional baseline risk factors for stroke and / or bleeding. Additional subgroups and details will be pre-specified in the SAP.

Analytical Approach

Consistency of treatment effects across subgroups, both in magnitude and direction, will be assessed by adding a covariate for the subgroup variable and the corresponding treatment-subgroup interaction to the respective stratified Cox proportional hazards model.

The objective of the subgroup analyses is to show the consistency of treatment effects across a wide variety of participant groups. As the number of subgroup analyses for baseline characteristics may be large, the probability of observing at least one statistically significant but spurious interaction is high despite the lack of a biological or pharmacological basis for expecting an interaction. Thus any significant interactions will be interpreted as “flags” to prompt further investigation.

If the interaction term is significant at the 5% type I error level in the analysis of the primary endpoint, secondary endpoints will be investigated to evaluate the plausibility of such an effect. Furthermore, in the analysis of key endpoints if the interaction term is significant at the 5% type I error level the likelihood ratio test proposed by Gail and Simon will be performed to test the hypothesis that there is no crossover or qualitative interaction at the 1% type I error level (H_0: The direction of treatment effect is the same for all levels of a subgroup variable vs. H_1: The direction of treatment effect is different for at least one level of a subgroup variable).

Following the test of interaction, the hazard ratio summarizing the treatment effect will be estimated separately within each level of a subgroup variable using stratified Cox proportional hazards models. Results will be presented graphically using forest plots.

The full list of subgroups will be provided in the SAP.

9.4 Interim Analysis

An IDMC is in place that will monitor the risk/benefit on an ongoing basis (Section 10.1.6.4).

An interim analysis is planned when approximately 460 participants with an adjudicated primary efficacy event have been observed (55% of the planned total number). The interim analysis is for futility and non-binding; therefore no adjustment of the type 1 error is needed.

It is recommended to stop the study before its planned completion for ethical reasons if the following criterion is fulfilled based on the results of the interim analysis:

- The point estimator of the cause-specific hazard ratio for the primary efficacy outcome is higher than or equal to 0.95.
  This guidance corresponds to a setting where the power loss for this futility scheme is 1%. Based on the results of the interim analysis and assuming the point estimate from the interim analysis governs the remainder of the study, the chance that the study would have reached its success criterion by 830 participants with events is about 3.8%. If the true hazard ratio for the primary efficacy outcome is 0.80 (see Section 9.5), the

probability to estimate a cause-specific hazard ratio of ≥0.948 (rounded to 0.95) at this stage is only 3.47%.

In accordance with the IDMC charter, the IDMC may deviate from this stopping criterion if other study data indicate a benefit or risk that may impact the recommendation.

The interim analysis will be conducted such that the ongoing study integrity is maintained. Only the independent statistical support group, who is responsible for providing the interim analysis results to the IDMC, will be unblinded to the individual treatment group assignments. Interim analysis results will not be shared with investigators, participants, or the study team who are involved in the conduct of the study nor will the results be available for submission before the final database lock.

9.5 9.5Sample Size Determination

A single study with a study-wise type-I error level of 5% is proposed to provide convincing evidence on the effect of asundexian vs. placebo on prevention of ischemic stroke. The number of participants with outcome events and the total sample size must be sufficiently robust to support the intended claims for efficacy and safety, respectively.

The target number of participants with a primary efficacy event was determined based on the primary hypotheses (see Section 9.1), a type-I error level of 5% for a two-sided log-rank test, and a power of at least 90% to detect a significant treatment effect, under the assumption that the 'effective' hazard ratio (including effects due to treatment discontinuation) is HR = 0.80.

The study will randomize approximately 12300 participants in a 1:1 fashion to study intervention, eventually targeting approximately 830 participants with a primary efficacy event leading to a planned duration until CEOT of about 30 months. The CEOT will be on or after a date that allows a minimum duration of 90 days for each participant. The study duration will be slightly longer due to CEOT visit window and safety follow up. The planning assumptions were reviewed and updated based on blinded data, and the sample size was increased.

This study will be event driven, which implies that the study duration depends on when the target number of participants have experienced a primary efficacy event.

The revised assumptions for sample size planning are:

- Cumulative incidences of the primary efficacy endpoint in the placebo arm: 1.5% after 1 month, 2.4% after 2 months, 3.2% after 3 months, 4.3% after 6 months, 5.4% after 9 months, 6.3% after 12 months, and +0.9% every 3 months thereafter (piecewise exponential distribution of events).
- Accrual pattern including seasonal variations (stops when the above-mentioned number of randomized participants is reached):

Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Randomized	3	52	220	294	462	635	613	723	716	735	695	557	537	555
Cumulative	3	55	275	569	1031	1666	2279	3002	3718	4453	5148	5705	6242	6797
Month	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**+1**	
Randomized	525	525	525	500	425	425	450	500	500	450	355	323	350	
Cumulative	7322	7847	8372	8872	9297	9722	10172	10672	11172	11622	11977	12300	+350	

- Treatment discontinuations (independent of efficacy or safety events) with an incidence risk of 6.5% in month 1, 1.75% during months 2 to 5, 1% during months 6 to 10, and 0.75% each month thereafter. Treatment discontinuation implies that a participant (irrespectively of randomization to asundexian or placebo treatment) is considered on placebo risk thereafter.
- During each month, approximately 0.3% of the participants in each treatment arm die, with a cumulative incidence of 3.5% per year.

Under the revised assumptions and assigning approximately 12300 participants randomly to study intervention, it is expected that a duration until CEOT of approximately 30 months will be sufficient to achieve the target number of participants with a primary efficacy event.

Note that the assumed 'effective' HR of 0.80, as per the estimand defined in Section 3, will include effects of treatment discontinuation (a consequence of choosing the treatment policy strategy to address treatment discontinuation). If there was no effect of treatment discontinuation on the risk to experience an event in the asundexian arm, the corresponding assumed hazard ratio comparing asundexian vs. placebo would decrease to 0.77. The sensitivity with respect to treatment discontinuation is as follows: If the incidence of treatment discontinuation doubles (i.e., 13% in the first month, 3.5% in the second month, and so on), then the power to detect a treatment effect drops from 90% to 80%.

Under the above-mentioned assumptions an analysis based on 830 participants with a primary efficacy outcome will show a significant treatment effect at a 5% significance level if the estimated hazard ratio is 0.87 or lower (minimal detectable effect).

In order to achieve the target number of participants with primary efficacy events and to preserve the target power of the study the (time-dependent) incidence rates for the primary endpoint will be monitored in a blinded fashion so that adjustments can be made to the number of participants to be randomized and / or the duration of follow-up.

To mitigate the risk of exposing participants to study intervention if it is unlikely to be efficacious, an interim analysis for futility will be conducted (see Section 9.4).

Sample size calculations were derived using the software PASS, versions 13, 2021 and 2022.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g. advertisements) must be submitted, reviewed and approved in accordance with national legislation and undergo scientific and ethical assessment before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants or their legally authorized representative and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. They or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB / IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented in a timely manner to the most current version of the ICF(s) during their participation in the study if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial.

A copy of the ICF(s) must be provided to the participants or their legally authorized representative.

Informed consent must be obtained before initiation of any study-specific procedures. The process of obtaining informed consent must be documented in participant's source documentation.

For country-specific requirements for Germany (DEU-1), see Section 10.11.4.1.

Pharmacogenetic samples will be taken in a subset of participants. Eligible participants will be asked to sign a corresponding informed consent.

10.1.4 Recruiting Strategy

Detailed description of the recruitment strategy will be provided in country-specific documentation as required.

10.1.5 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6 Committees Structure

10.1.6.1 Program Leadership Committee (PLC)

There will be a Program Leadership Committee for the overall Phase 3 OCEANIC program. The PLC consists of external experts in the areas of neurology and cardiology. It will include the Executive Committee heads of the Phase 3 studies with asundexian, as well as sponsor representatives, and will ensure the overarching integrity of the studies. The role of the PLC is to facilitate communication and alignment and to coordinate the high-level program wide strategy across the asundexian Phase 3 program. Details of the committee will be specified in the Committee Charter.

10.1.6.2 Executive Committee (EC)

The main task of the Executive Committee for OCEANIC-STROKE, which is composed of a panel of experts in the fields cardiology and neurology from the Population Health Research Institute (PHRI, Hamilton, Canada) as well as sponsor representatives, is to be actively engaged in the protocol development and the conduct, interpretation, and reporting of the results of the study. Furthermore, it will advise the sponsor on clinical, medical, and scientific questions, and support publications surrounding the study and the overall program. The EC will work collaboratively with other entities (including the sponsor and the Steering Committee) engaged in the relevant clinical study to coordinate communication with sites and site investigators. In addition, the EC will make an effort to engage and train a next generation of diverse clinical study investigators. Details of the committee will be specified in the Committee charter.

10.1.6.3 Steering Committee (SC)

Each Phase 3 study in the asundexian Phase 3 program will have a SC that reports to the Executive Committee for the study. Each SC will be made up of national leaders from participating countries. Some countries may have more than one national leader. SC members will have relevant expertise in thrombosis, cardiology, neurology, and / or clinical studies and / or will be recognized national leaders within their country. The SC will provide input into the design and execution of the clinical study, with a focus on issues relevant to specific countries. SC members will be in close contact with the sponsor's local operational team in their country. Details of the SC will be specified in the Committee charter.

10.1.6.4 Independent Data Monitoring Committee (IDMC)

Ongoing safety monitoring during the conduct of the study will be performed by an external and unblinded IDMC (efficacy data will also be assessed to determine the risk/benefit ratio and futility). An independent statistical analysis center (SAC) will be involved in processing unblinded data for the IDMC. Analysis periods and procedures will be defined in an operational charter (IDMC Charter) filed in the study file. Following data review, the IDMC will provide written recommendations that will be transferred to the sponsor. All other definitions will be provided in the IDMC charter.

10.1.6.5 Clinical Events Committee (CEC)

Potential and pre-specified clinical outcome events will be submitted for adjudication to an independent CEC. Adjudication of all bleeding events as well as efficacy events will be performed by members of the CEC who will review events in a blinded fashion and will adjudicate and classify the following events in a consistent and unbiased manner according to definitions further specified in the CEC charter. The adjudication will also include algorithmic approaches:

- Bleeding events according to the following classifications and definitions (refer to Section 8.3):
  - ISTH (major, clinically relevant non-major and minor)
  - BARC (type 1, 2, 3, 5)
- Death (CV death [including death with undetermined cause] or non-CV death)
- MI
- Stroke (ischemic, hemorrhagic, undetermined) and TIA

In addition, events that might be indicative of a potential outcome event will be reported as outcome events to ensure that no outcome event is missed. This includes for example hospitalization for cardiac chest pain with increased cardiac enzymes.

Data entry procedures and documentation necessary for case adjudication will also be described in the CEC charter. Adjudication results will be the basis for the final analysis.

10.1.7 Dissemination of Clinical Study Data

Bayer fulfills its commitment to publicly disclose study results through posting the result studies on public registries in accordance with applicable law and regulations.

Result Summaries of Bayer's sponsored clinical studies in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial

Information via Clinical Trial Registries and Databases". In addition, results of clinical drug studies will be provided on the publicly funded websites ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

In accordance with the current EU regulation, result summaries will be submitted within one year from the end of the studies in adult populations or within 6 months for studies in a pediatric population, in **all** participating countries. No preliminary data analysis (e.g. on EU data only) will be performed, as this might compromise data integrity and the scientific validity of the study.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical study data, study-level clinical study data, and protocols from clinical studies in patients for medicines and indications approved in the United States (US) and European Union (EU) on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical studies are considered for publication in the scientific literature irrespective of whether the results of the clinical studies are positive or negative.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF completion guidelines provided to the study sites.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.

Quality tolerance limits (QTLs) will be predefined in the Integrated Data Review Plan (IDRP) to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g. contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition to the on-site monitoring, a remote monitoring option is available. All study materials, including but not limited to drug accountability records or electronic source documentation, will be available for remote monitoring with view-only access, with

training provided prior to access being granted. Study staff will be available to meet via video conference or over the phone. Study monitors will be able to issue queries and request resolutions which will be completed by the designated study staff.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data, and its origin can be found in the Source Data Location List (SDLL).

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

The site must implement processes to ensure availability of all required source documentation (e.g. participant file, local laboratory report). The monitor will work with the site to collect key data points by completing the Source Data Location list.

Race and ethnic group may be entered directly into the CRF, without availability of corresponding source documentation. Thus, these CRF data will be the source and no additional source documentation will be available. For all other data, source documentation must be available at the site.

10.1.10 Study and Site Start and Closure

Study Start

The study start date is the date on which the clinical study will be open for recruitment of participants.

The start of a clinical study in EU is defined as the date on which the first site is declared by the sponsor to be ready to enroll in a country and clinical study will be open for recruitment of participants.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

Discontinuation of further study intervention development

For country-specific requirements for Germany (DEU-1), see Section 10.11.4.1.

For site termination:

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

Total number of participants at study level included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Additional information regarding publication policy can be found in the Steering Committee charter and the Publication Committee charter.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10–1 will be performed by the central laboratory unless specifically mentioned.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10–1: Protocol-required Safety Laboratory Tests

Laboratory Assessments	Parameters		
Hematology	Red blood cell (RBC) count Hemoglobin Hematocrit	White blood cell (WBC) count	Platelet count
Clinical Chemistry	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (AP) Gamma glutamyl transpeptidase (γGT) Bilirubin (total and fractionated) Creatine kinase (CK) Lactate dehydrogenase (LDH)		
	Blood urea nitrogen (BUN) Creatinine eGFR		
	Sodium Potassium		
	Uric acid Glucose Cholesterol (total)		

Abbreviations: ALT = Alanine aminotransferase, AP = Alkaline phosphatase, AST = Aspartate aminotransferase, BUN = Blood urea nitrogen, CK = Creatine kinase, eGFR = estimated glomerular filtration rate, γGT = Gamma glutamyl transpeptidase, LDH = Lactate dehydrogenase, RBC = Red blood cell (count), WBC = White blood cell (count)

Investigators must document their review of each laboratory safety report.

The name and address for the central laboratory service provider can be found in the documentation supplied by the vendor. In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

All exploratory biomarkers analyzed in a subset of participants (see Section 8.8) are not used routinely in practice and will be analyzed in batches. Therefore, timely reporting of the results will not be possible during the study and review of the results will not assist participant care.

10.2.1 Calculating Glomerular Filtration Rate

In accordance with established nephrology practice and guidelines, renal function will be assessed by means of the estimated glomerular filtration rate (eGFR), calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation refit without the race variable (Inker et al. 2021).

CKD-EPI equation (Conventional units [serum creatinine level is measured in mg/dL]):

$$GFR\ (mL/min/1.73\ m^2) = 142 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012\ [\text{if female}]$$

where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of (Scr/κ or 1.0), and max indicates the maximum of (Scr/κ or 1.0), and Age is measured in years.

GFR can be estimated using the calculator provided in the following link:
https://www.kidney.org/professionals/kdoqi/gfr_calculator

For measurement of renal function in Japan, please refer to Section 10.11.2.

10.2.2 Liver Safety: Follow-up Assessments and Suggested Actions

Abnormal laboratory results and / or clinical signs and symptoms indicative of liver injury and / or liver dysfunction should be reported as adverse event.

It is important to initiate follow-up immediately upon detection of such an adverse event and not to wait until the next scheduled visit. This applies to both abnormalities detected at local or central laboratory and might include additional samples for analyses in local laboratories.

Objectives of the follow-up assessments are to ensure participant safety and to identify the etiology of the adverse event as far as possible. The assessments are guided by clinical and regulatory requirements. The follow-up assessments and documentation of additional information as outlined below have to be initiated during intervention period and up to 2 weeks after last study intervention intake (safety follow-up) if the following criteria are met:

1. Elevation of ALT or AST in comparison to values obtained from central laboratory at baseline (randomization):
   a) Normal value (≤ ULN) at baseline: ALT or AST reaches > 3 x ULN, or
   b) Elevated value (> ULN) at baseline: ALT or AST increases by ≥ 1.5-fold compared to the lowest elevated baseline value and reaches > 4 x ULN

   AND
2. A confirmatory re-test has been obtained and confirms the prior elevation. A confirmatory re-test has to be performed as soon as possible, at the latest within 48-72 hours of the investigator becoming aware of the result and includes minimally: AST, ALT, AP and bilirubin (total and fractionated) (see Table 10–2).

For patients with AST elevation according to 1.a) or 1.b) and 2. in the context of a diagnosis of an AMI this elevation will not be considered meeting the criteria requiring further follow-up, unless judged otherwise by the investigator.

Follow-up assessments

- Repeating follow-up samplings for liver enzymes (ALT and AST) and serum total bilirubin tests two or three times weekly. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize (details see Table 10–2). Follow-up sampling should also include any other relevant abnormal liver parameter observed in prior testing (such as AP, albumin, γGT, CK or LDH), as clinically indicated. Follow-up sampling might be discontinued earlier than when values return to normal or participant baseline levels in case a confirmed clinical diagnosis unrelated to the study intervention has been established that explains the elevated liver enzymes and no further normalization is expected.
- Obtaining additional samples to assess further general chemistry, lipid metabolism and liver function parameters and complete blood count. This is part of the central laboratory sample (see Table 10–2).

Etiological follow-up assessments

- Ruling out acute viral hepatitis, autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis, hypoxic / ischemic hepatitis and biliary tract disease. This may require performing additional procedures, e.g. ultrasound examinations. A sample for further

etiology assessment should be obtained from a participant evaluated at a study site as soon as possible after a positive confirmatory re-test if needed for exploration of the underlying cause or if no confirmed diagnosis has yet been established. This sample includes several tests for ascertaining the etiology of the elevation; not all of these parameters might need to be analyzed if an unambiguous assignment of etiology can be made based on a fraction of those parameters (see Table 10–2: further etiology assessment; 1st and 2nd round).

- Considering gastroenterology or hepatology consultations.

Additional information

- Obtaining a detailed history of the symptoms and prior or concurrent diseases and risk factors including exposure to environmental chemical agents.
- Obtaining a history of concomitant drug use (including nonprescription medications, traditional Chinese medicine and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

Data for follow-up assessments (including relevant local laboratory results) and the additional information are to be recorded in the corresponding CRF pages, as applicable. This includes an update to the (S)AE report including the reported term(s) and the causality assessment in case of relevant findings.

For ALT or AST > 3 x ULN concurrent with a total bilirubin > 2 x ULN, every effort should be made to promptly clarify any possible underlying disease(s).

Table 10–2: Liver Laboratory Monitoring

Sample / Time point	Laboratory Test	Further aspects
Initial confirmatory re-test* within 48-72 hours of the investigator becoming aware of elevation	AST, ALT, AP, Bilirubin (total and fractionated) If not analyzed in prior sample: γGT, CK, LDH	If confirmed: Document (S)AE and additional information in CRF
Follow-up sampling* while ALT or AST are > 3 x or > 4 x ULN#: at least 2-3 times a week	ALT, AST, Bilirubin (total and fractionated)	Continue observation for clinical signs and symptoms
Follow-up sampling* when ALT and AST are ≤ 3 x or ≤ 4 x ULN#: once a week	ALT, AST	Follow-up generally ends earliest when values return to normal or participant baseline levels

Central laboratory sample*/** (after AST or ALT elevation# has been confirmed in a re-test) includes parameters for etiology assessment and should be taken as soon as possible (may be combined with first follow-up sampling)	• ALT, AST, AP, Bilirubin (total and fractionated), γGT, LDH, CK, CRP • PT / INR • Albumin, Cholinesterase • Glucose, HbA1c • Total cholesterol, Triglycerides • Complete blood count including WBC with differentials (absolute and relative values), Hemoglobin **Further etiology assessment** • Anti-hepatitis A virus antibodies (total, IgM) • Hepatitis B virus surface antigen, Anti-hepatitis B virus core IgM antibody; if positive, the following will be evaluated: Anti-hepatitis B virus antibodies (surface, core total, core IgG), Hepatitis B DNA, Anti-hepatitis D virus IgM antibodies • Hepatitis C RNA, Anti-hepatitis C virus IgM antibodies • Hepatitis E RNA, Anti-hepatitis E virus antibodies (IgM and IgG) • IgG • Antinuclear antibodies (ANA) • Anti-smooth muscle antibodies (ASMA) • Cytomegaly virus DNA, Anti-Cytomegaly virus IgM antibodies • Epstein-Barr virus DNA, Anti-Epstein-Barr virus IgM antibodies • Herpes simplex virus DNA • Anti-mitochondrial autoantibodies • Ferritin, Iron, Total iron binding capacity, Transferrin saturation • Ceruloplasmin • Anti-neutrophil cytoplasmic antibodies / Anti-neutrophil perinuclear antibodies • Alpha-1 antitrypsin level	Consider update of AE reporting terms in case of relevant findings

Abbreviations: ALT = Alanine aminotransferase, ANA = Antinuclear antibodies, AP = Alkaline phosphatase, ASMA = Anti-smooth muscle antibodies, AST = Aspartate aminotransferase, CK = Creatine kinase, CRF = Case report form, CRP = C-reactive protein, DNA = Desoxyribonucleic acid, γGT = Gamma glutamyl transpeptidase, HbA1c = Hemoglobin A1c, IgG = Immunoglobulin G, IgM = Immunoglobulin M, INR = International normalized ratio, LDH = Lactate dehydrogenase, PT = Prothrombin time, RNA = Ribonucleic acid, (S)AE = (Serious) adverse events, ULN = Upper limit of normal, WBC = White blood cell count.

refer to criteria for comparison to individual baseline value under 1.a) or 1.b) in Section 10.2.2.

* samples to be analyzed preferably via central lab; local lab is also acceptable if a site visit is not possible

** in case the investigator learns about an AE diagnosed by another treating physician, every effort should be made to obtain the parameters for further elucidation of etiology in a timely fashion, unless a clear etiology has already been established.

Suggested actions:

Participant management is at the discretion of the treating physician, but study intervention may be continued during confirmatory re-testing.

Follow-up assessments including sampling as outlined in Table 10–2 and documentation of additional information should be continued as specified above regardless of study intervention discontinuation. If follow-up assessments for ALT / AST are not possible, then the participant should interrupt and potentially permanently discontinue study medication.

Discontinuation of treatment should be considered if:

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks

- ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN or INR > 1.5)
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and / or eosinophilia (> 5%).

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease).

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and / or intensity of the condition.

New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE / SAE unless it is an intentional overdose taken with possible suicidal / self-harming intent. Such overdoses should be reported regardless of sequelae.

Sign, symptoms, or the clinical sequelae of suspected medication errors, misuse and abuse of either study intervention or a concomitant medication. Medication errors, misuse and abuse per se will not be reported as an AE / SAE, unless it is resulting in AE / SAE. Such medication errors, misuse and abuse should be reported regardless of sequelae.

Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and / or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition

The disease / disorder being studied or expected progression, signs, or symptoms of the disease / disorder being studied, unless more severe than expected for the participant's condition

Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE

Situations in which an untoward medical occurrence did not occur (social and / or convenience admission to a hospital)

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs / symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, meets the one or more of the criteria listed:

a. **Results in death**

b. **Is life threatening**

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. **Results in persistent or significant disability / incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly / birth defect**

f. **Other situations:**

Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

When an AE / SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE / SAE information.

It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE / SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and / or other clinical information. Whenever possible, the diagnosis (not the individual signs / symptoms) will be documented as the AE / SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE / SAE. The investigator will use clinical judgment to determine the relationship

A *reasonable possibility* of a relationship conveys that there are facts, evidence, and / or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

For causality assessment, the investigator will also consult the IB and / or product information, for marketed products.

The investigator must review and provide an assessment of causality for each AE / SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the sponsor.

The investigator may change his / her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and / or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and / or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally submitted documents.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form and transmit to the sponsor via PV.CaseProcessing@bayer.com.

- Contacts for SAE reporting can be found in the Investigator Site File.

SAE Reporting to the Sponsor via Paper CRF

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the sponsor via PV.CaseProcessing@bayer.com.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the Investigator Site File.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are considered WOCBP (fertile)

- Following menarche
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below):

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (> 40 IU/L [for US only: FSH levels > 40 mIU/mL and estradiol < 20 pg/mL]) is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. Mullerian agenesis, androgen insensitivity,

gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:

a) Documented hysterectomy

b) Documented bilateral salpingectomy

c) Documented bilateral oophorectomy

d) For individuals with permanent infertility due to an alternate medical cause other than the above (e.g. Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview

2. Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (> 40 IU/L [for US only: FSH levels > 40 mIU/mL and estradiol < 20 pg/mL]) is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

A list of contraceptives allowed during the study is reported as follows:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] 2. oral 3. intravaginal 4. transdermal 5. injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] 6. oral 7. injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: Calculating the Child-Pugh score

The severity of liver disease (Table 10–3) will determine the Child-Pugh score (Table 10–4).

Table 10–3: Grading of severity of liver disease

Factor	+1	+2	+3
Bilirubin (mg/dL)	< 2	2 – 3	> 3
Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
International Normalized Ratio	< 1.7	1.7 – 2.3	> 2.3
Ascites	None	Mild	Moderate/Severe
Encephalopathy	None	Grade I – II	Grade III – IV

Source: adapted from (Pugh et al. 1973)

Table 10–4: Child-Pugh score

Child-Pugh Class	A	B	C
Points	5 – 6	7 – 9	10 – 15

Source: adapted from (Pugh et al. 1973).

10.6 Appendix 6: ABCD^2 score

Criteria	Value	Points
Age ≥60 years	Yes / No	+1
Blood pressure ≥140/90 mmHg*	Yes / No	+1
Clinical features of the TIA	Unilateral weakness	+2
	Speech disturbance without weakness	+1
	Other symptoms	0
Duration of symptoms	< 10 minutes	0
	10-59 minutes	+1
	≥60 minutes	+2
History of diabetes	Yes / No	+1

*First BP assessment at the time of TIA: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg

Abbreviations: TIA = transient ischemic attack

Source: https://www.mdcalc.com/abcd2-score-tia#evidence

10.7 Appendix 7: Modified Rankin Scale

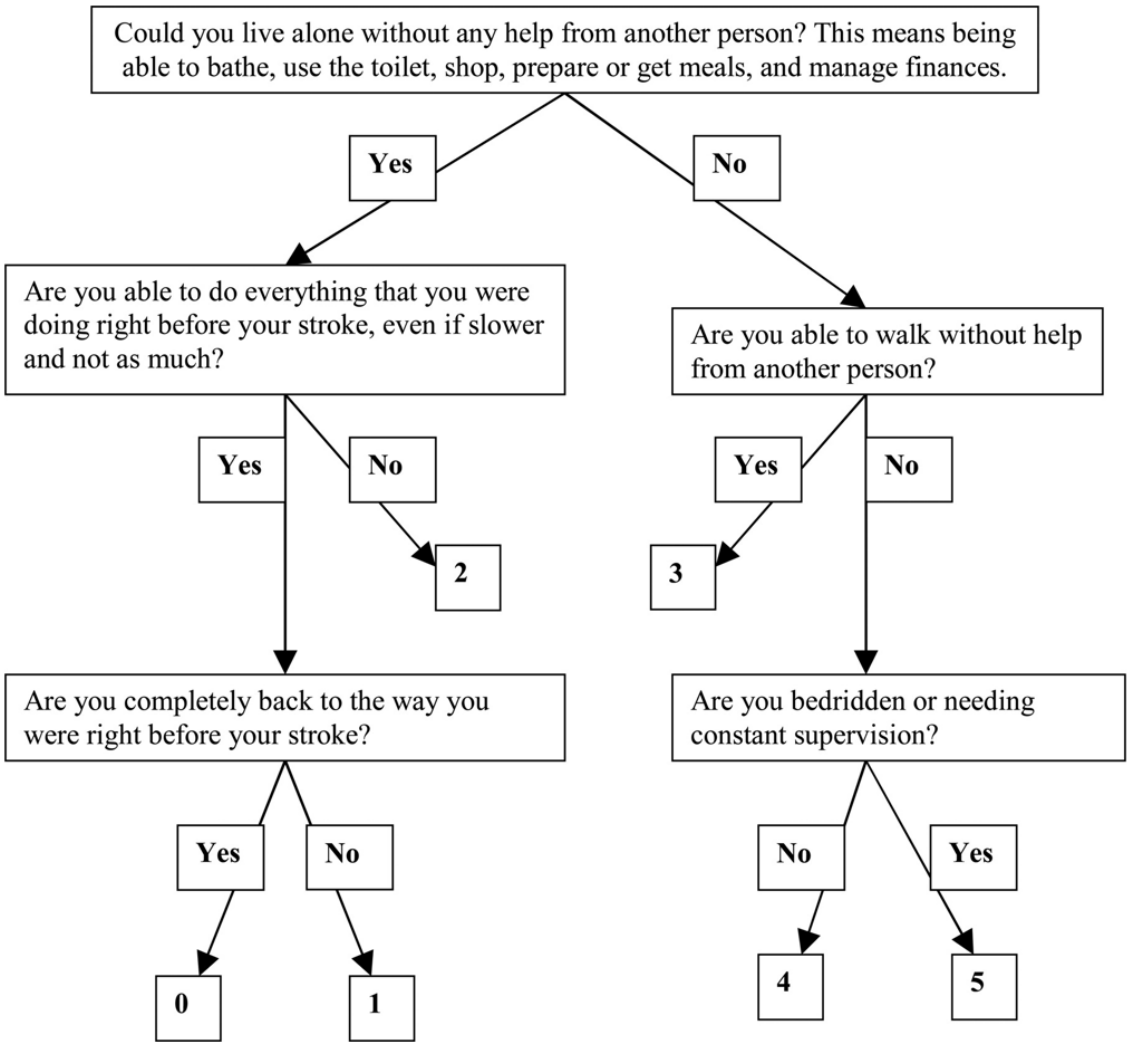
Table 10–5: Modified Rankin Scale (mRS) and Corresponding Sections of the Structured Interview

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

TOTAL (0–6): _____

Source: adapted from (Wilson et al. 2002)

Figure 10–1: The simplified mRS questionnaire algorithm



Source: (Bruno et al. 2010)

10.8 Appendix 8: NIHSS scale

NIH stroke scale (NIHSS)

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e. repeated requests to patient to make a special effort).

At the end the scores of all items need to be summed up.

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 **= Alert;** keenly responsive. 1 **= Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 **= Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 **= Answers** both questions correctly. 1 **= Answers** one question correctly. 2 **= Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 **= Performs** both tasks correctly. 1 **= Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 **= Normal.** 1 **= Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 **= Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

Instructions	Scale Definition	Score
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____ _____

Instructions	Scale Definition	Score
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____

Instructions	Scale Definition	Score
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____

Source: adapted from (Brott et al. 1989, Lyden et al. 1994, Pugh et al. 1973)

10.9 Appendix 9: Outcome Events: Data Collection

All outcome events (efficacy and safety) are to be captured and reported from randomization until a participant's last regular scheduled study visits (i.e. follow-up visit for participants taking study intervention until the regular end of the intervention period; in case of permanent discontinuation of study intervention, until the CEOT visit if the participant is still alive and if the participant agrees / as allowed by local regulations). The CRF will contain specific Outcome Event pages to capture the outcome events occurring throughout the study. Refer to Section 8.4.6 and Table 8–1 for more details.

The following points need to be considered when reporting outcome events in relation to the time of their occurrence:

- **After randomization** and **before the first intake** of the study intervention outcome events should be reported on the respective outcome event eCRF page.
- **After first intake**, if study intervention **has not been discontinued permanently** (unless due to reaching the CEOT visit), outcome events should be reported on the respective outcome event CRF page and up to the CEOT safety follow-up visit.
- **After first intake**, if study intervention **has been prematurely discontinued permanently**, outcome events should be reported on the respective outcome event CRF page through the CEOT visit (unless permanent discontinuation occurred less than 2 weeks prior to the CEOT visit, in which case reporting occurs until the CEOT safety follow-up visit).

Please also refer to Section 8.4.1 in relation to reporting of AEs.

10.10 Appendix 10: MRI Sub-study

Participants cannot be included in the MRI sub-study if they have contraindication to perform brain MRI (e.g. certain types of aneurysm clips, claustrophobia, patients that cannot lie supine for 30 minutes, patients whose body structure exceeds the restrictions of the local MRI instrument).

The required study MRI sequences are based on routine brain MRIs done for clinical care of acute stroke patients. The focus of this sub-study is to correlate baseline MRI findings with future events (e.g. covert brain infarction, recurrent strokes, intracranial bleeding), identify asundexian responders, further characterize the study population by MRI and add additional safety information on the asundexian 50 mg dose (to the Phase 2 study). MRI data will be transmitted to the central MRI Core Laboratory where MRI interpretation will be done blinded to treatment assignment to identify incident brain infarcts, comparing the initial study MRI to follow-up MRI. Details regarding the procedure, MRI requirements and logistics will be available in a MRI procedure manual.

The required study MRIs are to be performed in approximately 1000 participants with acute ischemic stroke (not TIA) at selected sites:

- Within 5 days of the onset of symptoms: either before randomization (as a clinically initiated MRI) or after randomization (as a study initiated MRI) and
- a final study MRI will be performed for participants at visit 5 (Week 26).

In summary, participants are required to undergo at least two MRIs that meet study requirements. Clinical MRIs are acceptable for study purposes as long as they comply with the minimum requirements detailed in the MRI procedures manual. The MRI requirements were designed to make it feasible that at most stroke centers the clinical MRIs done for an acute stroke will qualify for use in the study and not requiring an additional study MRI.

MRI procedure

The minimum requirements for the MRIs are outlined in the table below.

Study sites will be required to demonstrate that study-sponsored MRIs that meet the minimum study criteria outlined below can be obtained in advance of enrolling participants for the MRI sub-study. Detailed instructions will be provided to sites.

The MRIs will be transmitted to the central MRI Core Lab that will be responsible for analyzing all MRIs blinded to treatment assignment.

More detailed information regarding image acquisition and processing will be provided in a separate MRI procedures manual.

	Minimum Requirements
Sequences	FLAIR DWI ADC SWI, SWAN, GRE or equivalent per local MRI routine protocol
Field strengths	≥ 1 Tesla
Slice thickness	1 - 5 mm
Slice gap	≤ 2 mm

Abbreviations: ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, GRE = gradient recalled echo, FLAIR = fluid-attenuated inversion recovery, SWAN = susceptibility-weighted angiography, SWI = susceptibility weighted imaging

10.11 Appendix 11: Country/region-specific Requirements

10.11.1 China

10.11.1.1 CHN: Country/region-specific Changes Valid for China only

10.11.1.1.1 Overall Rationale

This section implements modifications of the original protocol to meet local requirements in China.

A description of changes and a brief rationale is outlined in the table below:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) 8.8. Biomarkers	Modifications made to specify no biomarker sampling will be carried out in China.	Biomarker samplings are not applicable to China.
3 Objectives, Endpoints and Estimands	Addition of footnotes to specify biomarkers will not be collected in China and therefore, no data from Chinese participants will be available for the analysis of the respective endpoints.	Biomarker samplings are not applicable to China.
3 Objectives and Endpoints	Footnote added “PK and PD analyses in Chinese participants will be performed to investigate ethnicity differences in stroke patients. Blood samples for pharmacogenetics (limited to CES1 genotyping analysis) will be collected in China. Other biomarker samples will not be collected in China and therefore, no data from Chinese participants will be available for the analysis of the respective endpoints.”	For clarification of the plan and purpose of PK, PD, and pharmacogenetics in China.
8.5 Pharmacokinetics	Text added: “PK analyses in Chinese participants will be performed to investigate ethnicity differences in stroke patients.” Text: “and optionally other metabolites” replaced by “and its metabolite M-10 (BAY 2826102)”.	
8.6 Pharmacodynamics	Text added “PD analyses in Chinese participants will be performed to investigate ethnicity differences in stroke patients.”	
8.7 Genetics	Text added “Blood samples for pharmacogenetics (limited to carboxylesterase 1 [CES1] genotyping analysis) will be collected in China”.	
6.5 Study Intervention Compliance 8 Study Assessments and Procedures	Text added “To meet China’s health authority expectation, memory aids will be dispensed to participants in China to support monitoring of participants’ interventions adherence and safety”.	To meet China’s health authority expectation.

10.11.1.1.2 Changes to the Protocol Text

Section 1.3 Schedule of Activities

Study periods Duration	**Screening/RND** ≤72 hours before RND *		**Intervention period** ~3-~31 months **, from RND until Common End of Treatment (CEOT) visit Early Termination (ET)										**Early Termination period***** ET until CEOT visit			**CEOT period** CEOT visit until 2 weeks after	
Visit number	**1**	**2 ***	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ET visit**	**ET SFU visit**	**≥3→12**	**CEOT** visit	**CEOT SFU visit**
Visit type	site	site	☎	site	site	☎	site	☎	site	☎	site	☎	site	☎ (site)	☎ (site)	site (☎)	☎
Month [M] Study days [D] / weeks [W] and allowed windows	**SCR** D-3 → 1	**RND / M0** D1	**M1** D30 ±4D	**M3** W13 ±1W	**M6** W26 ±1W	**M9** W39 ±1W	**M12** W52 ±1W	**M15** W65 ±1W	**M18** W78 ±1W	**M21** W91 ±1W	**M24** W104 ±1W	**M27** W117 ±1W	**ET** **ET**	**ET+2W** +1W	**≥M1→ M27** ≥D30→ W117 ±1W	**CEOT** CEOT±~3 W	CEOT visit +2W +1W
[.....]																	
Laboratory assessments																	
[....]																	
PK				X			X										
PD		X		X			X										
Pharmacogenetics		X															
[....]																	

Annotated Schedule of Activities (Annotated SoA)

[.....]

[....]	
PD	Refer to Table 1—2 regarding further details.
Pharmacogenetics	Refer to Table 1-2. Pharmacogenetics will be limited to CES1 genotyping analysis.

[.....]

An overview of the PK, PD and pharmacogenetics sampling is shown in Table 1—2:

Table 1—2: PK, PD and pharmacogenetics sampling

	Day 1 (Visit 2)	Month 3 (Visit 4)	Month 12 (Visit 7)
Sample timing *	Pre-dose	Pre-dose	Pre-dose
PK **	-	X	X
PD **	X	X	X
Pharmacogenetics (limited to CES1 genotyping)	X		

Abbreviations: PD, PK = Pharmacodynamic(s), -kinetic(s)

* at all visits: in order to collect pre-dose samples for PK and PD, participants should take their study intervention at the site only after blood sampling. The investigator must record the time when the study intervention is taken at the site. A phone call to remind the participants not to take the study intervention at home is recommended prior to study visit.

** if study intervention is temporarily discontinued, PK / PD blood samples should only be obtained if the study intervention has been restarted and sustained for at least 4 days, see Section 7.1.2

PK and PD will be collected in all Chinese participants (refer to Sections 8.5 and 8.6).

Blood for pharmacogenetics is generally planned to be collected at the randomization visit (Day 1), however, it can also be collected at a later visit in case it has not yet been taken and can be collected at any time in relation to study intervention intake at the respective visit.

The exact time of PK and PD sampling needs to be recorded, as well as the time of the most recent / associated study intervention intake (i.e. on the PK / PD sampling day, as well as on the day before that).

Section 3 Objectives, Endpoints, and Estimands

Table 3—1: Study Objectives and Endpoints

Objectives	Endpoints
[…]	
Other	
• To further investigate the study intervention and drugs with similar, e.g. mode-of-action-related effects, and to further investigate pathomechanisms deemed relevant to cardiovascular diseases and associated health problems	• PK[1] and various biomarkers [2] (e.g. diagnostic, safety, pharmacodynamic [1,2], monitoring, or potentially predictive biomarkers)

[1] PK and PD analyses in Chinese participants will be performed to investigate ethnicity differences in stroke patients

[2] Blood samples for pharmacogenetics (limited to CES1 genotyping analysis) will be collected in China. Other biomarker samples will not be collected in China and therefore, no data from Chinese participants will be available for the analysis of the respective endpoints.

Section 6.5 Study Intervention Compliance

[…]

To meet China's health authority expectation, memory aids will be dispensed to participants in China to support monitoring of participants' interventions adherence and safety.

[…]

Section 8 Study Assessments and Procedures

[…]

- To meet China's health authority expectation, memory aids will be dispensed to participants in China to support monitoring of participants' interventions adherence and safety.

[…]

Section 8.5 Pharmacokinetics

[…]

For the investigation of systemic exposure to asundexian and its relationship with treatment effects, the plasma concentrations of asundexian and its metabolite M-10 (BAY 2826102) will be determined at different time points using a sparse sampling approach

PK samples will be analyzed, using validated analytical methods. Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of calibration samples and QC samples will be reported in the Bioanalytical Report.

Section 8.6 Pharmacodynamics

[…]

Quality control and calibration samples will be analyzed concurrently with study samples. For selected PD parameters, the results of QC samples will be reported together with analyte concentrations in the Bioanalytical Report.

PD analyses in Chinese participants will be performed to investigate ethnicity differences in stroke patients.

[…]

Section 8.7 Genetics

Blood samples for pharmacogenetics (limited to CES1 genotyping analysis) will be collected in China.

[…]

Section 8.8 Biomarkers

This section is not applicable to China, as no biomarker samples will be collected in China.

[…].

10.11.2 Japan

10.11.2.1 JPN: Country/region-specific Changes Valid for Japan only

10.11.2.1.1 Overall Rationale

This section implements modifications of the original protocol to meet local requirements in Japan.

A description of changes and a brief rationale is outlined in the table below:

Section # and Name	Description of Change	Brief Rationale
10.2.1 Calculating glomerular filtration rate	The formula for calculating the estimated glomerular filtration rate was modified according to the recommendation by Japanese Society of Nephrology for the Japanese population.	The modified formula has been the standard for the local clinical practice in Japan and frequently used in other clinical studies with the Japanese population.

10.11.2.1.2 Changes to the Protocol Text

Section 10.2.1 Calculating glomerular filtration rate

In accordance with the recommendation by the Japanese Society of Nephrology, renal function at baseline and throughout the study will be assessed by means of the estimated glomerular filtration rate (eGFR), calculated using the Japanese Equation (JSN 2012, Matsuo et al. 2009).

Conventional units (serum creatinine level is measured in mg/dL)

GFR (mL/min/1.73 m^2) = 194 x (serum creatinine)$^{-1.094}$ x (Age)$^{-0.287}$ x (0.739 if female).

10.11.3 Republic of Korea

10.11.3.1 KOR-1: Country/region-specific Changes Valid for the Republic of Korea only

KOR-1 (19 JAN 2023)

Overall Rationale

This section implements modifications of the original protocol to meet local requirements in the Republic of Korea.

10.11.3.1.1 Overview of Changes

A description of changes and a brief rationale is outlined in the table below:

Section # and Name	Description of Change	Brief Rationale
Title Page	Change of the Sponsor´s Clinical Lead	Sponsor´s administrative changes
1.3 Schedule of Activities (SoA)	Only serum pregnancy testing is allowed. It will be performed at all site visits. Clarification added for hemoglobin, platelets, ALT and AST tests	Changes requested by MFDS to account for the safety characteristics of the study interventions
5.1 Inclusion Criteria	Only serum pregnancy testing is allowed.	
5.2 Exclusion Criteria	ALT / AST > 2.5 x ULN added to the exclusion criteria	
	Platelet count ≤ 100000/ mm^3 or hemoglobin < 9 g/dL added to the exclusion criteria	
7.1.1 Permanent Discontinuation of Study Intervention	Inclusion of discontinuation rule for severe thrombocytopenia	
8.3.8 Pregnancy Testing	Only serum pregnancy testing is allowed	
10.2.3 Thrombocytopenia: Follow-up Assessments and Suggested Actions	Inclusion of follow-up assessment and suggested actions in case of thrombocytopenia	

10.11.3.1.2 Changes to the Protocol Text

Section 1.3 Schedule of Activities

Study periods Duration	**Screening/RND** ≤72 hours before RND *		**Intervention period** ~3-~31 months **, from RND until Common End of Treatment (CEOT) visit Early Termination (ET)										**Early Termination period***** **ET until CEOT visit**			**CEOT period** CEOT visit until 2 weeks after	
Visit number	**1**	**2 ***	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ET visit**	**ET SFU visit**	**≥3→12**	**CEOT** visit	**CEOT SFU visit**
Visit type	site	site	☎	site	site	☎	site	☎	site	☎	site	☎	**site**	☎ (site)	☎ (site)	site (☎)	☎
Month [M] Study days [D] / weeks [W] and allowed windows	**SCR** D-3 → 1	**RND / M0** D1	**M1** D30 ±4D	**M3** W13 ±1W	**M6** W26 ±1W	**M9** W39 ±1W	**M12** W52 ±1W	**M15** W65 ±1W	**M18** W78 ±1W	**M21** W91 ±1W	**M24** W104 ±1W	**M27** W117 ±1W	**ET** **ET**	**ET+2W** **+1W**	**≥M1→ M27** **≥D30→ W117** **±1W**	**CEOT** CEOT±~3 W	CEOT visit +2W +1W
[…….]																	
Laboratory assessments																	
Safety blood sampling		X		X	X		X				X		X			X†	
Pregnancy test (if WOCBP)	X	X		X	X		X		X		X		X			X†	

[…….]

Annotated Schedule of Activities (Annotated SoA)

[…]

[…]	
Laboratory assessments	
Safety blood sampling	[…] Hemoglobin, platelets, AST and/or ALT values measured in the local laboratory for screening. Current local laboratory results available for the index hospitalization for the stroke can be used. Full safety laboratory assessments to be done at randomization in the central laboratory.
Pregnancy test (if WOCBP)	A WOCBP must have a negative serum pregnancy test before randomization.
[…]	

Section 5.1 Inclusion Criteria

[…]

Sex and Contraceptive / Barrier Requirements

8. Male or female

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants: there are no measures required for the study

Female participants: a female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 4

OR

- is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 during the study intervention period and for at least 4 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g. noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative serum pregnancy test before randomization, see Section 8.3.8.

[…]

Section 5.2 Exclusion criteria

9. Known significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis, or signs of coagulopathy) or known hepatic insufficiency classified as Child-Pugh B or C or known ALT / AST > 2.5 x ULN at randomization[5].

Footnote 5: Assessment of relevant laboratory parameters is only required if there is a suspicion of clinically relevant hepatic or renal impairment (e.g hepatic insufficiency or end stage renal disease). AST/ALT can be assessed on locally available test during screening or as part of hospitalization for index stroke.

[…]

18. Platelet count ≤ 100000/mm^3 or hemoglobin < 9 g/dL. Platelets and hemoglobin can be assessed on locally available test during screening or as part of hospitalization for index stroke.

Section 7.1.1 Permanent Discontinuation of Study Intervention

[…]

Specifically, a permanent discontinuation of study intervention may be required if any of the following occurs and will last throughout the expected remaining intervention period. Otherwise, an interruption of study intervention could be considered for the duration:

- […]
- severe thrombocytopenia (i.e. platelet count < 50000 / mm^3, refer to Section 10.2.3).

Section 8.3.8 Pregnancy Testing

A woman of childbearing potential must have a negative serum pregnancy test available before randomization.

In addition a serum pregnancy test is required at the end of relevant systemic exposure, which is either at the early termination visit for participants that prematurely discontinue intake of study intervention (unless study intervention has been discontinued since more than 7 days) or at the CEOT visit for participants that end the study intervention period regularly.

Further serum pregnancy tests should be performed in participants of childbearing potential at every site visit. At any time during study participation, additional pregnancy testing should be performed upon suspicion of pregnancy.

Section 10.2.3 Thrombocytopenia: Follow-up Assessments and Suggested Actions

Follow-up assessments

If platelet count is decreased < 100000 / mm^3, close monitoring is required through follow-up sampling to repeatedly monitor its value, as clinically appropriate (e.g. every 1 to 4 weeks, depending on the platelet count as well as its development).

Suggested actions

Participant management is at the discretion of the treating physician, and study intervention may be continued during confirmatory re-testing.

Temporary discontinuation of study intervention should be considered if platelet count is < 50000 / mm^3, which should be accompanied by more frequent monitoring; permanent discontinuation of study intervention should be considered if platelet count is < 20000 / mm^3.

When thrombocytopenia has sufficiently recovered (i.e. platelet count ≥ 100000 / mm^3 at follow-up laboratory tests), the investigator may consider re-starting study intervention based on medical judgement (e.g. resolving reversible cause such as radiotherapy to that might have led to the decrease in platelet count).

10.11.4 Germany

10.11.4.1 DEU-1: Country/region-specific Changes Valid for Germany only

10.11.4.1.1 Overview of Changes

A description of changes and a brief rationale is outlined in the table below:

Section # and Name	Description of Change	Brief Rationale
10.1.3 Informed Consent Process	A sentence added that the consent of participants incapable of consent at the time of enrollment into the study must be obtained later as soon as their condition allows	Changes requested by BfArM
10.1.10 Study and Site Start and Closure	Criteria for study termination have been clarified	

10.11.4.1.2 Changes to the Protocol Text

Section 10.1.3 Informed Consent Process

[…]

The consent of participants who are not capable of consent at the time of enrollment into the study must be obtained later as soon as their condition allows.

[…].

Section 10.1.10 Study and Site Closure

[…]

The risk-benefit ratio becomes unacceptable owing to, for example:

- New clinical relevant safety findings from this study (e.g. SAEs)
- Results of other clinical and/or preclinical studies (e.g. new findings to teratogenicity, carcinogenicity or reproduction toxicity)
- If the study conduct (e.g. recruitment rate, drop-out rate, data quality, protocol compliance) does not suggest a proper completion of the study within a reasonable time frame.

[…].

10.12 Appendix 12: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

Amendment 1 (29 NOV 2023)

This amendment/modification is considered to be substantial based on the relevant criteria of the European Union clinical trial legislation.

Overall Rationale for the Amendment:

New clinical pharmacology data on PK of crushed tablets (relative bioavailability of crushed vs intact 50 mg tablets of asundexian) became available supporting the delivery of crushed study intervention tablets in subjects with dysphagia. Therefore, exclusion criterion 4, excluding patients with dysphagia at time of randomization, is removed.

In addition, recent PK data for the concomitant use of atorvastatin (BCRP, P-gp and CYP3A4 substrate) and asundexian allow the removal of the recommendation for close monitoring.

Additionally to the analyses for the primary efficacy endpoint of ischemic stroke, the incidence over the first 90 days (secondary endpoint) and after 90 days (exploratory endpoint) will be explored to allow comparison with recent dual antiplatelet therapy trials.

Minor procedural changes are also incorporated in this amendment. NIHSS at time of hospital / ER presentation was added to capture the severity of stroke prior initiation of any specific stroke therapy, i.e. thrombolysis / thrombectomy. If available, images related to outcome event ischemic stroke will be collected centrally as exploratory analyses might be performed. Furthermore, the option for completion of the EQ-5D questionnaire with assistance has been added, taking into account that stroke patients with mild to moderate disabilities are recruited.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3. Objectives, Endpoints and Estimands 9.1.1 Multiplicity Adjustment	Secondary endpoint for ischemic stroke in the first 90 days added. Multiplicity adjustment revised to incorporate this secondary endpoint into statistical testing description.	To allow comparison to recent dual antiplatelet therapy trials.
3. Objectives, Endpoints and Estimands	Exploratory endpoint for ischemic stroke after the first 90 days added.	To complement the new secondary endpoint.
6.1 Study Intervention(s) Administered	Instructions for handling of study intervention revised to allow crushing of tablets.	Revised based on results from Phase 1 study.
5.2 Exclusion Criteria	Exclusion criterion 4 deleted	Revised based on results from Phase 1 study.
	Exclusion criterion 13 revised to remove moderate from the description of CYP3A4 inducer. Phenobarbital also removed.	Revised based on new classification.
1.3 Schedule of Activities	NIHSS at presentation (hospital / ER) added.	Additional time point for NIHSS collected as part of the index event.
	Imaging collection of ischemic stroke outcome events added.	Exploratory analyses might be performed.
1.3 Schedule of Activities 8.2.3.1 EuroQol Group 5-dimension questionnaire (EQ-5D)	Option for completion of the EQ-5D questionnaire with assistance added	To account for stroke patients with mild to moderate disabilities.
6.9 Prior and Concomitant Therapy	Reference to atorvastatin removed from potential for drug-drug interaction.	Revised based on results from completed Phase 1 study. In a dedicated clinical pharmacology study 50 mg asundexian did not show any clinically relevant effect on the exposure of 20 mg atorvastatin (a BCRP, P-gp and CYP3A4 substrate.
Throughout	Minor editorial revisions, clarifications, and corrections.	Minor, therefore not summarized.

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