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Title Page

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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

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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Version History

This Statistical Analysis Plan (SAP) for Study 20604 is based on the protocol Version 1.0 dated 12 SEP 2022, protocol version 2.0 dated 29 NOV 2023 and protocol version 3.0 dated 18 APR 2024.

SAP Version	Date	Change	Rationale
1.0	19 DEC 2022	Not applicable	Original version
2.0	04 JUN 2024	Addition of Ischemic stroke in the first 90 days as secondary endpoint, and beyond 90 days as an exploratory endpoint Rewording of intercurrent events related to a significant trial-continuity issue (e.g.	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. Version 3 of the protocol was to increase the sample size of the study

		caused by Covid-19 pandemic) Removal of PK analyses from this SAP Addition of categorization of countries to regions Definition of prohibited medications added The reference code for the primary efficacy analysis was amended to align with the requested analyses Subgroup analyses for potential liver events were updated based on learnings from AF study Addition of Appendix 8 describing the data handling for identification of intercurrent events Further editorial changes and clarifications on data handling The updates below were made to reflect the updated protocol. Sample size increased based upon review of blinded data. Interim analysis for futility added to mitigate the risk of exposing participants to study intervention in case of lack of efficacy. Sensitivity analyses for secondary efficacy endpoints were added in case the null hypothesis was rejected.	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 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 in case of lack of efficacy.

3.0	30 OCT 2025	Editorial changes and clarifications on data handling. Addition of Kaplan-Meier analysis for primary efficacy and safety. Definition of number needed to treat added. Definition of disabling stroke added. Exploratory efficacy analysis description expanded. Analysis of adverse events and liver events clarified. Definition of medical history of interest terms added. Clarification on handling of intercurrent events.	Clarification on data handling and derivation while programming the analysis datasets and tables. Kaplan-Meier analysis to allow comparison with historical studies.

List of Abbreviations

AE	Adverse Event
AF	Atrial fibrillation
AG	Joint stock company, *Aktiengesellschaft*
ALT	Alanine aminotransferase
ATC	Anatomical Therapeutic Chemical
AP	Alkaline Phosphatase
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
BARC	Bleeding Academic Research Consortium
BAS	Biomarker analysis set
BDG	Bayer Drug Grouping
BMI	Body mass index
CABG	Coronary artery bypass graft
CEC	Clinical Events Committee
CEOT	Common End of Treatment
CI	Confidence interval
CRF	Case report form
CRNM	Clinically relevant non-major
CSP	Clinical study protocol
CSR	Clinical study report
csHR	Cause-specific hazard ratio
CUIN	Cumulative incidence
CV	Cardiovascular
DTOI	Drug Topics Of Interest
e.g.	For example, *exempli gratia*
EC	Executive Committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EQ-5D	European Quality of Life group 5-Dimension questionnaire
ET	Early termination
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GFR	Glomerular filtration rate
i.e.	That is, *id est*
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Hemostasis
KM	Kaplan-Meier
M	Month
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mRS	Modified Rankin Scale
N	Total number of participants
NJ	New Jersey
NNT	Number needed to treat
NNTB	Number needed to treat for an additional beneficial outcome
NNTH	Number needed to treat for an additional harmful outcome
NOAC	Non-Vitamin K oral anticoagulant
NSAID	Nonsteroidal anti-inflammatory drug
OAC	Oral anticoagulant
OD	Once a day
$P2Y_{12}$	G_i-coupled platelet receptor for adenosine diphosphate
PD	Pharmacodynamic(s)

PDS	Pharmacodynamic analysis set
PH	Proportional Hazards
PK	Pharmacokinetic(s)
PROs	Patient Reported Outcomes
PT	Preferred term
RND	Randomization
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical analysis software
SDG	Standard Drug Grouping
sdHR	Sub-distribution Hazard Ratio
SFU	Safety follow-up
SoA	Schedule of activities
SOC	System organ class
TEAE	Treatment Emergent Adverse Event
TIA	Transient ischemic attack
ULN	Upper limit of normal
US / USA	United States / United States of America
vs.	As compared to, versus
W	Week
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

The SAP describes the final analysis of the OCEANIC-STROKE study following the common end of treatment (CEOT). Table, figure and listing specifications are contained in a separate document.

There are no changes to the analyses described in the protocol.

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 atrial fibrillation (AF) (cardioembolic stroke prevention)

OCEANIC-STROKE (study 20604) is an event-driven Phase 3 study and tests 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.

1.1 Objectives, Endpoints, and Estimands

Objectives and endpoints (primary, secondary and exploratory) of the study are shown in Table 1–1 and **estimands** in Sections 1.1.1, 1.1.2 and 1.1.3.

Table 1–1: 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:

1.1.1 Estimands Associated with the Primary Efficacy Objective

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*

Efficacy estimands for **superiority** assessment are described by the following attributes:

	Primary Efficacy Estimand	**Supplemental Efficacy Estimand 1**	**Supplemental Efficacy Estimand 2**	**Supplemental Efficacy Estimand 3**
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.	Same as Primary Efficacy Estimand	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, taking at least a single dose of the assigned treatment, and with the intention to be treated with antiplatelet therapy.	Same as Supplemental Efficacy Estimand 2
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.	Same as Primary Efficacy Estimand	Same as Primary Efficacy Estimand	Same as Primary Efficacy Estimand
Endpoint	Time from treatment assignment to first occurrence of ischemic stroke	Same as Primary Efficacy Estimand	Same as Primary Efficacy Estimand except from day of first intake of assigned treatment	Same as Supplemental Efficacy Estimand 2
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	Sub-distribution hazard ratio (sdHR) comparing the two treatment	Same as Primary Efficacy Estimand	Same as Supplemental Efficacy Estimand 1 (i.e. sdHR)

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*

Efficacy estimands for **superiority** assessment are described by the following attributes:

	Primary Efficacy Estimand	**Supplemental Efficacy Estimand 1**	**Supplemental Efficacy Estimand 2**	**Supplemental Efficacy Estimand 3**
		conditions		
Intercurrent events and strategies	• The treatment effect including effects of **early 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** (i.e. antiplatelet 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 requiring continuous anticoagulation**, e.g. due to diagnosis of atrial fibrillation / flutter, left ventricular thrombus, mechanical valve or other cardioembolic source of stroke, 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	Same as Primary Efficacy Estimand	Same as Primary Efficacy Estimand, except: • In case of **early discontinuation of assigned treatment**, observation time and events up to two days after the last intake of study treatment will be used (while on treatment strategy for the intercurrent event discontinuation of assigned treatment) • In case of **changes in therapy** (i.e. discontinuation of assigned treatment and initiation of indicated therapy) **due to a diagnosis requiring continuous anticoagulation**, e.g. due to diagnosis of atrial fibrillation / flutter, left ventricular thrombus, mechanical valve or other cardioembolic source of stroke, observation time and events up to two days after the last intake of study treatment will be used	Same as Supplemental Efficacy Estimand 2

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*

Efficacy estimands for **superiority** assessment are described by the following attributes:

	Primary Efficacy Estimand	**Supplemental Efficacy Estimand 1**	**Supplemental Efficacy Estimand 2**	**Supplemental Efficacy Estimand 3**
	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		(while on treatment strategy for the intercurrent event change of treatment due to atrial fibrillation)	

Rationale for the estimands associated with the primary efficacy objective:

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 to experience a subsequent ischemic stroke in the target population is highest during the first weeks and months after the index event (i.e. ischemic stroke or high-risk TIA). The risk declines over time but is still high. Relative to standard of care, which is chronic secondary prevention with antiplatelet therapy, it is expected that adding asundexian 50 mg will reduce the risk of experiencing an ischemic stroke. 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. There will be diverse patient journeys and treatments are not necessarily taken as prescribed. Assuming a beneficial effect of asundexian, using the proposed treatment policy strategy is considered conservative.

Using the treatment policy strategy for the above described intercurrent events when defining the primary efficacy estimand is similar to what has been addressed by an analysis according to 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 and 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.

To support decision making, supplemental analyses will be performed for the primary efficacy objective to provide additional insights into the understanding of the treatment effect: Supplemental Efficacy Estimands 2 and 3. As an alternative to the treatment effect including effects of treatment discontinuation (using the treatment policy strategy to address early discontinuation of assigned treatment) the treatment effect “while on treatment” will be assessed. This “while on-treatment” approach acknowledges that discontinuation of assigned treatment is a possibly informative competing risk (i.e. the assigned treatment may influence the occurrence of the intercurrent event itself). Therefore, Supplemental Efficacy Estimands 2 and 3 will use a “while on treatment” strategy for the intercurrent event of early discontinuation of assigned treatment.

Note that here “censoring” due to the occurrence of a competing event has a different interpretation to classical non-informative censoring: individuals censored due to the occurrence of a competing risk are not supposed to be represented by those individuals who remain in follow-up. We intend to quantify the rates and risks of the primary efficacy outcome, considering that participants could also discontinue assigned treatment or die instead. From the interpretation, this is different from the marginal treatment effect “had

individuals stayed on treatment", which might be associated with using a hypothetical strategy.

1.1.2 Estimands Associated with the Primary Safety Objective

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*

Estimands for **safety assessment** are described by the following attributes:

	Primary Safety Estimand	**Supplemental Safety Estimand 1**	**Supplemental Safety Estimand 2**	**Supplemental Safety Estimand 3**
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, taking at least a single dose of the assigned treatment, and with the intention to be treated with antiplatelet therapy.	Same as Primary Safety Estimand	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.	Same as Supplemental Safety Estimand 2
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.	Same as Primary Safety Estimand	Same as Primary Safety Estimand	Same as Primary Safety Estimand
Endpoint	Time to first occurrence of ISTH major bleeding from first day of compared treatment	Same as Primary Safety Estimand	Same as Primary Safety Estimand except from day of treatment assignment	Same as Supplemental Safety Estimand 2
Population-level summary	Cause-specific hazard ratio (i.e. ratio of cause-specific hazard rates of the primary safety endpoint) comparing the two treatment conditions	Sub-distribution hazard ratio (sdHR) comparing the two treatment conditions	Same as Primary Safety Estimand	Same as Supplemental Safety Estimand 1 (i.e. sdHR)

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*

Estimands for **safety assessment** are described by the following attributes:

	Primary Safety Estimand	**Supplemental Safety Estimand 1**	**Supplemental Safety Estimand 2**	**Supplemental Safety Estimand 3**
Intercurrent events and strategies	• In case of **early discontinuation of assigned treatment**, observation time and safety events up to two days after the last intake of study treatment will be used (while on 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	Same as Primary Safety Estimand	Same as Primary Safety Estimand, except: • The treatment effect including effects of **early discontinuation of assigned treatment** is of interest. Observation time and primary safety 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 changes in therapy** (i.e. discontinuation of assigned treatment and initiation of indicated therapy) **due to a diagnosis requiring continuous anticoagulation**, e.g. due to diagnosis of atrial fibrillation / flutter, left ventricular thrombus, mechanical valve or other cardioembolic source of stroke, is of interest. Observation time and primary safety 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)	Same as Supplemental Safety Estimand 2

Rationale for the estimands associated with the primary safety objective:

The key clinical question related to the primary safety endpoint is about comparing 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 or high-risk TIA. In comparison to placebo, it is expected that asundexian as a FXIa inhibitor does not lead to a clinically 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 a significant increase in ISTH major bleeding compared to placebo, 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 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 medications that are given after discontinuation. Therefore, the proposed primary estimand for the safety question addresses early treatment discontinuation using a "while on 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.

For Supplemental Safety Estimands 2 and 3 as an alternative to the "while on treatment" effect, the treatment effect including effects of treatment discontinuation (i.e. using the treatment policy strategy to address early discontinuation of assigned treatment) will be assessed. This approach is aligned with intercurrent event handling used for the Primary Efficacy Estimand and Supplemental Efficacy Estimand 1.

1.1.3 Estimands Supporting Secondary Objectives

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

The estimand for the secondary net clinical benefit objective is following the same approach/definition as done for the primary safety estimand.

Please refer to Section 4 for a description how data is handled in the statistical analysis to estimate the defined estimands.

1.2 Study Design

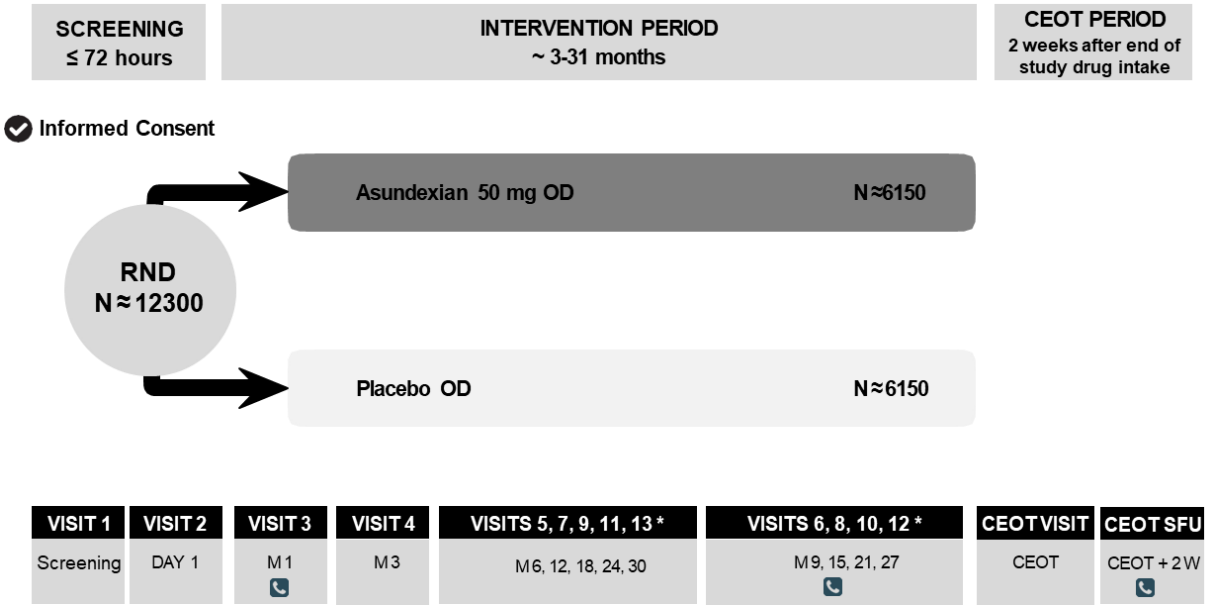
Study 20604 is a multicenter, international, randomized, placebo controlled, double-blind, parallel group, event driven Phase 3 study. The overall study design is depicted in Figure 1–1.

Approximately 12300 participants ≥ 18 years of age will be randomized in a 1:1 fashion to one of the 2 arms (approximately 6150 per arm), 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 of the protocol, inclusion criterion 6).

Figure 1–1: Study design overview



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

Day 1 is the day of randomization.

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

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

This is an event-driven study, and the sponsor will request termination of the intervention period once about 830 participants have experienced a primary efficacy endpoint event. The planned individual study duration is expected to be 3-31 months; however, the timelines may vary (i.e. longer or shorter than planned) depending on enrollment rate and incidence rate of the primary efficacy endpoint in the study. Please refer to the protocol for further details on the study design. The study will consist of the following study periods:

- **Screening period (from visit 1 until visit 2)**: Participants will be screened and have to be randomized within 72 hours after the onset of symptoms of the index event (i.e. non-cardioembolic ischemic stroke or high-risk TIA).

- **Intervention period (from visit 2 until the common end of treatment (CEOT) visit)**: The intervention period will be of variable length for each participant depending on the timepoint of individual randomization and accrual of outcome events in the study.
  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. The CEOT visit should occur as close as possible to the CEOT date, which is an actual calendar date at which time it is projected that the required number of primary endpoint events will have accrued (see Section 5 for details). If the number of events does not accrue as quickly as expected, then visits in the intervention period might need to be continued longer than anticipated.
- **Common End of treatment period (from CEOT visit until CEOT SFU visit)**

In the case that participants *permanently* discontinue study intervention earlier than planned:

- **Early termination (ET) period (ET until CEOT visit):** Participants discontinuing study intervention should continue with study visits until their CEOT visit. Further details on premature discontinuation of the study intervention are given in Section 7.1 of the protocol.

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

1.2.1 MRI sub-study

An MRI sub-study will be conducted at selected sites in approximately 1000 participants. In the sub-study an MRI at baseline and one follow-up MRI are planned that will be submitted to a central MRI core lab for interpretation. Details to MRI procedures and sequences can be found in Appendix 10.10 of the protocol and in the MRI manual.

A participant will be identified as taking part in the sub study, if the informed consent for the MRI sub-study was signed. In case the informed consent for the MRI sub-study was withdrawn on the same day as signed, participants will be considered as not participating in the MRI sub-study.

2. Statistical Hypotheses

As described in Section 4.1.4, 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 null hypotheses.

The aim related to the primary efficacy objective is to show that asundexian 50 mg is superior to placebo in preventing ischemic stroke in patients after an acute non-cardioembolic stroke or high-risk TIA. 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 conditions for the primary efficacy outcome” and in the alternative that

"there is a difference between the treatment conditions 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 at 90 days)
- 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 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 safety, secondary safety and net clinical benefit endpoints, no formal testing is planned, and therefore no test problem is stated.

2.1 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 at 90 days)
- 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 stratified logrank tests for the time-to-event endpoints.

3. Analysis Sets

For purposes of analysis, the following analysis sets are defined in Table 3–1.

Table 3–1: Definition of Analysis Sets

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 took 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 safety estimands, the net clinical benefit estimand as well as analyses of AEs.

All MRI analyses will be performed on an MRI analysis set, which will be defined outside of this document. The MRI analyses are out of scope of this SAP.

Final decisions regarding the assignment of participants to analysis sets will be made during the blinded review of study data and documented in the final list of important deviations, validity findings and assignment to analysis sets.

4. Statistical Analyses

4.1 General Considerations

The statistical evaluation will be performed by using the software SAS (release 9.4 or higher; SAS Institute Inc., Cary, NC, USA).

All data will be presented in the participant data listing as they are recorded on the Case Report Form (CRF), i.e. partially missing data will appear as such.

Data will be displayed by randomized study intervention arm. Tables will be shown by study intervention arm and overall. Analyses will be performed according to the randomized study intervention arm.

Adjudicated data (events and event dates) will be used unless otherwise stated.

4.1.1 Definitions and data handling rules

4.1.1.1 Baseline values

Baseline data for vital sign and laboratory values, as well as for other variables, are planned to be taken from measures at Visit 2/randomization (or the respective visit as per SoA). If the Visits 1 and 2 are combined, then the values from that combined visit are used. The time in relationship to the first intake of study intervention will not be considered. The rationale for not taking the time of measurement into account is that measurements from Visit 2 are considered more appropriate as baseline measure, even if they are taken shortly after start of study intervention, compared to previous measurements that might have been taken several days before.

If the Visit 2 (or the respective visit as per SoA) values are not available, then the latest values taken before first administration of study intervention will be considered (e.g., values between randomization and first study intervention or values taken on Visit 1). For participants

randomized but not treated, the randomization date will be considered instead. In case of more than one available value before first administration of study intervention/randomization, the non-missing value before and closest to first study intervention/randomization will be taken. For laboratory parameters, if no central lab value exists to derive the baseline value, local laboratory values according to the above criteria can be used to derive a baseline value.

4.1.1.2 Repeated measurements at the same visit

If more than one measurement is available for a given visit and no special reason for the additional observation was provided in the eCRF, the last observation will be used pre-randomization and the first observation will be used post-randomization in the analysis.

4.1.1.3 Pre-specified and investigator reported events

If more than one entry exists for pre-specified medical history or procedures terms, the investigator reported term will overwrite any pre-specified term of the name, i.e. the occurrence of that medical history or procedure will be a yes.

4.1.1.4 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 study (CEOT). 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 study (CEOT) with respect to the occurrence and timing of key outcome events, including stroke, death, MI and bleeding events. Assumptions made to handle missing data will be assessed for robustness via sensitivity analyses.

If a key endpoint event occurrence date, AE start date or censoring date 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 and year of the event are known, then the day will be imputed as the 1st day of the month. If the known month and year of the adverse event is the same as the month and year of the first dose of study intervention, then impute the adverse event start date as first dose of study intervention (use randomization date for the not treated participants).
- If only the year of the event is known, then the 1st of January will be imputed. If the known month and year of the adverse event is the same month and year as the first dose of study intervention, then impute the adverse event start date as first dose of study intervention (use randomization date for the not treated participants).
- If year, month and day are unknown, then the date will be imputed as the date of first intake of study intervention. In case the date of first intake of study intervention is missing (i.e. for in the FAS who never initiated treatment), the randomization date will be used instead.

If a prior/concomitant medication start date is incomplete and following all attempts to get an approximate date by the investigator, a date will be imputed or ongoing assumed using the following algorithm:

- If only the month and year of the event are known, then the day will be imputed as the 1st day of the month.
- If only the year of the event is known, then the 1st of January will be imputed.
- If year, month and day are unknown, then the date will be imputed by the minimum of (date of signed informed consent, imputed medication end date).
- If a medication end date exists and the imputed start date is after the end date, then the start date is set to the end date of the medication.

If a prior/concomitant medication end date is incomplete, and the medication is not marked as ongoing then following all attempts to get an approximate date by the investigator, a date will be imputed or ongoing assumed using the following algorithm:

- If only the month and year of the end date are known, then the day will be imputed as the last day of that month (i.e. 28, 29, 30 or 31).
- If only the year of the event is known, then the 31st December will be imputed.
- If year, month and day are unknown and the participant died, then the end date will be imputed as the date of death.
- If year, month and day are unknown and the participant did not die, then the medication will be assumed to be ongoing.
- If the imputation rules for partial end dates leads to an implausible date (e.g. after date of death), then the date will be imputed as the last plausible date.

If exposure (study intervention) start date is incomplete following all attempts to get an approximate date by the investigator, a date will be imputed using the following algorithm:

- If only the month and year of the exposure are known, then the day will be imputed as the first day of the month.
- If only the year of the event is known, then the 1st of January will be imputed.
- If year, month and day are unknown, then the date will be imputed as date of first intake of study intervention. In case there is no date of first intake of study intervention (i.e. for participants in the FAS who never initiated treatment), no date will be imputed.
- If exposure end date exists and the imputed start date is after the end date, the start date is set to the exposure end date.
- If this imputation rule leads to an implausible date (e.g. earlier than the first intake of study intervention), then the date will be imputed as the earliest plausible date (e.g., the start date of the exposure) but not later than the last date where it is known that the participant took drug.

If exposure (study intervention) end date is incomplete following all attempts to get an approximate date by the investigator, a date will be imputed using the following algorithm:

- If only the month and year of the end date are known, then the day will be imputed as the last day of that month (i.e. 28, 29, 30 or 31).
- If only the year of the event is known, then the 31st December will be imputed.
- If year, month and day are unknown and the participant died, then the end date will be imputed as the date of death.
- If year, month and day are unknown and the participant did not die, then the end date will be imputed as date of last contact.
- If the imputed exposure end date is later than CEOT visit date or date of death, then exposure end date will be set to the earlier of the CEOT visit date and the date of death.

For study intervention, the time under risk will be handled in a conservative matter, i.e., missing study intervention end date will be imputed by the latest date known the study intervention was taken.

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 described in Section 4.1.1.12.

4.1.1.5 Date of last contact and study completion

The date of last contact will be defined as the latest of the following dates, if existing,

- last available subject visit date for the participant (this will be set to the latest of the individual randomization date and study intervention intake date for participants without any data after randomization or first day of study intervention.)
- last available date on the participant's study intervention exposure
- last available date of any event, for which the participant must be alive to have had; for example adverse event, date of clinical outcome event or hospitalization or procedure, including death
- the date information about the participant was provided and the participant was alive at that time (subject status page)
- the date of withdrawal of consent

Note the last contact date cannot be later than the date of death, if it exists. Some participants may have a date of death after withdrawal of consent, because this is permitted to be collected for some regions.

A participant will be counted as a study completer if the date of last contact is after the date of request of termination of the study intervention period by the sponsor or if the participant died prior to this date. The "date of request for termination of the study intervention" is defined as the earliest date of the CEOT Visit window, i.e., August 4, 2025. In all other cases the participant will be considered a study non-completer. For a participant not completing the study for reason withdrawal of consent there will be data on the CRF page "Withdrawal from Informed Consent(s)/Informed Assent", otherwise the reason for non-completion will be imputed as "Lost to follow-up". These reasons may not match CRF reasons for non-completion of epochs/periods.

In parallel, completion and non-completion (including reasons) of study epochs will be presented as reported by the investigator. The number of participants completing epochs will not necessarily match the numbers for study (non-)completion.

4.1.1.6 Treatment emergent period

For the treatment emergent period all events starting from first intake of study intervention up until 2 days after the last intake of study intervention will be counted. If the last contact date is prior to 2 days after the last intake of study intervention, then the treatment emergent period will end at the last contact date.

Events on the day of first study intervention intake will be counted as treatment emergent if the time of occurrence is later than the time of first study intervention intake. If the event is on the same date as first study intervention intake but either the time of intake or time of event is missing, then the event will be assumed as treatment emergent.

4.1.1.7 Adjudication of events and classification of investigator reported bleeding

Potential and pre-specified clinical outcome events will be submitted for adjudication to an independent clinical event committee (CEC). Adjudication of all bleeding events as well as efficacy events will be performed by the CEC. The following events will be reviewed in a blinded fashion as well as adjudicated and classified in a consistent and unbiased manner according to definitions further specified in the CEC charter, e.g. using algorithmic approaches.

- Bleeding events will be classified as follows:
  - According to ISTH bleeding criteria:
    - ISTH Major Bleeding (defined in Section 8.3.1.1 of the protocol),
    - ISTH Clinically Relevant Non-Major Bleeding (defined in Section 8.3.2.1 of the protocol),
    - Minor Bleeding (defined in Section 8.3.2.2 of the protocol).
  - According to BARC criteria (Note: type 4: CABG-related bleeding criterion is not applicable to this study) (defined in Section 8.3.3.1 of the protocol)
    - BARC type 2, 3 and 5 bleeding
    - BARC type 1 bleeding.
- Death (CV death [including death with undetermined cause] or non-CV death)
- Myocardial Infarction (MI)
- Stroke (ischemic, hemorrhagic, undetermined)
- Transient ischemic attack (TIA).

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.

4.1.1.8 Death/ Fatal AEs

There may be deaths captured on the CRF pages "Death" and "Outcome Event" that do not have corresponding adverse event entries. Deaths that do not have a corresponding AE page will be included/considered for the estimands, as well as fatal AEs.

4.1.1.9 Disease-related events, (S)AEs and Outcome events

Event type

For this study some disease-related events (DREs) (see 8.4.6 of the protocol for further details) are part of the efficacy outcome events in participants after an acute non-cardioembolic ischemic stroke or high-risk TIA. Because the DREs pertaining to efficacy endpoints are typically associated with the disease under study, they will not be reported as (S)AEs by the investigator but will be reported as outcome events. If an efficacy outcome event is in the investigator's opinion worse (e.g. in intensity, frequency or duration) than expected for a participant or possible related to study intervention then it may be reported as an (S)AE as well as an outcome event. Safety outcome events (i.e. all bleeding) or efficacy outcome events with a symptomatic bleeding component are not exempted and will be reported as (S)AEs, in addition to outcome events (see 8.4.6 of the CSP for further details).

Timeframe for event reporting

(S)AEs will be collected from the start of study intervention until a participant's respective safety follow-up visit (see 8.4.1 of the CSP 20604 for further details). Therefore, for participants discontinuing study intervention early, adverse events will not be collected during the period from the safety follow up visit (approximately 2 weeks after last study intervention) until the CEOT visit. In contrast, outcome events (efficacy and safety) will be collected until the CEOT visit if the participant is no longer taking study intervention (see 10.9 of the CSP 20604 for further details) and until the CEOT safety follow up visit if the participant completed study intervention less than 2 weeks before the CEOT visit.

4.1.1.10 Blind Review of important deviations and validity findings

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis sets. Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an SAP amendment and, if applicable, in an additional analysis plan.

4.1.1.11 Classification of regions

The countries or regions in the study will be classified in the following pooled regions

Country or Region	Pooled Region
Argentina	South America
Australia	Western Europe, Australia and Israel
Austria	Western Europe, Australia and Israel
Belgium	Western Europe, Australia and Israel
Brazil	South America

Country or Region	Pooled Region
Bulgaria	Eastern Europe
Canada	North America
China	Asia
Colombia	South America
Czechia	Eastern Europe
Denmark	Western Europe, Australia and Israel
Finland	Western Europe, Australia and Israel
France	Western Europe, Australia and Israel
Germany	Western Europe, Australia and Israel
Greece	Western Europe, Australia and Israel
Hungary	Eastern Europe
India	Asia
Israel	Western Europe, Australia and Israel
Italy	Western Europe, Australia and Israel
Japan	Asia
Kazakhstan	Eastern Europe
Latvia	Eastern Europe
Lithuania	Eastern Europe
Malaysia	Asia
Netherlands	Western Europe and Australia and Israel
Norway	Western Europe, Australia and Israel
Poland	Eastern Europe
Portugal	Western Europe, Australia and Israel
Slovakia	Eastern Europe
South Korea	Asia
Spain	Western Europe, Australia and Israel
Sweden	Western Europe, Australia and Israel
Switzerland	Western Europe, Australia and Israel
Taiwan	Asia
Turkey	Asia

Country or Region	Pooled Region
United Kingdom	Western Europe, Australia and Israel
USA	North America

4.1.1.12 Prohibited medications

Prohibited medications will be identified based on Bayer specific drug groupings. Prohibited medications include:

- Medications with a combination of level 2 groups strong CYP3A inducers and clinical P-gp inducers (DGCODEL2: B_000021 and B_000012)
- Medications with a combination of level 2 groups strong CYP3A inhibitors and clinical P-gp inhibitors (DGCODEL2: B_000022 and B_000013).

4.1.2 Derivation of time-to-event variables, censoring and incomplete dates

For the efficacy, safety events and net clinical benefit time-to-event outcomes, see Sections 4.2 and 4.3, the endpoint is the time to first occurrence of the outcome event of interest, which can be a single outcome or a composite.

For estimands using the treatment policy strategy to address early discontinuation of assigned treatment, time-to-event endpoints will be derived as the number of days from the individual participant's randomization date (planned at Visit 2) to the date of onset of the respective endpoint event.

Date of Event – Date of randomization + 1.

The time-to-event endpoint for participants who have not experienced the respective endpoint event until their CEOT visit (if available) will be censored as follows:

- for participants who reach their CEOT visit without the event of interest, the censoring date will be the date of their CEOT visit,
- for participants without a CEOT visit, the censoring date will be the date of last contact (see Section 4.1.1.5).

Events that occurred after CEOT visit will be listed only.

For estimands using the while on treatment strategy, the start date for the time to event interval will be the date of first intake of study intervention (rather than randomization date). Time-to-event endpoints will be derived as

Date of Event – Date of first intake of study intervention + 1.

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 regarding the occurrence and timing of key outcome events to a minimum.

For those estimands where the "while on treatment" strategy is proposed to address the intercurrent event of "early discontinuation of treatment", see estimand definition in Section 1.1.2 for example, the occurrence of this intercurrent event will be considered a "soft" competing risk in the analysis, i.e. events of interest will be counted up to the date of last intake of study intervention plus 2 days. With this, censoring for the competing event early discontinuation starts two days after last treatment intake. Also, in case the study intervention

is taken up to the planned end date (day before the CEOT visit), the event of interest will be counted up to the date of last intake of study intervention plus 2 days.

For all estimands, 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.

For estimands using the "while on treatment" strategy (i.e. analyses using the SAF) events occurring on the same day as first study intervention intake will be considered an outcome event of interest if either the time of occurrence is later than the time of first study intervention intake or if the time of first study intervention intake or time of the event is missing.

4.1.3 Multiple imputation of unobserved follow-up time

For the primary efficacy estimand as a sensitivity analysis, it is planned 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. The method proposed here is aligned with the "proper-like" imputation from He et al. (2022) [7] and there is example SAS code within that paper. For example, it is assumed that after withdrawal of informed consent (or lost to follow-up) participants remain untreated if they have not already discontinued their study intervention earlier. Thus, when for a given estimand the intercurrent event "treatment discontinuation" is addressed by the treatment policy strategy (e.g., the primary efficacy estimand), unobserved follow-up time will be modelled based on participant data observed after treatment discontinuation. Unobserved follow-up time will be multiply imputed using hazard rates estimated from those participants who have observed data after 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 violated, rather than the exponential distribution 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 after early discontinuation of study intervention (i.e. randomized treatment) and who have not experienced the event of interest prior to study intervention discontinuation. For these participants, estimate the hazard rate for the off-treatment period separately for each study intervention arm. The off-treatment period for this purpose is defined as from the date of last intake of study intervention + 2 calendar days to the earliest of the outcome event of interest or the date of censoring (as defined above).
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 parameters for the Exponential distribution from the normal distribution using the estimates for the hazard rate in step 1 to incorporate variability in the estimated hazard rates. The seed to be used will be 20604. Drawing from the exponential distribution reflects the assumption of constant hazards over time.

- 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.

If the imputed time to event is before the 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 participants.

3. Analyze the time to the outcome event of interest based on the complete time to event data (observed + imputed).
4. Repeat steps 2 and 3 multiple times and use Rubin's rule [10] for combining analysis results from multiply imputed datasets using an approximate proper imputation.

Tipping Point Methodology applied to the imputation of incomplete follow up time

To assess the sensitivity of the incomplete follow up imputation to changes in the hazard rate for the off treatment period, the incomplete follow up time will be imputed using a range of different assumptions for the off-treatment hazard rates [8][11].

The following methods and assumptions will be applied: The estimated hazard rates from step (1) will be varied independently for each study intervention arm, and range from very low hazard rates (leading to all participants with incomplete follow up time being censored) to extremely high hazard rates (leading to most/all participants with missing follow up time being with an outcome event). As a starting point, this will include scenarios for following multipliers of the estimated hazard rates per treatment arm under (1): 0.1, 0.3, 0.5, 0.7, 0.9, 1, 1.5, 3, 5, 10, 15, 25 and 50. These might be amended as needed to identify the potential tipping point.

For each combination of hazard rates steps (2), (3) and (4) will be repeated and results will be displayed in a heat map.

4.1.4 Descriptive statistics

All variables will be analyzed by descriptive statistical methods. Generally, confidence intervals will be presented as two-sided 95% confidence intervals.

Metric data

The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data.

Categorical data

Frequency tables will be generated for categorical data.

Time-to-event data

- For time-to-event variables, the observed numbers of participants with an event of interest and, if applicable, the competing event, will be reported together with the proportion by study intervention and overall.
- Endpoint events after (administrative) censoring, will be summarized, as applicable.
- Incidence rate estimates for the time to event endpoints and, if applicable, the competing event, will be displayed with 95% confidence intervals by study intervention and overall where appropriate.

Incidence rates will be estimated as number of participants with the respective event of interest divided by the cumulative at-risk time in the reference population, where a participant is no longer considered at risk once the event-of-interest or a competing event, whichever comes first, occurred.
Nelson–Aalen estimates of the cumulative hazard for the event of interest by study intervention arm will be used to explore if the hazards are reasonably constant over time as applicable. The (cause-specific) Nelson-Aalen estimator for event E at time *t* is defined as:

$$\hat{\Lambda}_E(t) = \sum_{t_j \le t} \frac{\#Participants\ with\ an\ event\ E\ at\ t_j}{\#Participants\ under\ risk\ at\ t_j},$$

(Allignol, Beyersmann and Schmoor 2016 [2]). If Nelson–Aalen estimates of the cumulative hazard for an event-of-interest by intervention arm indicate that the hazards are not reasonably constant over time, piecewise incidence rates, with appropriately chosen cut-points, will be estimated and presented.

- The cumulative incidence risk for the event-of-interest, i.e. the proportion of participants with an event of interest over the course of time taking competing risk into account, and, if applicable, the cumulative incidence risk for the competing risk will be estimated for time-to-event variables using **Aalen-Johansen** estimators by study intervention. Estimates will be displayed using plots and complementary tables. The plots of cumulative incidence rates will be truncated at the time point when at least 10% of participants are still under risk [14]. This ensures that any visual signs of treatment differences do not look more extreme than they really are.
  The Aalen-Johansen estimator is a non-parametric estimator based on the cause-specific Nelson-Aalen estimator and the Kaplan-Meier (KM) estimator $\hat{S}(t)$ and is defined as:

$$\widehat{AJ}_E(t) = \sum_{t_j \le t} \hat{S}(t_{j-1})(\hat{\Lambda}_E(t_j) - \hat{\Lambda}_E(t_{j-1})) .$$

- The difference between the Aalen-Johansen estimators for the two study interventions at month 12 and 6 monthly thereafter will be presented with 95% confidence intervals. The difference will only be presented for a timepoint if at least 10% of the population are still at risk at that timepoint.

  As the Aalen-Johansen estimator is approximately normally distributed, (Aalen, Borgan and Gjessing 2008 [1]), the difference of Aalen-Johansen estimators is also approximately normally distributed. Thus, the two-sided 95% confidence interval up to month 12 for example is obtained via:

$$\left[(\widehat{AJ}^{Asundexian}(12) - \widehat{AJ}^{Placebo}(12)) \pm z_{0.975}\sqrt{\sigma^2(\widehat{AJ}^{Asundexian}(12)) + \sigma^2(\widehat{AJ}^{Placebo}(12))} \right],$$

  with $\widehat{AJ}^{TRT}(12)$ the Aalen-Johansen estimator for treatment TRT at month 12, $z_{0.975}$ the 97.5% quantile of the standard normal distribution and $\sigma^2(\widehat{AJ}^{TRT}(12))$ the estimated variance of the Aalen-Johansen estimator at month 12, estimated with the Aalen method.

To derive the Aalen-Johansen estimators for the cumulative incidence with the corresponding confidence intervals, SAS program code corresponding to the following will be used:

```
ods output cif=cif;

PROC LIFETEST DATA = <dataset> ALPHA=0.05 ERROR=AALEN;
  STRATA  / GROUP=trtgrpn;
  TIME ttevalue * status(0)/eventcode=1;
                    /* CIF for event of interest type 1 (e.g. bleeding) */
RUN;
PROC LIFETEST DATA = <dataset> ALPHA=0.05 ERROR=AALEN;
  STRATA  / GROUP=trtgrpn;
  TIME ttevalue * status(0)/eventcode=2;
                                  /* CIF for (competing) event of type 2 */
RUN;

/*
where
dataset  = name of dataset
trtgrpn  = variable coding randomized treatment group
           (0 = placebo control group, 1 = asundexian treatment)
ttevalue = time to first occurrence of outcome event or competing event or
           censoring
status   = status of the participant at event time (0 = right-censored,
           1 = event of interest, 2 = competing event)
alpha has been set as 0.05 in this example
*/
```

- In addition to the Aalen-Johansen analyses, Kaplan Meier estimates and curves will be prepared for the primary efficacy and primary safety outcomes to allow for an indirect data comparison with historical studies. As these analyses do not consider intercurrent events, all assessments of the treatment effects will be done using Aalen-Johansen estimates only.

Number needed to treat (NNTs)

The number of patients needed to treat for an additional beneficial outcome (NNTB) compared to the placebo group or the number of patients needed to treat for an additional harmful outcome (NNTH) will be calculated based on the absolute risk difference of the corresponding Aalen-Johansen estimates and confidence intervals by time period for the treatment group comparisons. The term NNT will be used for all outputs and have a positive value if it is NNTB and a negative value when it is the NNTH. Confidence intervals for NNTs will be only calculated if the confidence interval for the difference of Aalen-Johansen estimates does not encompass zero.

4.1.5 Stratification

Regression models and statistical tests will be stratified (where applicable) by the randomization stratification factor of whether participants were planned to receive dual antiplatelet therapy with ASA and a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor) or not. This stratification factor will not be re-derived based on study data. Given that the

treatment effect is adjusted for the randomization strata, it is considered as a conditional treatment effect.

Models using the stratification factor as a subgroup variable (by-variable) will not use the corresponding factor as a covariate in the model. If the stratification factor has to be removed from at least one subgroup model, then to allow comparisons between the subgroups it will be removed from all subgroup models for that variable.

4.2 Primary Endpoints/Estimands Analysis

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

4.2.1 Primary Efficacy Estimand

4.2.1.1 Definition of Endpoint

The primary efficacy endpoint is the time from randomization to the first occurrence of ischemic stroke. The estimand is defined in Section 1.1.1; the derivation of the time to event is described in Section 4.1.1.12.

4.2.1.2 Main Analytical Approach

Data for the primary efficacy endpoint will be summarized using the set of descriptive statistics for time-to-event endpoints (see Section 4.1.4), with the exception of estimating incidence rates. The probability to experience a subsequent ischemic stroke is highest during the first weeks after an acute non-cardioembolic ischemic stroke or high-risk TIA, with a declining risk over time. Thus, cumulative incidence estimates for meaningful timepoints over the duration of the study are better suited to describe the data than rates.

In line with the “while alive” strategy applied to address the intercurrent event “death” for the primary efficacy estimand, see Section 1.1.1, “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 primary efficacy 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 assigned to 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 competing risk “death”.

To derive the cause specific hazard ratios and the corresponding confidence intervals, SAS program code corresponding to the following will be used:

```
ODS OUTPUT ParameterEstimates = cshr modelANOVA=cspval;

PROC PHREG DATA = <dataset>;
   MODEL ttevalue*status(0,2)=trtgrpn / RL ALPHA=0.05  TYPE3(SCORE);
   STRATA dapt;
RUN;

/* modeling event of interest and all competing events where status ≠ 0 */


/*
where
dataset  = name of time-to-event -dataset
trtgrpn  = variable coding randomized antithrombotic treatment group
ttevalue = time to first occurrence of outcome event or competing event or
           censoring
status   = status of the participant at event time (0 = right-censored,
           1 = event of interest, 2 = competing event)
dapt     = binary strata, planned use of dual antiplatelet therapy with
           ASA and P2Y12i (=1) vs. no planned use of dual antiplatelet
           therapy with ASA and P2Y12i (=0)

alpha has been set as 0.05 in this example
*/
```

The primary efficacy null hypothesis will be tested using a two-sided stratified log-rank test, equivalent to the score test from the Cox PH analysis.

All analyses described in this section will be repeated for the subgroups described in Section 4.6.5.

4.2.1.3 Sensitivity Analyses

The plausibility of the proportional hazards assumption will be visually assessed via plots of the scaled Schoenfeld residuals over time, Nelson-Aalen estimates of the cumulative hazard and via the Chi-Square test of the residuals [5].

For the main analysis, missing follow-up time will be simply handled by censoring at the last available point in time for which data on the outcome has been obtained. In addition, sensitivity analyses with regard to the missing follow-up time will be performed as described in Section 4.1.3. Subgroup analyses will be performed without imputation of missing follow-up time.

4.2.1.4 Supplementary Analyses

Supplemental Efficacy Estimand 1

In a supplementary analysis the primary efficacy objective will be explored from a different angle, comparing the probability for the occurrence of a primary efficacy outcome over time in contrast to the hazard rates. This estimand is the Supplemental Efficacy Estimand 1 (see Section 1.1.1) with the population-level summary of the sub-distribution hazard ratio (sdHR) based on a Fine-Gray model [3]. 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 an *x*-fold decrease of the odds of the occurrence of the primary efficacy outcome when comparing asundexian with placebo.

The estimated sub-distribution hazard ratios (sdHRs) and their associated confidence intervals comparing participants assigned to asundexian versus placebo with respect to the primary efficacy outcome will be presented together with estimates of the sdHRs for the competing risk "death". The model will be stratified by whether participants are planned to receive dual antiplatelet therapy with ASA and a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor) or not.

The SAS code for the Fine-Gray model is as below:

```
ODS OUTPUT ParameterEstimates = fg1;
PROC PHREG DATA = <dataset>;
   CLASS trtgrpn; /* modeling for event of interest type 1 (bleeding) */
   MODEL ttevalue*status(0) = trtgrpn / EVENTCODE(FG) = 1 RL;
   STRATA dapt;
RUN;

ODS OUTPUT ParameterEstimates = fg2;
PROC PHREG DATA = <dataset>;
   CLASS trtgrpn;             /* modeling for competing event type 2 */
   MODEL ttevalue*status(0) = trtgrpn / EVENTCODE(FG) = 2 RL;
  STRATA dapt;
RUN;

/*  where
dataset  = name of dataset
trtgrpn  = variable coding randomized intervention groups
ttevalue = time to first occurrence of outcome event or competing event
           or censoring
status   = status of participant at event time (0 = right-censored,
           1 = event of interest, 2 = competing event,...)
dapt     = binary strata, planned use of dual antiplatelet therapy with
           ASA and P2Y12i (=1) vs. no planned use of dual antiplatelet
           therapy with ASA and P2Y12i (=0)
*/

/* Combine (sub-distribution) HR estimates and confidence intervals from
datasets fg1 and fg2 for the models for the event of interest and the
competing events in one table. */
```

Gray's (Gray, 1988) [6] test for equivalence of the cumulative incidence functions, stratified by the two stratum variables, will be performed. The SAS code for Gray's test is as below:

```
ODS OUTPUT GrayTest = Gtest;

PROC LIFETEST DATA = <dataset> ERROR = AALEN;
   TIME ttevalue*status(0) / EVENTCODE = 1;
                           /* for event of interest type 1 (bleeding) */
 STRATA dapt / GROUP=trtgrpn;

RUN;

/*  where
dataset  = name of dataset
trtgrpn  = variable coding randomized intervention groups
ttevalue = time to first occurrence of outcome event or competing event
           or censoring
status   = status of participant at event time (0 = right-censored,
           1 = event of interest, 2 = competing event, ...)
dapt     = binary strata, planned use OF dual antiplatelet therapy with
           ASA and P2Y12i (=1) vs. no planned use OF dual antiplatelet
           therapy with ASA and P2Y12i (=0)
*/
/* Take p-value from Gtest and combine with other results in the
table.*/
```

Supplemental Efficacy Estimand 2 and 3

The supplemental efficacy estimands 2 and 3 will be summarized as in Section 4.1.4.

In line with the "while on treatment" strategy proposed to address intercurrent events for these estimands, see Section 1.1.1, both "death" and "premature end of exposure to 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.

For the supplemental efficacy estimand 2, as described in 4.2.1.2 for the primary efficacy estimand, the csHRs and their associated confidence intervals for participants taking asundexian versus placebo will be derived. The results will be presented together with estimates of the csHRs for the associated competing risk "death or premature end of exposure to assigned treatment".

For the supplemental efficacy estimand 3 the sub-distribution hazard ratios (sdHRs) and their associated confidence intervals for participants assigned to asundexian versus placebo will be derived from a Fine-Gray model as described for the supplemental efficacy estimand 1 above. The results will be presented together with estimates of the sdHRs for the associated competing risk.

4.2.2 Primary Safety Estimand

4.2.2.1 Definition of Endpoint

The primary safety endpoint is the time from first intake of study intervention to the first occurrence of ISTH major bleeding. The primary safety estimand is defined in Section 1.1.2

and different bleeding classifications in Section 4.1.1, the derivation of time to event endpoints is described in Section 4.1.1.12.

4.2.2.2 Main Analytical Approach

In line with the "while on treatment" strategy proposed to address intercurrent events for the primary safety estimand, see Section 1.1.2, 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.

Data for the primary safety endpoint will be summarized using the set of descriptive statistics for time-to-event endpoints (see Section 4.1.4).

For the primary safety estimand, as described in Section 4.2.1.2 for the primary efficacy estimand, the csHRs and their associated confidence intervals for participants taking asundexian versus placebo 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 risk "death or premature end of exposure to assigned treatment".

The primary safety null hypothesis, see Section 2, will be tested using a stratified two-sided log-rank test, equivalent to the score test from the Cox PH analysis.

All analyses described in this section will be repeated for the following subset of the subgroups defined in Section 4.6.5: type of index event; planned dual antiplatelet therapy with ASA and a $P2Y_{12}$ inhibitor; weight groups; age groups; eGFR; sex; race; region; history of prior stroke or TIA; NIHSS score (≤5, >5); intravenous thrombolysis; endovascular therapy; treated with a combination of moderate CYP3A inducers and clinical P-gp inducers prior to randomization (Day -1); and treated with a combination of moderate CYP3A inhibitors and clinical P-gp inhibitors prior to randomization (Day -1).

4.2.2.3 Sensitivity Analyses

The plausibility of the proportional hazards assumption will be assessed as described above for the primary efficacy outcome in Section 4.2.1.3. If Nelson–Aalen estimates of the cumulative hazard for the primary safety outcome by intervention arm indicate that estimated hazards are not reasonably constant over time, piecewise incidence rates, with appropriately chosen cut-points, will be estimated and presented. Because the primary interest for the safety analyses is in the treatment effect while patients are exposed to study intervention, it is expected that there is no missing follow-up time, thus, dispensing with the need for the multiple imputation of the missing follow-up time sensitivity analyses.

4.2.2.4 Supplementary Analyses

Supplemental Safety Estimand 1

For the supplemental safety estimand 1 the sub-distribution hazard ratios (sdHRs) and their associated confidence intervals for participants assigned to asundexian versus placebo will be derived from a Fine-Gray model as described for the supplemental efficacy estimand 1 in Section 4.2.1.4. The results will be presented together with estimates of the sdHRs for the associated competing risks of "death or premature discontinuation of study intervention".

Supplemental Safety Estimand 2 and 3

The supplemental safety estimand 2 will be summarized as in Section 4.1.4, these summary statistics will also apply for supplemental safety estimand 3.

For the supplemental safety estimand 2, as described in 4.2.1.2 for the primary efficacy estimand the csHRs and their associated confidence intervals for participants taking asundexian versus placebo will be derived. The results will be presented together with estimates of the csHRs for the associated competing risk "death".

For the supplemental safety estimand 3 the sub-distribution hazard ratios (sdHRs) and their associated confidence intervals for participants assigned to asundexian versus placebo will be derived from a Fine-Gray model as described for the supplemental efficacy estimand 1 in Section 4.2.1.4. The results will be presented together with estimates of the sdHRs for the associated competing risk.

The csHR and results of the two-sided stratified log-rank test, equivalent to the score test from the Cox PH model will be compared to the results from the primary safety estimand analysis.

4.3 Secondary Estimands Analysis

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

4.3.1 Secondary Efficacy Endpoints

4.3.1.1 Definition of Secondary Efficacy Endpoints

The secondary efficacy endpoints are time to first occurrence from randomization of:

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

As per CSP section 8.2.2.3, 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 a recurrent stroke or an increase of 1 point if the last available mRS before the recurrent stroke event was ≥ 3. For the 90-day assessment the mRS nearest to 90 days, but at least 30 days after the recurrent stroke will be used. If measurements of mRS are missing, then mRS from up to 365 days after the event start date will be used. In case the patient dies, then a mRS assessment of 6 will be imputed at the day of death. If no mRS assessment is available and the patient is alive at CEOT, then it will be considered as missing data. If multiple assessments are equally distant from day 90, then the mRS with the highest value will be chosen.

4.3.1.2 Main Secondary Efficacy Analytical Approach

The analysis of the secondary efficacy endpoints will follow the principles described for the main analyses of the primary efficacy endpoint, see Section 4.2.1.2, with the exception of estimating incidence rates.

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 death will not be a competing risk for the all-cause mortality endpoint.

To conduct the analysis for ischemic strokes in the first 90 days, all participants still in the study at Day 90, who were without an ischemic stroke and without a competing risk until Day 90 will be censored at Day 90. The csHRs, as well as the sdHRs and their associated confidence intervals comparing participants assigned to asundexian versus placebo will be displayed together with the cumulative incidences at several time points until Day 90.

4.3.1.3 Sensitivity Secondary Efficacy Analyses

For secondary efficacy endpoints for which the null hypothesis is rejected (see Section 2.1), sensitivity analyses with regard to the missing follow-up time will be performed as described in Section 4.1.3. Subgroup analyses will be performed without imputation of missing follow-up time.

4.3.1.4 Supplementary Secondary Efficacy Analyses

The supplementary analysis of the secondary efficacy endpoints will follow the principles described for the first supplementary analysis of the primary efficacy endpoint (i.e. Supplemental Efficacy Estimand 1), see Section 4.2.1.4.

4.3.2 Secondary Safety Endpoints

Death excluding fatal bleeding will be the competing risk for the safety endpoints fatal bleeding and all bleeding.

4.3.2.1 Definition of Secondary Safety Endpoints

The secondary safety endpoints are time to first occurrence from first study intervention intake of:

- 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

Fatal bleeding is defined as adjudicated BARC bleeding type 5a or 5b.

4.3.2.2 Main Secondary Safety Analytical Approach

The analysis of the secondary safety endpoints will follow the principles described for the main analyses of the primary safety endpoint, see Section 4.2.2.2.

4.3.2.3 Sensitivity Secondary Safety Analyses

No sensitivity analyses are planned for the secondary safety endpoints.

4.3.2.4 Supplementary Secondary Safety Analyses

The supplementary analysis of the secondary safety endpoints will follow the principles described for the supplementary analyses of the first supplementary analysis of the primary safety endpoint (i.e. Supplemental Safety Estimand 1), see Section 4.2.2.4.

For the ISTH and BARC bleeding events the observed number of participants with individual classifications will be reported together with the proportion. In addition, the incidence rate will be displayed with a 95% confidence interval. The classifications displayed will be ISTH major bleeding, CRNM bleeding, minor bleeding and BARC bleedings type 1, 2, 3a, 3b, 3c, 5a and 5b.

The number of participants with bleeding events in the treatment emergent data scope by bleeding site (e.g. ear, eye, GI etc.) will be summarized by study intervention and overall. The table by bleeding site will be repeated for ISTH major bleeding, CRNM bleeding and minor bleeding.

The number of participants with bleeding (separately for both ISTH definition and BARC bleeding definition) according to investigator reported outcome and after adjudication (cross classification) will be reported. The details of participants with ISTH major bleeding, ISTH CRNM bleeding, and minor bleeding will be listed.

4.3.3 Secondary Net Clinical Benefit Endpoints

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. Also, fatal bleeding will not be a competing risk for the net clinical benefit endpoints containing fatal bleeding.

4.3.3.1 Definition of Secondary Net Clinical Benefit Endpoints

The Secondary Net Clinical Benefit Endpoints are time from first study intervention intake to first occurrence of:

- Composite of ischemic stroke or ISTH major bleeding
- Composite of CV death, all stroke, myocardial infarction or ISTH major bleeding
- Composite of all-cause mortality, disabling stroke, fatal bleeding, symptomatic intracranial hemorrhage

4.3.3.2 Main Secondary Net Clinical Benefit Analytical Approach

The analysis of the secondary net clinical benefit endpoints will follow the principles described for the main analyses of the primary safety endpoint, see Section 4.2.2.2.

4.3.3.3 Sensitivity Secondary Net Clinical Benefit Analyses

No sensitivity analyses are planned for the secondary net clinical benefit endpoints.

4.3.3.4 Supplementary Secondary Net Clinical Benefit Analyses

The supplementary analysis of the secondary net clinical benefit endpoints will follow the principles for the supplementary analyses of the first supplementary analysis of the primary safety endpoint (i.e. Supplemental Safety Estimand 1), see Section 4.2.2.4.

4.4 Exploratory Endpoints Analysis

4.4.1 Definition and Analytical Approach for Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Modified Rankin Scale (mRS)
- Ischemic stroke after the first 90 days
- EuroQol Group 5-dimension (EQ-5D) questionnaire.

Descriptive summary statistics for the mRS will be displayed by visit together with a categorical summary of the mRS and a graphical display by bar charts. The number and percentage of participants with an mRS of 0-2 and 3-6, as well as 0-1 and 2-6, will be displayed in addition. At Month 3 (Visit 4), the distribution of scores on the modified Rankin scale will be compared between the two treatment groups by an ordinal logistic regression model with treatment and stratification factor as covariates. The common odds ratio together with its 95% confidence interval will be displayed. In case a participant died prior to his or her Month 3 assessment, a mRS of 6 will be imputed for the analysis. In case a participant did not die prior to the Month 3 visit but does not have a mRS for Month 3 then the latest available mRS prior to Month 3 will be used. In both cases the latest mRS prior to day 98 (the upper limit of the expected visit time) will be chosen for the imputation.

To derive the common odds ratios and the corresponding confidence intervals, SAS program code corresponding to the following will be used:

```
ODS OUTPUT OddsRatios=OddsRatios;

PROC LOGISTIC DATA=<dataset>;
   CLASS trtgrpn dapt;
   model aval = trtgrpn dapt;
   oddsratio trtgrpn;
run;


/*
where
dataset  = name of dataset including mRS at Month 3
trtgrpn  = variable coding randomized antithrombotic treatment group
dapt     = binary strata, planned use of dual antiplatelet therapy with
           ASA and P2Y12i (=1) vs. no planned use of dual antiplatelet
           therapy with ASA and P2Y12i (=0)

alpha has been set as 0.05 in this example

*/
```

The analysis for ischemic strokes after the first 90 days will only include participants still in the study at Day 90, who were without an ischemic stroke and without a competing risk until Day 90. For those participants, the Day 1 will be redefined to Day 91 after randomization and the relative day of an ischemic stroke or a competing risk will be derived in reference to Day 90. The csHRs, as well as the sdHRs and their associated confidence intervals comparing participants assigned to asundexian versus placebo will be displayed together with the cumulative incidences as for the primary efficacy analysis. It has to be noted that this subgroup is not a randomized one and might be affected by any treatment effect.

The health state index values derived from the EQ-5D descriptive system will be analyzed separately to support health economic evaluations. For the CSR, a categorical summary of the EQ-5D questions will be produced by visit together with summary statistics for the VAS score also by visit. The EQ-5D VAS will be analyzed using a mixed model for repeated measures (MMRM) analysis including change from baseline in EQ-VAS score as a dependent variable, visit as a fixed repeated effect, interaction between visit and study treatment, and baseline EQ-VAS score, study intervention and the stratification factor as covariates. The mean and standard deviation of the change from baseline in EQ-VAS from the MMRM model will be plotted over time.

4.4.2 Definition and Analytical Approach for Exploratory Safety Endpoints

The exploratory safety endpoints are time to first occurrence from first intake of study intervention of:

- Gastrointestinal bleeding
- BARC type 3 and 5 bleeding
- BARC type 2, 3 and 5 bleeding
- BARC type 1 and 2 bleeding

The analysis of the time to event exploratory safety endpoints will follow the principles described for the main and supplementary analyses of the primary safety endpoint, see Section 4.2.2.2 and Section 4.2.2.3.

The number of participants with more than one ISTH major bleeding event will be displayed by a categorical frequency table. Number of participants with more than one bleeding event will be counted while alive and exposed to treatment and displayed using the SAF.

Bleeding sites for gastrointestinal bleedings will be summarized with a frequency table.

4.4.3 Definition and Analytical Approach for Exploratory Net Clinical Benefit Endpoint

The exploratory net clinical benefit endpoint is:

- Total number of hospitalizations due to efficacy or safety outcome events

The total number of hospitalizations per participant will be displayed by means of descriptive statistics and a categorical (0, 1, 2, 3, 4, 5-6, 7-9, ≥10) frequency table. On-treatment hospitalizations will be compared using the SAF and on-study hospitalizations will be compared using the FAS. Only hospitalizations reported on or after randomization will be included, while also excluding hospitalizations reported for medical history or the index event.

- On–study hospitalizations are defined as hospitalizations starting on the day of randomization or after randomization until last scheduled visit.
- On-treatment hospitalizations are defined as hospitalizations from first intake of study intervention up until 2 days after last intake of study intervention.

4.5 Other Safety Analyses

4.5.1 Extent of Exposure

Treatment duration will be defined as the number of days from the day of first study intervention intake up to and including the day of last study intervention intake, ignoring temporary study invention interruptions, and will be summarized using descriptive statistics by study arm and overall.

$$\begin{aligned}\text{Treatment duration} \\ &= \text{Date of last intake of study intervention} \\ &- \text{Date of first intake of study intervention} + 1 \text{ day}\end{aligned}$$

The treatment dose of asundexian or placebo will be summarized as the average dose in mg per day using descriptive statistics by study arm and overall. Placebo will be imputed as 0 mg per dose. In addition, the treatment dose for asundexian or placebo will be categorized into 4 groups, ≤ 5 mg, >5 to 25 mg, >25 to 55 mg and >55 mg and will be summarized by study arm and overall.

The compliance (as percentage) will be calculated as:

$$\frac{100 \times Number\ of\ tablets\ taken}{Number\ of\ planned\ tablets}$$

The number of planned tablets is calculated as:

$$\begin{aligned}&(\text{days from randomization to last intake of study intervention} + 1) \times \\ &< \text{number of planned tablets per day} >\end{aligned}$$

All tablets, including the placebo tablets, will be counted. For participants who withdraw prematurely from the study intervention, compliance will be calculated up to the time of last dose. Compliance values will be reviewed for plausibility and extreme values (e.g. > 200 %) may be adjusted. For example, if bottles are not returned then assuming all dispensed tablets were taken could lead to implausibly large compliance values. In this study tablets not returned can be recorded as lost if not taken so it is hoped compliance values will be in a plausible range; however a review will be done to check this.

The compliance for asundexian/placebo will be summarized descriptively by study arm and overall. In addition, percent of compliance will be categorized into 3 groups, < 80%, ≥80 to 120%, and >120 %, and the categories will be summarized by study arm and overall.

4.5.2 Adverse Events

All adverse events (AEs) will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA, the current version at the time of analysis) preferred terms (PTs) grouped by system organ class (SOC).

Study procedure-related (S)AEs recorded prior to start of study intervention will be considered as pre-treatment AEs. AEs that occurred or worsened after the first dose of study intervention up to 2 days after the last dose of study intervention will be considered as

treatment-emergent AEs (TEAEs). In cases of uncertainty due to partial dates, the worst-case approach will be applied, i.e., the AE will be classified as treatment emergent.

AEs that started 3 days or later after last dose will be considered as post-treatment AEs. Determination of whether an event is treatment-emergent will be derived after the missing or incomplete AE start date is imputed. Imputation rules for missing and incomplete AE start data are described in Section 4.1.1.12.

AEs starting before first administration of study intervention but worsening at or after the date of first study intervention and before or at the date of last study intervention + 2 days will be considered as two events, a pre-treatment AE and a TEAE. The pre-treatment AE will stop at the time of worsening and the new TEAE will start at the time of worsening. Same applies in case an AE starts at or after the date of first study intervention, but before the date of last study intervention + 2 days and worsens afterwards, then e.g. leading to a TEAE and a post-treatment AE.

Reasons for worsening of an AE:

- AE intensity/grade is worsened (e.g.: moderate to severe)
- AE changed to a serious event
- AE ends with death
- AE changed to drug-related

In case of premature permanent discontinuation of study intervention, (S)AE reporting is not required after the participant's early termination follow-up visit (see Section 7 of the protocol for further details), therefore there may be safety and efficacy outcome events that are not reported as AEs.

Certain disease-related events (DREs) do not need to be reported as AEs but are documented as efficacy outcome events, regardless of when they occurred, see Section 4.1.1.9 for summary definition and Section 8.4.6 of CSP for detailed definition.

Overall summaries of the number of participants with any AEs, pre-treatment AEs, TEAEs, and post-treatment AEs will be generated by study arm and overall.

The number of participants with

- post-treatment AEs,
- SAEs,
- TEAEs,
    - study intervention-related TEAEs,
    - acetylsalicylic acid related and other antiplatelet therapy related TEAEs,
    - TEAEs resulting in premature or permanent discontinuation of study intervention,
    - TEAEs by maximum intensity,
    - study intervention-related TEAEs by maximum intensity,
- non-serious TEAEs,
- serious TEAEs,
    - study intervention-related serious TEAEs,

  - acetylsalicylic acid related and other antiplatelet therapy related serious TEAEs,
  - serious TEAEs resulting in discontinuation of study intervention,
- hemorrhagic TEAEs
- AEs with fatal outcome, and
- TEAEs with fatal outcome

will be summarized by study arm and overall using PTs grouped by SOC. Listings of serious TEAEs, AEs with fatal outcome, and deaths not attributed to AEs will be provided.

Hemorrhagic TEAEs will be identified by the SMQ "Haemorrhages".

In case of events with different intensity within a participant, the maximum reported intensity will be used. If intensity is missing, the event will be considered as severe. If the same event is reported as both unrelated and related to the study intervention within a participant, the event will be considered as related to study intervention. If the study intervention relationship is missing, the event will be considered as being related to the study intervention.

4.5.3 Additional Safety Assessments

4.5.3.1 Laboratory Data

The number of participants with treatment-emergent high or low abnormal laboratory values will be summarized for each laboratory parameter by study intervention arm and overall. For summaries of abnormal laboratory values the measurements from both scheduled / unscheduled visits, as well as measurements from both central and local laboratory will be considered.

Continuous laboratory parameter values (from Table 10-1 of the protocol) including the change from baseline will be summarized by visit and by study arm and overall. For the by visit laboratory parameter summaries the measurements from scheduled visits and the central laboratory will be considered.

Central laboratory data is defined as data from Lab with LBNAME = "Labcorp".

If for laboratory parameters results are reported as below or above a quantification limit (i.e. if LBSTRESC starts with a "<" or ">") then the respective numerical value of the quantification limit will be used and the DTYPE will be set to "LLOQ" or "ULOQ" respectively.

The laboratory parameter eGFR from the central lab will be derived based on the CKD-EPI formula [12] with the exception for sites from Japan. For Japanese sites, a Japanese Equation formula [13] will be used. For the statistical analyses, eGFR derived from both formulas will be analyzed together.

4.5.3.2 Vital Signs

Vital sign (systolic and diastolic blood pressure, heart rate) values including the change from baseline will be summarized by visit and by study arm and overall.

4.5.3.3 Electrocardiogram

The number of participants with abnormal electrocardiograms findings at baseline will be summarized by primary diagnostic category.

4.5.3.4 Analyses of liver events according to protocol

For adverse events that meet the criteria of a liver event according to Section 10.2.2 of the CSP, overall summaries of the number of participants with any AEs, TEAEs, and post-treatment AEs will be generated by study intervention arm and overall. The number of participants with any AE, TEAEs, study intervention-related TEAEs, TEAEs resulting in discontinuation of study intervention, TEAEs by maximum intensity, study intervention-related TEAEs by maximum intensity, SAEs, serious TEAEs, study intervention-related serious TEAEs, serious TEAEs resulting in discontinuation of study intervention, AEs with fatal outcome, and TEAEs with fatal outcome and post-treatment AEs will be summarized by study arm and overall using PTs grouped by SOC.

The adverse event summaries above, except for TEAE by maximum intensity and study intervention-related TEAEs by maximum intensity, will be repeated for the subgroups of participants who had

a) normal ALT and AST laboratory values at baseline (≤ ULN)

b) at least one abnormal (>ULN) ALT or AST laboratory value at baseline.

In addition, AEs who meet the criteria of a liver event will be listed. Separate listings will be created for participants according to a) and b).

Adverse events that meet the criteria of a liver event according to the protocol will be identified according to the documentation status in the eCRF (i.e. if a liver event was reported in the respective eCRF form) and will not be reprogrammed.

The cumulative incidence risk for treatment-emergent AEs and study-intervention related TEAEs will be estimated using Aalen-Johansen estimators and will be reported by figures displaying cumulative incidence curves and by tables containing the cumulative probabilities at selected timepoints and their 95% CIs.

Individual patient profile plots will be generated showing adverse events, liver values and co-medication information for participants with a reported liver event in the eCRF or for participants which qualify as a potential Hy's law cases (Total bilirubin ≥ 2×ULN and AST or ALT ≥ 3×ULN).

4.5.3.5 Screening and analyses of potential drug-induced liver injuries

The reports in (1) to (8) below will be repeated 3 times for the following sets of participants.

a) All participants in the SAF with at least one safety laboratory measurement after start of study intervention

b) As (a) plus with normal (≤ ULN) ALT and AST laboratory values at baseline

c) As (a) plus with at least one abnormal (> ULN) ALT or AST laboratory value at baseline.

For summaries b) and c), potential events will only be considered if the participants also reported a liver event according to Section 10.2.2 of the CSP.

The measurements from both scheduled / unscheduled visits, repeated assessments on the same day, as well as measurements from both central and local laboratory will be considered, unless otherwise specified.

1) Hepatocellular DILI screening plot (total bilirubin × ALT or AST): Each participant is plotted based on their maximum total bilirubin (y-axis) and transaminase (x-axis, ALT or AST, whichever is higher). Concurrent elevations, where concurrent is defined as total bilirubin elevation occurring on or within 30 days after the maximum transaminase elevation, will be highlighted. Dashed lines represent total bilirubin and transaminase cut-offs of 2×ULN and 3×ULN, respectively.

   For participants with maximum concurrent total bilirubin ≥ 2xULN and transaminase ≥ 3xULN a listing of adverse events will be displayed.

2) Cholestatic DILI screening plot (total bilirubin × AP): Each participant is plotted based on their maximum total bilirubin (y-axis) and AP (x-axis). Concurrent elevations, where concurrent is defined as total bilirubin elevation on or within 30 days after the AP elevation, will be highlighted. Dashed lines represent total bilirubin and AP cut-offs of 2×ULN and 2×ULN, respectively.

   For participants with maximum concurrent total bilirubin ≥ 2xULN and AP ≥ 2xULN a listing of adverse events will be displayed.

In addition, the following summary will be provided:

3) Number of participants with potential hepatocellular DILI by study intervention arm: Provide number of participants in each quadrant of hepatocellular DILI screening plot.

   - Total bilirubin ≥ 2×ULN and any transaminase value ≥ 3×ULN
   - Total bilirubin ≥ 2×ULN and all transaminase values < 3×ULN
   - Total bilirubin < 2×ULN and any transaminase value ≥ 3×ULN

4) Number of participants with potential cholestatic DILI by study intervention arm: Provide number of participants in each quadrant of cholestatic DILI screening plot.

   - Total bilirubin ≥ 2×ULN and AP ≥ 2×ULN
   - Total bilirubin ≥ 2×ULN and AP < 2×ULN
   - Total bilirubin < 2×ULN and AP ≥ 2×ULN

5) Incidence and exposure-adjusted incidence rate (EAIR) of the worst treatment-emergent hepatic laboratory value will be provided by the following laboratory parameters with category:

   - ALT: > 2×ULN, > 3×ULN, > 5×ULN, > 8×ULN, >10×ULN, >20×ULN
   - AST: > 2×ULN, > 3×ULN, > 5×ULN, > 8×ULN, >10×ULN, >20×ULN
   - Total bilirubin: > 2×ULN
   - AP: ≥ 1.5×ULN
   - gamma GT: ≥ 2×ULN

6) Incidence and exposure-adjusted incidence rate (EAIR) of treatment emergent biochemical triggers based on upper limit normal value will be provided by the following laboratory parameters with category:

   - ALT >3× ULN or AST >3× ULN
   - ALT >5× ULN or AST >5× ULN

- ALT >8× ULN or AST >8× ULN
- ALT >10× ULN or AST >10× ULN
- ALT >20× ULN or AST >20× ULN
- ALT >3× ULN or AST >3× ULN and total bilirubin ≥ 2× ULN
- AP ≥ 2 ULN and total bilirubin ≥ 2× ULN

For criteria of ALT or AST / AP and total bilirubin, elevation can occur at different timepoints and the first assessment contributing to the event will be considered for derivation of EAIR.

7) Incidence and EAIR of treatment emergent biochemical triggers based on baseline value (BL) will be provided by the following laboratory parameters with category:

- ALT >3× BL or AST >3× BL and total bilirubin >2× BL
- ALT >3× BL or AST >3× BL
- ALT >5× BL or AST >5× BL
- ALT >2× BL or AST >2× BL with total bilirubin > 2× BL and > ULN
- AP >2× BL and > ULN with total bilirubin > 2× BL and > ULN

If measurements are elevated compared to baseline, but they are still within the normal range, these measurements will not be considered for the analysis.

8) Incidence and EAIR will be provided for TEAE with Standardized MedDRA Queries (SMQ) 'Drug related hepatic disorders - comprehensive search'

Summary 5) will be repeated considering only participants from SAF with abnormal ALT, AST, total bilirubin or AP respectively, summarizing based on baseline values (BL) instead of ULN:

- ALT: > 2×BL, > 3× BL, > 5× BL, > 8× BL, > 10× BL, >20× BL
- AST: > 2×BL, > 3× BL, > 5× BL, > 8× BL, > 10× BL, >20× BL
- Total bilirubin: > 2×BL
- AP: ≥ 1.5×BL.

If measurements are elevated compared to baseline, but they are still within the normal range, these measurements will not be considered for the analysis.

Summary 8) will be repeated considering only participants from SAF with at least one elevated baseline AST, ALT, TB or AP.

The EAIR is derived by dividing the sum of the number of participants with specific events during their exposure time by the total exposure-time at risk of all participants in 100 years. The exposure-time at risk for a participant is the sum of the days from start of study intervention until the minimum of (the last date of treatment-emergent period, death date, first date of specific event) in days divided by 365.25*100. For criteria of ALT or AST / AP and total bilirubin, elevation can occur at different timepoints and the first assessment contributing to the event will be considered for derivation of EAIR.

100× (1-α) % confidence limit for EAIR is derived as follows

Lower confidence limit

$$CI_l = \frac{\chi^2_{2Y,\alpha/2}}{2 \times (total\ exposure\ time/(365.25 \times 100))}$$

Upper confidence limit

$$CI_u = \frac{\chi^2_{2Y,1-\alpha/2}}{2 \times (total\ exposure\ time/(365.25 \times 100))}$$

Where Y is the observed number of events and $\chi^2_{h,\alpha}$ is the α quantile of the chi-squared distribution with h degrees of freedom.

Risk difference with 95% confidence intervals will be provided, if appropriate. The unstratified Miettinen and Nurminen method [9] will be used for 95% CI for risk difference.

4.6 Other Analyses

4.6.1 Pharmacokinetics

The PK analyses will be presented separately from the CSR and will be described in a separate analysis plan.

4.6.2 Pharmacodynamics

The pharmacodynamic analyses will be presented separately from the CSR and will be described in a separate analysis plan.

4.6.3 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 of the protocol for details.

4.6.4 Biomarkers

Blood sampling for exploratory biomarker analyses might be done only in a subset of study sites and biomarker analyses will be presented separately from the CSR and will be described in a separate analysis plan.

4.6.5 Subgroup analyses

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

The following subgroups are considered to be potentially prognostic and predictive for efficacy or safety outcome events:

- Stroke subtype of index event by TOAST classification (large artery atherosclerosis, lacunar stroke (small vessel occlusion), other determined etiology, undetermined etiology).
- The criteria of inclusion criterion 3 related to atherosclerosis and non-lacunar stroke:

- Medical history or vascular imaging evidence of atherosclerosis (Yes/No)
- Brain imaging demonstrating an acute non-lacunar infarct (Yes/No/no imaging done)

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: planned dual antiplatelet therapy with ASA and a P2Y12 inhibitor (Yes/No)
- Type of index event (non-cardioembolic ischemic stroke/high-risk TIA)
- Age Group (<65 years, 65 – 75 years, >75 years)
- Weight (<60, 60-90, >90 kg)
- Sex (male/female)
- Region (North America/South America/Western Europe, Australia and Israel/Eastern Europe/Asia)
- Body mass index (<25, ≥25 to <30, ≥30 kg/m^2)
- Race (White, Asian, Black, other)
- eGFR (<15, 15-<30, 30-<60, 60-90, >90 mL/min/1.73m^2)
- History of stroke or TIA prior to index event (Yes/No)
- NIHSS score of index event at randomization (≤3, 4-7, ≥8)
- NIHSS score of index event at presentation (≤3, 4-7, ≥8)
- mRS score of index event at Day 7 (0-2, ≥3)
- Intravenous Thrombolysis for index stroke and/or Endovascular therapy for index stroke (Intravenous Thrombolysis only/ Endovascular therapy only/ Intravenous Thrombolysis and endovascular therapy/ None)
- Hypertension prior to randomization (Yes/No)
- Diabetes prior to randomization (Yes/No)
- Fragility of participant (fragile (age > 75 years and eGFR < 60 mL/min/1.73m^2) vs. non-fragile (age ≤ 75 years or eGFR ≥ 60 mL/min/1.73m^2))

If the number of participants is too small within a subgroup, then the subgroup categories may be redefined prior to unblinding the study.

Exploratory subgroups

Additional exploratory subgroups (utilized for the primary efficacy and safety estimands) are

- Age Group (<65 years, 65 – 75 years, 76 – 84 years, >84 years)
- Weight (≤50, >50 - ≤70, >70 - ≤90, >90 - ≤110, >110 kg)
- Anemia at baseline (Hemoglobin (< 13 g/dL in men or < 12 g/dL in women) vs. (≥13 g/dL in men or ≥ 12 g/dL in women)) (Yes/No)

- Treated with a combination of moderate CYP3A inducers and clinical P-gp inducers prior to randomization (Day -1) (yes/no)
- Treated with a combination of moderate CYP3A inhibitors and clinical P-gp inhibitors prior to randomization (Day -1) (yes/no)
- Liver Disease prior to randomization (Day -1) (Yes/No), defined by the SMQ "Hepatic disorders"
- ASA (see Section 6.1.3) use prior to randomization (Day -1) (Yes/No)
- ASA (see Section 6.1.3) use prior to index event (Yes/No)
- $P2Y_{12}$ Inhibitor use prior to randomization (Day -1) (Yes/No)
- $P2Y_{12}$ Inhibitor use prior to index event (Yes/No)
- NSAID use prior to randomization (Day -1) (Yes/No)
- Statin use prior to randomization (Day -1) (Yes/No)
- NIHSS score of index event at randomization (≤5, >5)
- NIHSS score of index event at presentation (≤5, >5)
- Medical history of atherosclerosis (Yes/No)
- Vascular imaging evidence of atherosclerosis (Yes/No/no imaging done)
- Time from index stroke to randomization (≤24 hours; >24 to 48 hours; >48 to 72 hours; >72 hours):, this subgroup is only relevant for participants with a stroke as index event
- Argatorban given within the period from index event (at time of or after index event) to prior to randomization (Day -1) (yes, no)
- Ozagrel or ozagrel sodium taken within the period from index event (at time of or after index event) to prior to randomization (Day -1) (yes, no)
- Argatorban or ozagrel or ozagrel sodium taken within the period from index event (at time of or after index event) to prior to randomization (yes, no)
- Ipsilateral stenosis of index event (>=50%, 1-49%, Aortic arch atherosclerosis, 0%, Uncertain/Unavailable, No ipsilateral stenosis)

$P2Y_{12}$ Inhibitor will be identified based on standardized medication names including either "CLOPIDOGREL", "PRASUGREL" or "TICAGRELOR".

NSAID and statin are defined using the standard drug grouping.

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 [4] 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.

4.7 Interim Analyses

An IDMC is in place that will monitor the risk/benefit on an ongoing basis during the study.

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; 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 of the CSP), the probability to estimate a cause-specific hazard ratio of $\geq$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 an additional 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.

4.8 Changes to Protocol-planned Analyses

No changes to protocol planned analyses have been made. However, there are some additional analyses compared to the protocol. The protocol suggested producing the plot of the log of negative log of estimated survivor functions versus the log of time, this has been updated to a plot of the Schoenfeld residuals. In Section 1.1.2, for the text regarding the intercurrent event strategy for “change in background therapy”, a correction from “primary efficacy events” to “primary safety events” was done compared to the protocol text. In Section 4.6.5, the variables sex and region were added to the list of potential prognostic variables instead of

listing them as neither prognostic nor predictive. Also, two of the predictive and prognostic criteria based on inclusion criterion 3 were combined into one predictive and prognostic subgroup variable, while the two separate criteria were added as exploratory subgroups.

Section 9.1 of the protocol states, “For the primary and secondary safety endpoints, no formal testing is planned and no test problem is stated.” However, Section 9.3.2.2 states, “The primary safety superiority null hypothesis, see Section 9.1, will be tested using a stratified log-rank test”. Section 9.1 is the accurate one and no formal safety hypothesis testing will be performed in this study. The p-values for the safety analyses will be exploratory only.

5. Sample 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 2), a type-I error level of 5% for a two-sided log-rank test, and at a power of least 90% to detect a significant treatment effect, under the assumption that the ‘effective’ hazard ratio (including effects due to treatment discontinuation) is 0.80.

The study will randomize approximately 12300 participants in a 1-to-1 fashion to study intervention, eventually targeting approximately 830 participants with a primary efficacy event and a minimum treatment duration of 90 days leading to a planned duration until CEOT of about 30 months. 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 1.1, 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).

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 in case of lack of efficacy, an interim analysis for futility will be conducted (see Section 4.7).

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

6. Supporting Documentation

6.1 Participant disposition

The number of participants enrolled, randomized and valid for the analysis sets will be summarized for each study site by study intervention arm and overall and by study site.

The number of participants randomized will further be summarized by pooled regions and country or region and by study arm and overall.

The number of sites will be summarized by country.

The number of participants with important protocol deviations and the number of screen failures will be summarized overall and by study arm, country/region and study site.

The number of participants per important deviation category and validity finding will be presented by study arm and overall.

A disposition summary for each study period (intervention period and ET/CEOT period) will be presented summarizing the number of participants starting and completing the respective

study period, the number of participants discontinuing each period and the primary reason for discontinuation. This will be presented overall and for each study arm.

The number of participants completing the overall study will be provided by study intervention arm and overall. See Section 4.1.1.5 for the definition of participants who completed the study.

The number and proportion of participants still in the study by visit will be reported. Similarly, the number and proportion of participants still on-treatment by visit will be reported.

The distribution of time from randomization to the date of last follow-up contact (see Section 4.1.1.5 for date of last contact) for participants in the FAS will be summarized using descriptive statistics. The cumulative incidence risk will be estimated using cause-specific Aalen-Johansen estimator and reported via both figure displaying the cumulative incidence curves and table containing the cumulative probability for the relative days and its 95% CI.

For the time in study follow-up, the competing risks "death" and "lost to follow-up/withdrawal of consent" will be accounted for.

In addition, the duration of study intervention (treatment), treatment interruptions (= number of days study intervention interrupted / days from first intake of study intervention to last intake of study intervention) and duration of follow up will be reported using standard summary statistics.

Other details regarding visit adherence (e.g., visit completed in person, by telephone, through third party) and completion may be summarized using frequency tables by visit and study intervention group.

6.1.1 Demography and other baseline characteristics

Demographic and baseline data as collected in the CRF will be evaluated descriptively for the FAS, by study arms and overall. In the case that the FAS is a different subgroup of participants to the SAF a subset of tables may be repeated on the SAF. No statistical tests will be performed to compare these characteristics across study arms.

Demographic variables include sex, race, ethnicity, age, weight, height, body mass index (BMI) and tobacco / nicotine use (never, former, current), and planned antiplatelet therapy as per stratification, while baseline characteristics include TOAST classification, NIHSS of index event at presentation at hospital, at time of randomization and at Day 7 after the index event, modified Rankin Scale, brain and vascular imaging results, and time from index event to randomization.

Demographics and baseline characteristics will also be displayed by planned dual antiplatelet therapy (as per stratification) with ASA and a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor) (Yes/No).

The baseline categories used for subgroup analysis (see Section 4.6.5) will be displayed as part of the demographics and baseline characteristics.

In addition, the following variables will be displayed:

- Moderate renal dysfunction with eGFR 30-59 ml/min/1.73m^2 (yes/no)
- Chronic Kidney Disease (yes/no)

- Coronary Artery Disease (yes/no)
- Peripheral Artery Disease (yes/no)
- Crushed study intervention taken at any timepoint (yes, no)
- Application of study intervention via feeding tube at any timepoint (yes, no)
- Concomitant cilostazol taken for at least one day within the treatment period (yes, no)
- Concomitant prasugrel taken for at least one day within the treatment period (yes, no)
- Medical history of atherosclerosis (Yes/No)
- Vascular imaging evidence of atherosclerosis (Yes/No/not done)
- Hemorrhagic transformation of index stroke (Yes/No)
- Brain imaging (CT scan only; MRI only; CT scan and MRI)
- Vascular imaging (done/not done)
- Time from index event to randomization (≤24 hours; 24 to 48 hours; 48 to 72 hours; >72 hours)
- Intravenous Thrombolysis for index stroke (Yes/No)
- Endovascular therapy for index stroke (Yes/No)
- Intravenous Thrombolysis for index stroke and/or Endovascular therapy for index stroke (Intravenous Thrombolysis only/ Endovascular therapy only/ Intravenous Thrombolysis and endovascular therapy/ None)

Results from the vascular and brain imaging procedures, as well as the Heidelberg bleeding classification of hemorraghic transformations of the index event will be displayed descriptively.

6.1.2 Medical history

Medical history data will be evaluated by frequency tables, showing the number and percentage of participants with medical history findings (i.e., previous diagnoses, diseases or surgeries) using MedDRA Primary System Organ Class / Preferred Term. This frequency table will be produced for all findings and for findings that are considered relevant for the participant's study eligibility. The medical history of interest will be defined in the following way:

Medical history of interest	Selection criteria
Aortic arteriosclerosis	*Aortic arterosclerosis (PT) excluding lower level term 'Aortic sclerosis' and 'Aortic calcification'*
Cardiac failure chronic	Cardiac Failure (MLG)

Carotid artery stenosis	Carotid artery stenosis: Carotid artery stenosis (PT) or carotid endarterectomy (PT) or carotid artery stent insertion (PT)
Carotid artery stent insertion	Carotid artery stent insertion (PT)
Carotid endarterectomy	Carotid enarterectomy (PT)
Cerebrovascular accident	ischemic CNS vascular conditions SMQ + PT sub selection list*
Chronic kidney disease	Renal failure chronic (MLG)
Coronary artery bypass	Coronary artery bypass graft (PBMQ)
Coronary artery disease	Coronary Artery disease: Coronary Artery disease (PT) or Unstable Angina (PT) or MI (MLG) or coronary artery bypass graft (PBMQ) or percutaneous coronary intervention (PBMQ)
Diabetes mellitus	Diabetes Mellitus (PT)
Gastrointestinal haemorrhage	Gastrointestinal tract hemorrhage (MLG)
Hyperlipidaemia	Hyperlipidemia (MLG)
Hypertension	Hypertension (SMQ, narrow scope)
Myocardial infarction	Myocardial infarction (MLG)
Percutaneous coronary intervention	Percutaneous Coronary intervention (PBMQ)
Peripheral arterial occlusive disease	Peripheral arterial disease (PBMQ)
Transient ischaemic attack	Transient ischemic attack (PT)

* For Cerebrovascular accident following PTs will be selected: Subcortical stroke, Cortical hand stroke, Vertebrobasilar infarction, Parietal lobe stroke, Thalamic stroke, Occipital lobe stroke, Claude's syndrome, Cerebral infarction foetal, Cerebellar infarction, Cerebral ischaemia, Cerebrovascular accident, Cerebral infarction, Brain stem infarction, Middle cerebral artery stroke, Lateral medullary syndrome, Embolic stroke, Embolic cerebellar infarction, Internal capsule infarction, Spinal stroke, Vertebrobasilar stroke, Cerebellar stroke, Lacunar stroke, Perinatal stroke, Basal ganglia stroke, Cerebral septic infarct, Basal ganglia infarction, Brain stem stroke, Thrombotic cerebral infarction, Post procedural stroke, Thalamic infarction, Ischaemic cerebral infarction, Ischaemic stroke, Embolic cerebral

infarction, Stroke in evolution, Spinal cord infarction, Migrainous infarction, Lacunar infarction, Spinal cord ischaemia, Thrombotic stroke.

6.1.3 Prior and concomitant medication

For prior and concomitant medications, the following definitions apply:

- Prior medication: Medication taken before start of the study intervention intake, (regardless of when it ended).
- Concomitant medication: Medication taken during treatment period, i.e., between first and last study intervention intake (regardless of when it started or ended).

Prior and concomitant medication will be coded to Anatomical Therapeutic Chemical (ATC) classification codes according to the World Health Organization Drug Dictionary (WHO-DD, current version at the time of analysis). It is expected that the standard and Bayer drug groupings (SDG and BDG) will be used to identify some categories of medications, e.g. antiplatelet therapy. The number of participants taking prior and concomitant medication will be presented by study arm and overall using ATC classes and subclasses. The prior medications will be reported for the FAS and the SAF, but the concomitant medications for the SAF only. The concomitant medication table will be repeated including prohibited medications only.

The use of ASA for antiplatelet therapy will be distinguished from other indications based on the dosage. ASA doses ≤325 mg/d will be included as ASA for antiplatelet therapy ; ASA doses above as ASA for other indications.

The number of participants with Standard of Care background treatment of antiplatelet therapy will be summarized for ASA, Clopidogrel (and Clopidogrel with ASA for antiplatelet therapy), Dipyidamole (and Dipyidamole with ASA) and Cilostazol (and Cilostazol with ASA) for the following timepoints: ongoing at randomization, prior to index event, Day 1, Day 90, Day 180 and 6 monthly thereafter, end of treatment. The duration (in days) of standard of care background treatment will also be summarized.

Tables in similar format to the concomitant medication table will be produced for the SAF and the three sets of medications below:

- ongoing prior/concomitant medication at start of study intervention (medications stopping on day of first intervention will be excluded),
- concomitant medication started during the treatment period (medications starting on the first day of intervention are included, but medications starting on the last day of study intervention are excluded).
- medications that started after stop of study intervention (medications starting on the last day of study intervention will be included).

Separate tables will be provided for anticoagulants, antiplatelet therapy used and for CYP3A inhibitors and inducers for the SAF. These tables will be repeated for ongoing at start of treatment period, started during treatment period and started after treatment period.

6.1.4 Drug groupings

Medications of interest are identified by using Drug Groupings and Bayer DTOIs.

There, Antiplatelet therapies are identified as “Platelet aggregation inhibitors, excluding heparin”. Anticoagulants are “Antithrombotic vitamin K antagonists”, “Antithrombotic direct-acting thrombin inhibitors”, “Other antithrombotic drugs”, “Antithrombotic direct-acting factor Xa inhibitors”, “Antithrombotic low molecular weight heparins (LMWH) and heparinoids “, “Other antithrombotic heparins “.”, ASA is “Acetylsalicylic acid and its salts”. CYP3A inhibitors are “Weak CYP3A inhibitors”, “Moderate CYP3A Inhibitors”, “Strong CYP3A4 inhibitors”. CYP3A Inducers are “Weak CYP3A inducers”, “Moderate CYP3A inducers”, “Strong CYP3A4 inducers”. P-gp inducers and inhibitors are “Clinical P-gp inducers”, “Clinical P-gp inhibitors”.

7. References

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8. Appendix

8.1 Intercurrent events

The handling of intercurrent events is described in the respective efficacy and safety sections of the SAP. Treatment policy, while alive and while on treatment are proposed as strategies to handle the intercurrent events, for which the actual intercurrent event does not necessarily need to be identified (i.e. if not considered as an event for competing risk). In addition, it is planned to further summarize the number of participants with intercurrent events as well as

the timing of the intercurrent events. This section describes how each intercurrent event and its timing will be identified.

Change in background therapy

Based on the concomitant medications as reported by the investigator and considering the start and end dates of these concomitant medications (after imputation for incomplete dates), the intake of each antiplatelet therapy (aspirin, clopidogrel, prasugrel, cilostazol. dipyridamole and ticagrelor) will be identified for each study day from randomization onwards. To avoid changes due to acute treatment of the index event, stable antiplatelet therapy is considered after 7 days from randomization. From Day 8 onwards, if a previously taken medication is stopped or when an additional antiplatelet therapy is initiated, this will be identified as the respective intercurrent event for change in background therapy. The first date where a medication is discontinued, or a new therapy is initiated will be considered as the event date for the intercurrent event of change in background therapy.

If the established background therapy at Day 7 results in a dual antiplatelet therapy, a change to single antiplatelet therapy is expected between 3 weeks and 3 month. Therefore, only the second change in background therapy will be considered as an intercurrent event.

Changes within single or dual antiplatelet therapy will not be considered as change in background therapy.

Changes in therapy (i.e. discontinuation of assigned treatment and initiation of indicated therapy) due to a diagnosis requiring continuous anticoagulation

To identify this intercurrent event, all participants who have discontinued the study treatment due to AEs will be identified. If for these participants in addition an anticoagulation medication is initiated within 7 days on or after the treatment end date, the respective treatment discontinuation will be considered for the intercurrent event of changes in therapy due to a diagnosis requiring anticoagulation. The respective treatment end date will be considered as the event date of the intercurrent event.

Early discontinuation of assigned treatment

This intercurrent event will include all premature treatment discontinuations, except for those that are counted for the intercurrent event of changes in therapy due to a diagnosis requiring anticoagulation or which occur after the respective event of interest. The treatment end date will be considered as the event date of the intercurrent event.

Death

The death date of a participant will be considered as the intercurrent event date.

Intercurrent events related to a significant trial-continuity issue

This intercurrent event will be monitored but as the impact would ultimately result in a treatment discontinuation, it will not be separately analyzed.

Multiple intercurrent events on one day

If more than one intercurrent event happens on the same day, the order of events in the tables will be arbitrary (e.g. alphabetical order) except death, which is the last event to happen.