Document Type:	Statistical Analysis Plan
Official Title:	A multicenter, international, randomized, active comparator-controlled, double-blind, double-dummy, parallel group, 2-arm Phase 3 study to compare the efficacy and safety of the oral FXIa inhibitor asundexian (BAY 2433334) with apixaban for the prevention of stroke or systemic embolism in male and female participants aged 18 years and older with atrial fibrillation at risk for stroke
NCT Number:	NCT05643573
Document Date:	08-Feb-2024

Title Page

Protocol Title: A multicenter, international, randomized, active comparator-controlled, double-blind, double-dummy, parallel group, 2-arm Phase 3 study to compare the efficacy and safety of the oral FXIa inhibitor asundexian (BAY 2433334) with apixaban for the prevention of stroke or systemic embolism in male and female participants aged 18 years and older with atrial fibrillation at risk for stroke

Protocol Number: 19767

Compound Number: Asundexian (BAY 2433334)

Short Title: Phase 3 study to investigate the efficacy and safety of the oral factor XIa (FXIa) inhibitor asundexian (BAY 2433334) compared with apixaban in participants with atrial fibrillation at risk for stroke (OCEANIC-AF)

Sponsor Name: Bayer AG

Legal Registered Address:

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Regulatory Agency Identifier Number(s):

Registry	ID
IND	141805
EudraCT	2022-000758-28

Date: 08 FEB 2024

Version: 2.0

Statistical Analysis Plan template version: 4.0

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.
The approval of the Statistical Analysis Plan is documented in a separate signature document.

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Version History

This Statistical Analysis Plan (SAP) for Study 19767 is based on the protocol Version 1.0 dated 01 SEP 2022.

SAP Version	Date	Change	Rationale
1.0	01 DEC 2022	Not applicable	Original version
2.0	08 FEB 2024	See change log	Final version

List of Abbreviations

AE	Adverse Event
AF	Atrial fibrillation
AG	Joint stock company*, Aktiengesellschaft*
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
ATC	Anatomical Therapeutic Chemical
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
BARC	Bleeding Academic Research Consortium
BAS	Biomarker analysis set
BDG	Bayer Drug Grouping
BID	Twice a day*, Bis in die*
BMI	Body mass index
CABG	Coronary artery bypass graft
CEC	Clinical Events Committee
CEOT	Common End of Treatment
CHADS2	Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke or transient ischemic attack
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products
CRF	Case report form
CRNM	Clinically relevant non-major
CRP	C-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical study report
csHR	Cause-specific hazard ratio
CV	Cardiovascular
DCT	Decentralized clinical trial
DRE	Disease-related event
DTOI	Drug Topics Of Interest
EAIR	Exposure-Adjusted Incidence Rate
e.g.	For example, *exempli gratia*
EC	Executive Committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ePRO	Electronic Patient Reported Outcomes
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
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISTH	International Society on Thrombosis and Hemostasis
M	Month
MCDA	Multi-criteria Decision Analysis
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction

mRS	Modified Rankin Scale
N	Total number of participants
NJ	New Jersey
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)
PKS	Pharmacokinetic analysis set
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
SSRI	Selective serotonin reuptake inhibitors
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
TIA	Transient ischemic attack
ULN	Upper limit of normal
US / USA	United States / United States of America
VAS	Visual Analog Scale
vs.	As compared to, versus
W	Week
WHODrug / WHODrug Global	WHODrug Dictionary is an international classification of medicines created by the WHO Programme for International Drug Monitoring, managed by the Uppsala Monitoring Centre, and licensed at Bayer as subscription service called WHODrug Global.

1. Introduction

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

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

1. Prevention of stroke and systemic embolism in patients with atrial fibrillation (AF) (cardioembolic stroke prevention).
2. CCI [redacted]

OCEANIC-AF (study 19767) will be an event-driven Phase 3 study (expected treatment duration of 9-33 months; refer to Section 5 for more details) and will test asundexian against apixaban, a FXa inhibitor (NOAC), in participants with AF.

CCI [redacted]

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

On 19 November 2023, the sponsor followed a recommendation of the IDMC to stop the study early due to lack of efficacy. Therefore, all analyses are of exploratory nature.

1.1 Objectives, Endpoints, and Estimands

Objectives and endpoints (primary, secondary and exploratory) are reported in Table 1-1.

Table 1-1: Study objectives and endpoints

Objectives	Endpoints
Primary	
Efficacy	
To demonstrate that asundexian is superior (at least non-inferior) when compared with apixaban for prevention of stroke and systemic embolism in participants with atrial fibrillation at risk for stroke	• Composite of stroke or systemic embolism*
Safety	
To demonstrate that asundexian is superior to apixaban as assessed by ISTH major bleeding in participants with atrial fibrillation at risk for stroke	• ISTH major bleeding*
Net clinical benefit	
To demonstrate that asundexian is superior to apixaban with respect to benefit and risk	• Composite of stroke, systemic embolism, or ISTH major bleeding*

Objectives	Endpoints
Secondary	
Efficacy	
To compare the effects of asundexian and apixaban with respect to composite and individual efficacy endpoints	• Composite of ischemic stroke, or systemic embolism* • All-cause mortality* • Ischemic stroke* • CV death* • Composite of CV death, stroke, or myocardial infarction*
Safety	
To compare asundexian and apixaban with respect to composite and individual bleeding endpoints	• Composite of ISTH major or clinically relevant non-major bleeding* • Clinically relevant non-major bleeding* • Hemorrhagic stroke* • Intracranial hemorrhage* • Fatal bleeding* • Minor bleeding*
Net clinical benefit	
To compare the benefit and risk of asundexian and apixaban with respect to a composite of efficacy and safety endpoints	• Composite of stroke, systemic embolism, ISTH major bleeding, or all-cause mortality* • Composite of disabling stroke (mRS ≥ 3), critical bleeding‡, or all-cause mortality*
Exploratory	
Efficacy	
To further investigate the efficacy of the study intervention	• Composite of CV death, stroke, or systemic embolism* • Systemic embolism* • Hemorrhagic stroke* • Disabling stroke (mRS ≥ 3)*
To investigate the effect of the study interventions on quality of life	• EQ-5D
Safety	
To further investigate the safety of the study intervention	• Total number of ISTH major bleeding events • Gastrointestinal bleeding* • All bleeding* • BARC type 3 and 5 bleeding* • BARC type 2, 3 and 5 bleeding* • BARC type 1*

Objectives	Endpoints
Net clinical benefit	
To further investigate the benefit and risk of the study intervention	• 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, ISTH = International Society on Thrombosis and Hemostasis, MI = myocardial infarction, mRS = modified Rankin Scale, PK = Pharmacokinetic(s).

* Time to first occurrence

‡ Critical bleeding is defined as symptomatic bleeding in either of the following critical locations (intracranial, intraspinal, pericardial, intra-articular, or retroperitoneal) or as intraocular bleeding with compromised vision or intramuscular bleeding with compartment syndrome

The estimands for the primary efficacy, safety and net clinical benefit objectives are described as follows:

1.1.1 Estimands Associated with the Primary Efficacy Objective

Primary Efficacy Objective: *to demonstrate that asundexian is superior (at least non-inferior) when compared with apixaban for prevention of stroke and systemic embolism in participants with atrial fibrillation at risk for stroke* Efficacy estimands for **non-inferiority** and 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 individuals with AF at risk for stroke	Same as primary	Adult individuals with AF at risk for stroke exposed to at least one dose of assigned treatment.	Same as Supplemental Efficacy Estimand 2
Treatment condition	**Investigational:** once daily oral administration of 50 mg of asundexian **Control:** twice daily oral administration of 5 mg of apixaban (or reduced dose of 2.5 mg).	Same as primary	Same as primary	Same as primary
Endpoint	Time to first occurrence of stroke or systemic embolism from day of treatment assignment	Same as primary	Same as primary 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 primary endpoint) comparing the two treatment conditions	Sub-distribution hazard ratio (sdHR) comparing the two treatment conditions	Same as primary	Same as Supplemental Efficacy Estimand 1

Primary Efficacy Objective: *to demonstrate that asundexian is superior (at least non-inferior) when compared with apixaban for prevention of stroke and systemic embolism in participants with atrial fibrillation at risk for stroke* Efficacy estimands for **non-inferiority** and for **superiority** assessment are described by the following attributes:				
Intercurrent events and strategies	• Early discontinuation of assigned treatment: addressed by the treatment policy strategy, i.e. the treatment effect including effects of treatment discontinuation is of interest and primary efficacy endpoint events and observation time will be used regardless of treatment discontinuation • Death: addressed by the "while alive" strategy, i.e. primary endpoint events and observation time up until death will be used • Treatment with dual antiplatelet therapy: addressed by the treatment policy strategy, i.e. the treatment effect includes the effect of dual antiplatelet therapy • Other intercurrent events related to COVID-19: will be handled according to the treatment policy strategy, i.e. the treatment effect includes the effect of intercurrent events related to COVID-19 (other than the mentioned intercurrent events).	Same as primary	Same as primary except • Early discontinuation of assigned treatment: addressed by the "while on-treatment" strategy, i.e. primary efficacy endpoint events and observation time up until premature discontinuation of assigned treatment will be used.	Same as Supplemental Efficacy Estimand 2

Rationale for the estimands associated with the primary efficacy objective:

[redacted]

CCI

[redacted]

1.1.2 Estimands Associated with the Primary Safety Objective

Primary Safety Objective: *to demonstrate that asundexian is superior to apixaban in participants with atrial fibrillation as assessed by ISTH major bleeding* 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 individuals with AF at risk for stroke exposed to at least one dose of treatment.	Same as primary	Adult individuals with AF at risk for stroke	As Supplemental Safety Estimand 2
Treatment condition	**Investigational**: once daily oral administration of 50 mg of asundexian **Control**: twice daily oral administration of 5 mg of apixaban [or reduced dose of 2.5 mg]	Same as primary	Same as primary	Same as primary
Endpoint:	Time to first occurrence of ISTH major bleeding from day of first intake of compared treatment	Same as primary	Same as primary safety estimand except from day of treatment assignment	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	As Supplemental Safety Estimand 1

Primary Safety Objective: *to demonstrate that asundexian is superior to apixaban in participants with atrial fibrillation as assessed by ISTH major bleeding* Estimands for **safety assessment** are described by the following attributes:				
Intercurrent events and strategies:	• Early discontinuation of assigned treatment: addressed by the "while on-treatment" strategy, i.e. primary safety events and observation time prior to the occurrence of the intercurrent event (i.e. up to the date of last intake of assigned treatment plus 2 calendar days) will be used • Death: addressed by the "while alive" strategy, i.e. primary safety events and observation time up until death will be used • Treatment with dual antiplatelet therapy: addressed by the treatment policy strategy, i.e. the treatment effect includes the effect of dual antiplatelet therapy • Other intercurrent events related to Covid-19: will be handled according to the treatment policy strategy, i.e. the treatment effects include the effect of intercurrent events related to Covid-19 (other than the mentioned intercurrent events)	Same as primary	Same as primary except Early discontinuation of assigned treatment: addressed by the treatment policy strategy, i.e. the treatment effect including effects of treatment discontinuation is of interest and primary safety endpoint events and observation time will be used regardless of treatment discontinuation	As Supplemental Safety Estimand 2

Rationale for the estimands associated with the primary safety objective:

CCI

1.1.3 Estimands Associated with the Primary Net Clinical Benefit Objective

Primary Net Clinical Benefit Objective: *To demonstrate that asundexian is superior when compared to apixaban with respect to benefit and risk*

Estimands for **net clinical benefit assessment** are described by the following attributes:

	Primary Net Clinical Benefit Estimand	**Supplemental Net Clinical Benefit Estimand 1**	**Supplemental Net Clinical Benefit Estimand 2**	**Supplemental Net Clinical Benefit Estimand 3**
Population	Adult individuals with AF at risk for stroke exposed to at least one dose of treatment	Same as primary	Adult individuals with AF at risk for stroke	As Supplemental Net Clinical Benefit Estimand 2
Treatment condition	**Investigational:** once daily oral administration of 50 mg of asundexian **Control:** twice daily oral administration of 5 mg of apixaban [or reduced dose of 2.5 mg]	Same as primary	Same as primary	Same as primary
Endpoint:	Time to first occurrence of stroke (including hemorrhagic stroke), systemic embolism, or ISTH major bleeding (excluding hemorrhagic stroke) from day of first intake of compared treatment	Same as primary	Same as primary net clinical benefit estimand except from day of treatment assignment	As Supplemental Net Clinical Benefit Estimand 2
Population-level summary	Cause-specific hazard ratio (i.e. ratio of cause-specific hazard rates of the net clinical benefit endpoint) comparing the two treatment conditions	Sub-distribution hazard ratio (sdHR) comparing the two treatment conditions	Same as primary	As Supplemental Net Clinical Benefit Estimand 1

Primary Net Clinical Benefit Objective: *To demonstrate that asundexian is superior when compared to apixaban with respect to benefit and risk* Estimands for **net clinical benefit assessment** are described by the following attributes:				
Intercurrent events and strategies:	• Early discontinuation of assigned treatment: addressed by the "while on-treatment" strategy, i.e. events of the net clinical benefit endpoint and observation time prior to the occurrence of the intercurrent event (i.e. up to the date of last intake of assigned treatment plus two calendar days) will be used • Death: addressed by the "while alive" strategy, i.e. net clinical benefit events and observation time up until death will be used • Treatment with dual antiplatelet therapy after treatment assignment (i.e. randomization): addressed by the treatment policy strategy, i.e. the treatment effects include the effect of dual antiplatelet therapy • Other intercurrent events related to COVID-19: will be handled according to the treatment policy strategy, i.e. the treatment effects include the effect of intercurrent events related to Covid-19	• Same as primary	Same as primary except • Early discontinuation of assigned treatment: addressed by the treatment policy strategy, i.e. the treatment effect including effects of treatment discontinuation is of interest and primary net clinical benefit endpoint events and observation time will be used regardless of treatment discontinuation	• As Supplemental Net Clinical Benefit Estimand 2

Rationale for the estimands associated with the primary net clinical benefit objective:

CCI [redacted]

1.1.4 Secondary Estimands

Estimands for secondary efficacy, safety and net clinical benefit endpoints are defined following the same approach as done for their respective primary estimands.

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

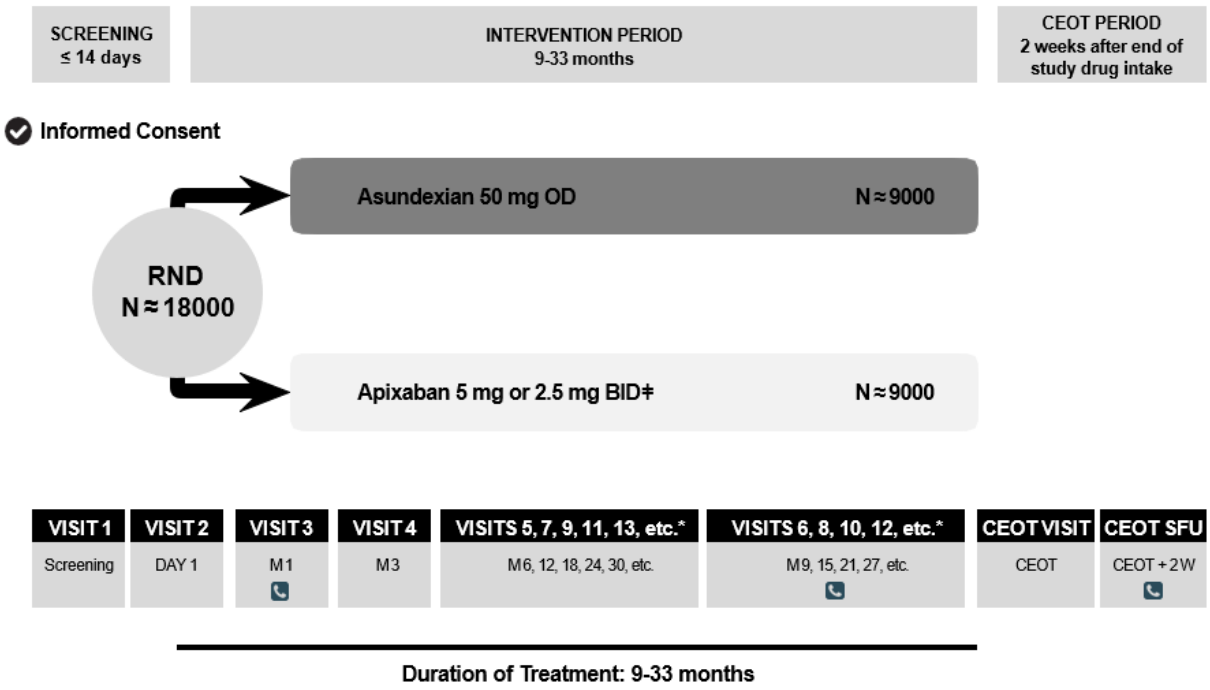
Study 19767 is a multicenter, randomized, active comparator-controlled, double-blind, double-dummy, parallel group, Phase 3 study. The overall study design is depicted in Figure 1–1.

Approximately 18000 participants ≥ 18 years of age, will be randomized to 1 of the 2 arms (approximately 9000 participants per arm), as follows:

- 1 investigational study intervention arm (asundexian) or
- 1 active comparator arm (apixaban),

in addition to their potential background therapy (see Section 6.9 of the CSP 19767).

Figure 1–1: Study design overview



Abbreviations: BID = bis in die (twice a day), CEOT = common end of treatment, M = month, N = total number of participants, OD = once a day, RND = randomization, SFU = safety follow-up, W = weeks

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

ǂ the usual dose of apixaban is 5 mg BID, reduced to 2.5 mg BID for participants with 2 or more of the following criteria: age 80 years or older, body weight ≤ 60 kg, or serum creatinine level ≥ 1.5 mg/dL

Notes: Participants receiving asundexian will also receive the apixaban matching placebo.
Participants receiving apixaban will also receive the asundexian matching placebo.
After discontinuation of study intervention, further anticoagulation therapy (e.g. NOAC) is at discretion of the investigator.
Decentralized clinical trial participants will have the screening visit split in a "part a" to initiate operational logistics and a "part b" to perform screening procedures.

Patients will be eligible for the study based on their CHA_2DS_2-VASc risk score, among other criteria. With a score of ≥ 3 if male or ≥ 4 if female, patients can get enrolled straight into the study. Patients with a CHA_2DS_2-VASc score of 2 if male or 3 if female can participate in the study by meeting <u>at least one</u> of the following enrichment criteria in addition:

- age ≥ 75
- previous stroke, transient ischemic attack, or systemic embolism
- renal dysfunction with eGFR < 50 ml/min/1.73 m^2 within 14 days prior to randomization
- prior episode of non-traumatic major bleeding
- current single agent antiplatelet therapy planned to continue for at least 6 months after randomization
- ≤ 6 consecutive weeks of treatment with oral anticoagulant prior to randomization

In order to offer study participation to patients who might be unwilling or unable to participate in a conventional, on-site study, a fully remote decentralized clinical trial (DCT) model may be implemented in select countries where feasible and local laws / regulations allow (refer to Section 10.10 of the CSP 19767, if applicable). For sites participating in the DCT model, remote visit activities are completed in place of on-site visits.

Randomization will be first stratified by participation in the conventional study model vs. the DCT model. This will be succeeded by stratification for current use vs. no current use of single agent antiplatelet therapy planned to continue for at least 6 months after randomization. Following stratification, participants will be assigned randomly via IRT to one of the two arms, in a 1:1 ratio. The randomization ratio will be controlled by blocks dynamically allocated by region/country.

This is an event-driven study, and the sponsor will request termination of the intervention period once about 340 participants have experienced a primary efficacy endpoint event and about 340 have experienced a primary safety endpoint event, whichever occurs latest. The planned individual study duration is expected to be 10-34 months; however, the timelines may vary (i.e. shorter or longer than planned) depending on enrollment rate and incidence rate in the study. Please refer to the CSP 19767 for the study design, however in summary the study will consist of the following study periods:

- **Screening period (from visit 1 until visit 2)**.

- **Intervention period (from visit 2 until the Common End of Treatment (CEOT) visit)**: The intervention period will be of variable length depending on when the participant entered the study. The shortest participant intervention period is expected to be 9 months (amongst those last to enter the study) and the longest 33 months (amongst those first to enter 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 CSP 19767.

Details of study procedures and their timing are summarized in the SoA (Section 1.3 of the CSP 19767).

1.2.1 Decentralized Clinical Trial Model

CCI [redacted]

2. Statistical Hypotheses

Due to the early termination of the study on 19th November 2023 all testing is exploratory; no separate non-inferiority testing will be done. [redacted]

2.1 Multiplicity Adjustment

Due to the early termination of the study, all testing is exploratory and no multiplicity adjustment will be done.

3. Analysis Sets

For purposes of analysis, the 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 (including participants who did not receive study intervention).
Adjusted Full Analysis Set (aFAS)	All participants in the Full Analysis Set excluding participants randomized in Site 20076
Safety Set (SAF)	All participants randomized to study intervention and who took at least 1 dose of study intervention. In case a participant received study intervention and was not randomized, whether to include them in the SAF will be assessed and confirmed prior to unblinding.
Adjusted Safety Set (aSAF)	All participants in the Safety Set excluding participants randomized in Site 20076

In September 2023, the Japanese Ministry of Health, Labour and Welfare (MHLW) detected GCP violations at the site management organization Medipharma. Medipharma was involved in the study at one site (site 20076). The ministry recommended not to use any of the data from the affected site.

Unless otherwise specified (e.g. Supplemental Efficacy Estimands 2 and 3), the aFAS will be used for analyses addressing efficacy estimands. Analysis using the aFAS will utilize the randomized study intervention group.

Unless otherwise specified (e.g. Supplemental Safety Estimands 2 and 3), the aSAF will be used for analyses addressing the primary safety estimand, other estimands relating to bleeding endpoints, the net clinical benefit estimands and analyses of AEs.

In general summary tables will only be produced for either the aFAS or the aSAF depending on the type of data to be summarized.

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) and ValidR (version 3.5.2 or higher).

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.

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 values will be the measurements from Visit 2 (or the respective visit as per SoA) regardless of the clock time in relationship to the first intake of study intervention. The rationale for not taking the time of measurement into account is that a measurement from Visit 2 shortly post study intervention intake is considered more appropriate as baseline than a measurement from several days/weeks previously.

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). In case of more than one available value before first administration of study intervention, the non-missing value before and closest to first study intervention will be taken. In case no study intervention was taken, baseline values are defined as the latest value taken before randomization. Subgroup definitions will be done only on central lab assessment.

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 study participation 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 MI, stroke, systemic embolism, death and bleeding. 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 date 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 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 medication. In case the date of first intake of study medication is missing (i.e. for in the FAS who never initiated treatment), the date randomization will be used instead.

If this imputation rule leads to an implausible date (e.g. earlier than the first intake of study medication or the randomization), then the date will be imputed as the earliest plausible date (e.g., the randomization date) but not earlier than the last date where the participant is known event free.

If any exposure 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 medication. In case any date of intake of study medication is missing (i.e. for in the FAS who never initiated treatment), no date will be used.

If this imputation rule leads to an implausible date (e.g. earlier than the first intake of study medication or the randomization), then the date will be imputed as the earliest plausible date (e.g., the start date of the exposure) but not earlier than the last date where it is known that the participant took drug.

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 min (date of signed informed consent, imputed medication end date).

If a medication end date exists and the imputed start date is after the start date, then the end date of the medication will be imputed as start date instead.

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.

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 4.1.2.

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

- 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 drug exposure
- last available date of any known date patient has to be alive before the event, for example adverse event, date of clinical outcome event or hospitalization or procedure, including death dates
- 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 then. 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.

The date of request of termination of the study intervention period is set to the date of the decision to terminate the study, the 19th November 2023.

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.

Events starting 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 the first study intervention intake but the time of the adverse event start cannot be compared to the time of first intake (e.g. adverse event time not collected), then the event will be assumed as treatment emergent.

4.1.1.7 Adjudication 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 members of the CEC who will review events in a blinded fashion and will adjudicate and classify the following events in a consistent and unbiased manner according to definitions further specified in the CEC charter. The adjudication will also include algorithmic approaches:

- Bleeding events according to the following classifications and definitions:
  - According to ISTH bleeding will be classified as
    - ISTH Major Bleeding (defined in Section 8.3.1.1 of the CSP 19767),
    - Clinically Relevant Non-Major Bleeding (defined in Section 8.3.2.1 of the CSP 19767),
    - Minor Bleeding (defined in Section 8.3.2.2 of the CSP 19767).
  - According to BARC criteria bleeding will be classified as follows: (defined in Section 8.3.3.1 of the CSP 19767; Note: type 4: CABG-related bleeding is not applicable to this study)
    - BARC type 3 and 5 bleeding
    - 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)
- Systemic embolism
- Potential outcome event (e.g. TIA and hospitalization for cardiac chest pain with increased cardiac enzymes).

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

4.1.1.8 Death/Fatal AEs

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

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 CSP for further details) are part of the efficacy outcome events in participants with AF. 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 19767 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 19767 for further details) and until the CEOT safety follow up visit if the participant completed study intervention less than 2 week 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 in the study will be classified in the following regions

Country	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
Bulgaria	Eastern Europe
Canada	North America
China	Asia
Czechia	Eastern Europe
Denmark	Western Europe, Australia and Israel
Estonia	Eastern Europe
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
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

Romania	Eastern Europe
Singapore	Asia
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
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 CYP3A4 inducers” and “Clinical P-gp inducers”
- Medications with a combination of level 2 groups “Strong CYP3A4 inhibitors” and “Clinical P-gp inhibitors”

4.1.1.13 CHA_2DS_2-VASc Score for Atrial Fibrillation

To support the patient demographics and for use as a subgroup the $CHA_2D\ S_2$-VASc score will be calculated at randomization/baseline.

The $CHA_2D\ S_2$-VASc score is calculated based on

- **Congestive heart failure**, increases score by 1, use medical history pre-specified terms “Chronic Heart Failure”, or “Hypertrophic cardiomyopathy”, or corresponding Preferred Terms "Cardiac failure chronic", or "Hypertrophic cardiomyopathy";
- **Hypertension,** increases score by 1, use medical history pre-specified term “Arterial Hypertension”, or corresponding Preferred Term "Hypertension";
- **Age 75 years or older**, increases score by 2;
- **Diabetes mellitus,** increases score by 1, use medical history pre-specified term “Diabetes Mellitus”, or corresponding Preferred Term "Diabetes mellitus";

- **Stroke / TIA / thromboembolism,** increases score by 2, use medical history pre-specified terms “Stroke”, “Transient Ischemic Attack”, or “Systemic embolism”, or corresponding Preferred Terms "Cerebrovascular accident", "Transient ischaemic attack", or "Embolism arterial";
- **Vascular disease,** increases score by 1, use medical history pre-specified terms “Myocardial Infarction”, “Coronary Artery Disease”, “Peripheral arterial occlusive disease”, “Complex Aortic plaque”, “Pulmonary embolism”, or “Deep Vein Thrombosis”, or corresponding Preferred Terms "Myocardial infarction", "Coronary artery disease", "Peripheral arterial occlusive disease", "Aortic arteriosclerosis", "Pulmonary embolism", or "Deep vein thrombosis"
, and medical procedures history pre-specified terms “Coronary Artery bypass Grafting” or “Percutaneous Coronary Intervention”, or corresponding Preferred Terms "Coronary artery bypass", "Percutaneous coronary intervention";
- **Age 65-74,** increases score by 1;
- **Sex Category**, increases score by 1 for female sex.

Missing values will lead to an implicit “no” answers to a specific question, i.e. only confirmed risk factor will be counted for the score.

4.1.1.14 $CHADS_2$ Score for Atrial Fibrillation

To support the patient demographics and for use as a subgroup the $CHADS_2$ score [10] will be calculated at randomization/baseline.

The $CHADS_2$ score is calculated based on

- **Congestive heart failure**, increases score by 1, use medical history pre-specified term “Chronic Heart Failure”, or corresponding Preferred Term "Cardiac failure chronic";
- **Hypertension,** increases score by 1, use medical history pre-specified term “Arterial Hypertension”, or corresponding Preferred Term "Hypertension";
- **Age 75 years or older**, increases score by 1;
- **Diabetes mellitus,** increases score by 1, use medical history pre-specified term “Diabetes Mellitus”, or corresponding Preferred Term " Diabetes mellitus";
- **Stroke / TIA,** increases score by 2, use medical history pre-specified terms “Stroke” or “Transient Ischemic Attack”, or corresponding Preferred Terms "Cerebrovascular accident" or "Transient ischaemic attack";

Missing values will lead to an implicit “no” answers to a specific question, i.e. only confirmed risk factor will be counted for the score.

4.1.1.15 ORBIT-AF and HAS-BLED Score

To support the patient demographics, the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) bleeding score [14] and modified HAS-BLED score [15] will be calculated at randomization/baseline.

The ORBIT-AF bleeding score is calculated based on

- **O**lder, Score 1 for 75 years or older;

- **R**educed hemoglobin (<13 g/dL in men and <12 g/dL in women), or hematocrit (<40% in men and <36% in women) or history of anemia (Score 2);
- **B**leeding history, Score 2 for any history of all major or gastrointestinal bleeding documented at the baseline visit;
- **I**nsufficient kidney function, Score 1 for eGFR < 60 ml/min/1.73 m^2 ;
- **T**reatment with an antiplatelet agent, Score 1.

Missing values will lead to an implicit "no" answers to a specific question, i.e. only confirmed risk factor will be counted for the score.

The modified HAS-BLED score is calculated based on the sum of

- **H**ypertension, Score 1 for uncontrolled hypertension (as per medical history term "Hypertension") with a baseline systolic BP > 160 mmHg (0/1);
- **A**bnormal renal or liver function, Score 1 represented by for serum creatinine ≥ 2.26 mg/dL (200 µmol/L) AND Score 1 represented by for bilirubin > 2x ULN with AST/ALT/AP > 3x ULN (0/1/2);
- **S**troke, Score 1 for history of stroke (0/1);
- **B**leeding, Score 1 for prior major bleeding and medical history of anemia (0/1);
- **L**abile INR, not collected for this study (0/1);
- **E**lderly, Score 1 for > 65 years (0/1);
- **D**rugs, Score 1 for antiplatelet agents or NSAIDs (also score 1 for alcohol use however this is not collected for this study) (0/1/2).

Missing values will lead to an implicit "no" answers to a specific question, i.e. only confirmed risk factor will be counted for the score.

Antiplatelet agents and NSAIDs assessed in ORBIT-AF bleeding score and modified HAS-BLED score will be identified by use of Standard Drug Groupings

4.1.1.16 Disabling Stroke

Participants with a stroke will be assessed for their resulting disability using the modified Rankin Scale (mRS) 7 days after the event and at the next visit, at least 2 months post the stroke (see Section 8.2.1.1 and 10.8 of the CSP 19767 for further details). A disabling stroke is defined as a stroke, of any type, associated with a mRS of ≥ 3 at the 2nd mRS assessment (i.e. between 2 and 5 months after the stroke). An exploratory endpoint of short-term disabling stroke will also be analyzed based on the mRS score from 7 days after the stroke.

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

As reported in Sections 4.2 and 4.3, for efficacy, safety and net clinical benefit time-to-event outcomes, the variable 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 variables 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.

Due to the early termination of the study it was decided that the main analyses for the treatment regimen will not stop on the individual date of CEOT visit, but at the time of the request of study termination. Therefore, the time-to-event variable for participants who have not experienced the respective endpoint event will be censored on the earlier of:

1. 19th November 2023 (the date of the decision of the study stop),
2. the date of last contact as defined in Section 4.1.1.5.

As a second supplementary time frame, the original planned time frame will be used. For this purpose, the time-to-event variable for participants who have not experienced the respective endpoint event until their CEOT visit (as 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 their date of last contact as defined in Section 4.1.1.5.

For estimands using the while exposed to assigned 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).

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

Note that for participants using the DCT model there will be a lag between randomization and first study intervention intake due to direct to participant supply. This difference will be accounted for in the analysis within the stratification by study type (DCT vs conventional).

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

All efforts will be made to reduce incomplete follow-up with regard to the occurrence and timing of key outcome events 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. 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 aSAF) 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 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.
- 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.
  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.
  For the primary efficacy, safety and net clinical benefit endpoints **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:

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

  [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 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:

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

  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 antithrombotic treatment group
           (0 = apixaban 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
*/
```

4.1.4 Stratification

In general, unless there are problems with convergence or too few events in a stratum, statistical models will be stratified by

- Study type (conventional study model vs. DCT model)
- Single agent antiplatelet therapy planned to continue for at least 6 months after randomization (Current use vs. No current use).

These two baseline covariates are the randomization strata (and not re-derived).

Models that are by study type or single agent antiplatelet therapy will not use the corresponding factor as a covariate in the model.

When assessing a model across subgroups if a stratification factor has to be removed from at least one subgroup category model then, to allow comparisons across the subgroup categories, it will be removed from all subgroup category models.

4.2 Primary Endpoints/Estimands Analysis

The following subsections describe the planned statistical analyses addressing the primary efficacy, safety and net clinical benefit 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 the composite of stroke or systemic embolism. The estimand is defined in Section 1.1.1 and further details of the derivation of time to event endpoints are described in Section 4.1.2.

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 4.1.3).

In line with the "while alive" strategy proposed 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 instantaneous rate of the occurrence of the primary efficacy outcome in participants assigned to asundexian versus apixaban according to the defined estimand, cause-specific hazard ratios (csHRs) and their associated confidence intervals for participants assigned to asundexian versus apixaban 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 dct saap;
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)
dct      = binary strata, participants in conventional study model (=0) vs.
           participants in DCT model (=1)
saap     = binary strata, Current use single agent antiplatelet therapy (=1)
           vs. No current use single agent antiplatelet therapy (=0)

alpha has been set as 0.05 in this example

*/
```

All efficacy hypotheses, see Section 2, will be tested in an exploratory manner using a two-sided stratified log-rank test, based on the score test from the Cox PH model.

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

4.2.1.3 Sensitivity Analyses

If Nelson-Aalen estimates of the cumulative hazard for the primary efficacy outcome by study 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.

The plausibility of the proportional hazards assumption will be visually assessed via plots of the scaled Schoenfeld residuals over time and via the Chi-Square test of the residuals [7].

For the main analysis, missing follow-up time will be handled by censoring at the last available timepoint for which data on the outcome exists.

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 [5]. 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 apixaban.

The estimated sub-distribution hazard ratios (sdHRs) and their associated confidence intervals comparing participants assigned to asundexian versus apixaban 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 study model (DCT vs conventional study) and single agent antiplatelet therapy (Current use vs No current use).

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 */
   MODEL ttevalue*status(0) = trtgrpn / EVENTCODE(FG) = 1 RL;
   STRATA dct saap;
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 dct saap;
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, ...)
dct      = binary strata, participants in conventional study model (=0)
           vs. participants in DCT model (=1)
saap     = binary strata, Current use single agent antiplatelet therapy
          (=1) vs. No current use single agent antiplatelet therapy (=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 [9] 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 */
  STRATA dct saap / 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, ...)
dct      = binary strata, participants in conventional study model (=0)
           vs. participants in DCT model (=1)
saap     = binary strata, Current use single agent antiplatelet therapy
          (=1) vs. No current use single agent antiplatelet therapy (=0)
*/
/* Take p-value from Gtest and combine with other results in the
table.*/
```

Supplemental Efficacy Estimands 2 and 3

Data for the supplemental efficacy estimands 2 and 3 will be summarized as in Section 4.1.3.

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 aSAF.

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 apixaban 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 apixaban will be derived from a Fine-Gray model as described for the supplemental efficacy estimand 1 earlier in this section. 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, based on the score test from the Cox PH model will supplement the results from the primary efficacy estimand analysis.

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 4.1.1.7, the derivation of time to event endpoints is described in Section 4.1.2.

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 aSAF.

Data for the primary safety endpoint will be summarized using the set of descriptive statistics for time-to-event endpoints (see Section 4.1.3).

For the primary safety estimand as described in 4.2.1.2 for the primary efficacy estimand the csHRs and their associated confidence intervals for participants taking asundexian versus apixaban 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”.

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

All analyses described in this section will be repeated for the set of subgroups defined for the baseline variables: risk factors for apixaban dose; current use of single agent anti platelet therapy; study model; AF; weight; age group; eGFR; sex; race; region; stroke or TIA prior to randomization; treated with moderate CYP3A inhibitors + inducers at randomization and CHA_2DS_2-VASc Score.

4.2.2.3 Sensitivity Analyses

CCI [redacted]

CCI [redacted]

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 apixaban 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 Estimands 2 and 3

The supplemental safety estimand 2 will be summarized as in Section 4.1.3, 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 apixaban 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 apixaban 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, based on the score test from the Cox PH model will supplement the results from the primary safety estimand analysis.

4.2.3 Primary Net Clinical Benefit Estimand

4.2.3.1 Definition of Endpoint

The primary net clinical benefit endpoint is the time from start of study intervention to first occurrence of stroke (including hemorrhagic stroke), systemic embolism, or ISTH major bleeding (excluding hemorrhagic stroke). The primary net clinical benefit estimand is defined in Section 1.1.3 and different bleeding classifications in Section 4.1.1.7, the derivation of time to event endpoints is described in Section 4.1.2.

4.2.3.2 Main Analytical Approach

The analysis of the primary net clinical benefit endpoint will be as the main analyses of the primary safety endpoint, see Section 4.2.2.2.

The primary net clinical benefit superiority null hypothesis, see Section 2, will be tested using a stratified log-rank test based on the score test from the Cox PH analysis.

All analyses described in this section will be repeated for the set of subgroups: Risk factors for apixaban dose (0-1, 2-3); current use of single agent anti platelet therapy (yes/no); study model (DCT vs. conventional study).

4.2.3.3 Sensitivity Analyses

No sensitivity analyses are planned for the primary net clinical benefit endpoint.

4.2.3.4 Supplementary Analyses

Supplemental Net Clinical Benefit Estimand 1

For the supplemental net clinical benefit estimand 1 the analysis will follow that of the supplemental safety estimand 1 in Section 4.2.2.4.

Supplemental Net Clinical Benefit Estimands 2 and 3

The supplemental net clinical benefit estimands 2 and 3 will follow the principles described for the supplemental safety estimands 2 and 3, see Section 4.2.2.4.

4.3 Secondary Endpoints/Estimands Analysis

The analysis of estimands associated with secondary endpoints will follow the principles as described for the respective primary efficacy, safety and net clinical benefit 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:

- Composite of ischemic stroke or systemic embolism (Secondary Efficacy Estimand 1)
- Ischemic stroke
- Composite of CV death, stroke and myocardial infarction
- CV death
- All-cause mortality

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.

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.

4.3.1.3 Sensitivity Secondary Efficacy Analyses

No sensitivity analyses are planned for the secondary efficacy endpoints.

4.3.1.4 Supplementary Secondary Efficacy Analyses

The supplementary analysis of the secondary efficacy endpoints will follow the principles described for the supplementary analyses of Supplemental Efficacy Estimand 1, see Section 4.2.1.4.

4.3.2 Secondary Safety Endpoints

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
- Clinically relevant non-major bleeding
- Hemorrhagic stroke
- Symptomatic intracranial hemorrhage
- Fatal bleeding
- Minor bleeding

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. For the endpoint "fatal bleeding" death will not be considered as competing event.

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 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, CRNM bleeding, and minor bleeding will be listed.

4.3.3 Secondary Net clinical benefit Endpoints

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 (including hemorrhagic stroke), systemic embolism, ISTH major bleeding (excluding hemorrhagic stroke), or all-cause mortality

- Composite of disabling stroke (mRS ≥ 3), critical bleeding or all-cause mortality

See Section 4.1.1.7 for the definition of ISTH major bleeding.

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 described for the supplementary analyses of 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:

- Composite of CV death, stroke and systemic embolism *
- Systemic embolism *
- Hemorrhagic stroke *
- Disabling stroke (modified Rankin Scale [mRS] ≥ 3 at next visit (at least 2 months after stroke)) *
- Short-term disabling stroke (modified Rankin Scale [mRS] ≥ 3 at day 7) *
- Fatal ischemic stroke
- Composite of non-fatal ischemic stroke and systemic embolism *
- Composite of fatal ischemic stroke and systemic embolism *
- Composite of all-cause mortality, stroke and myocardial infarction *
- Ischemic disabling stroke (modified Rankin Scale [mRS] ≥ 3 at next visit (at least 2 months after stroke)) *
- Hemorrhagic disabling stroke (modified Rankin Scale [mRS] ≥ 3 at next visit (at least 2 months after stroke)) *
- Composite of stroke and systemic embolism, up to 7 days after last study intervention @ (Exploratory Efficacy Estimand 1)
- Composite of stroke and systemic embolism, up to 30 days after last study intervention @ (Exploratory Efficacy Estimand 2)
- EuroQol Group 5-dimension questionnaire (EQ-5D).

* Time from randomization to first occurrence.

@ Time from first study intervention intake to first occurrence.

The analyses of the time to first occurrence exploratory efficacy endpoints will follow the principles described for the main and supplementary analyses of the primary efficacy endpoint, see Section 4.2.1.2, and Section 4.2.1.4.

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.

4.4.2 Definition and Analytical Approach for Exploratory Safety Endpoints

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

- Gastrointestinal bleeding
- All bleeding
- BARC type 3 and 5 bleeding
- BARC type 2, 3 and 5 bleeding
- BARC type 1 bleeding
- ISTH non-fatal major bleeding
- ISTH major bleeding, up to 7 days after last study intervention (Exploratory Safety Estimand 1)

The total number of ISTH major bleeding events per participant and number of subjects with more than one bleeding event are also exploratory safety endpoints.

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 4.2.2.4.

Major bleedings will be also described by localization (e.g., intracranial and extra-cranial and outcome (e.g.: resulting in death; resulting in disability; recovered without sequels).

The total number of ISTH major bleeding events 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 ISTH major bleeding events will be displayed using the aSAF and on-study ISTH major bleeding events will be displayed using the aFAS. Tables for on-study CRNM bleeding and minor bleeding events will also be included.

Number of subjects with more than one bleeding event will be counted while alive and exposed to treatment and displayed using the aSAF.

4.4.3 Definition and Analytical Approach for Exploratory Net clinical benefit Endpoints

The exploratory net clinical benefit endpoints are:

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

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 aSAF and on-study hospitalizations will be compared using the aFAS. On – study hospitalizations are defined as all hospitalizations starting on the day of randomization or after randomization until last scheduled visit. On-treatment hospitalizations are defined as all 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 intervention 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 apixaban will be summarized as the average dose in mg per day using descriptive statistics by study arm and overall. In addition, the treatment dose for asundexian or apixaban will be categorized into 6 groups, ≤ 2 mg, >2 to 3 mg, >3 to 6 mg, >6 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:

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

The number of planned tablets is calculated as:

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

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-asundexian and apixaban/placebo-apixaban 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 AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA, the version defined in SDTM domain TS) preferred terms (PTs) grouped by system organ class (SOC).

Any AEs related to study procedures recorded from signing of informed consent but prior to first study intervention intake 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).

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 4.1.2.

AEs starting before 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 CSP 19767 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 19767 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 intervention arm and overall.

The number of participants with

- TEAEs,
- study intervention-related TEAEs,

- TEAEs resulting in discontinuation of study intervention,
- TEAEs by maximum intensity,
- study intervention-related TEAEs by maximum intensity,
- non-serious TEAEs,
- SAEs,
- serious TEAEs,
- study intervention-related serious TEAEs,
- serious TEAEs resulting in discontinuation of study intervention,
- AEs with fatal outcome,
- TEAEs with fatal outcome, and
- post-treatment AEs

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.

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 CSP 19767) 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, unless specified otherwise. For all other analyses only central laboratory values will be used.

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 with the exception for sites from Japan. For Japanese sites, a Japanese Equation formula will be used. For the statistical analyses, eGFR derived from both formulas will be analyzed together.

The laboratory tables will be repeated for the subgroups DCT and conventional study (only for the aSAF).

4.5.3.2 Vital Signs

Vital sign (systolic and diastolic blood pressure, heart rate) values will be summarized by study intervention arm and overall.

The vital signs tables will be repeated for the subgroups DCT and conventional study.

4.5.3.3 Electrocardiogram

The baseline mean ventricular rate will be summarized using descriptive statistics by study intervention arm and overall.

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

The ECG tables will be repeated for the subgroups DCT and conventional study.

4.5.3.4 Analyses of liver events according to protocol

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4.5.3.5 Screening and analyses of potential drug-induced liver injuries

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CCI

CCI

CCI [redacted]

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 CSP 19767 for details.

4.6.4 Biomarker

The 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 outcome will be performed to assess consistency of the investigational intervention effect across subgroups.

The following factor is considered a potential predictive factor:

- Risk factors for apixaban dosage at randomization (utilized for the primary efficacy, safety and net clinical benefit estimands)

As described in Section 6.1 of the CSP 19767, a 2.5 mg dose of apixaban is indicated for participants with any 2 of the following criteria: age 80 years or older, body weight of 60 kg or less, or serum creatinine level of 1.5 mg per dL (133 µmol/L) or more. For each participant, the dose selection will be based on the values at the randomization visit. As the lower apixaban dosage might decrease the efficacy treatment effect, the "apixaban dosage" factor (apixaban higher dosage group (0-1 risk factor) versus apixaban lower dosage group (2-3 risk factors)) might be predictive of the treatment effect. Since the aim of the study is to show superiority or at least non-inferiority for all participants it seems reasonable not to conduct two different studies. This holds true since the proportion of participants with 2 or 3 risk factors for apixaban dosage is to be estimated at about 10%. Whether a participant has 0-1 or 2-3 risk factors at time of randomization will be re-derived based on the data collected for the 3 factors.

The following factors that define subgroups are known or expected to possibly show different risks of efficacy events across the different levels of the factor and are therefore considered potential prognostic factors will be utilized for the primary efficacy estimand.

- The stratification factors
    - Participation in conventional study model vs. DCT model.
      Participants in the DCT might be different (e.g. in age or socio-economic group) compared to conventional study participants.
    - Current use vs. no current use of single agent antiplatelet therapy planned to continue for at least 6 months after randomization.
      Participants on single agent antiplatelet therapy may have a higher risk of bleeding.
- CHA_2DS_2-VASc score (2&3 vs. > 3 for male participants, 3&4 vs. >4 for female participants) (utilized for the primary efficacy and safety estimands)
- BMI (< 25; ≥ 25 to < 30; ≥ 30 kg/m^2) (utilized for primary efficacy estimand)
- eGFR (<50; 50-80; >80 ml/min/1.73 m^2), reflecting the known higher risks for an event and the recommendation of lowering the apixaban dose for decreased kidney function (utilized for the primary efficacy and safety estimands)
- Race (White, Black, Asian, other), with focus on the known differences in the risk profile for Asian / non-Asian and Black / Non-Black participants (utilized for the primary efficacy and safety estimands).
- Region: North America; South America; Western Europe, Australia and Israel; Eastern Europe; Asia (utilized for the primary efficacy and safety estimands)

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

CCI [redacted]

- [redacted]
- [redacted]

[redacted]

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

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 [6] 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 in a table and graphically using forest plots.

The cumulative Aalen-Johansen probability over time will be reported by subgroup in tables and plots, apart from for exploratory subgroups.

4.7 Interim Analyses

Due to the early stopping of the trial, the interim analysis did not take place. CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI

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. Some additional exploratory endpoints were added in response to Scientific Advice from the EMA (Doc Ref: EMADOC-360526170-1176060). Some additional exploratory subgroups have been added that may be required for the PMDA submission. 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. The baseline ORBIT-AF bleeding score, HAS-BLED score and $CHADS_2$ score have been added to the demographic summary.

Due to a request of the Japanese Ministry of Heath, Labour and Welfare, the data of the site number 20076 is not used in the main analysis. The analysis set is for the main analysis is for that reason re-defined as aFAS and aSAF.

After the decision to end the trial due to lack of efficacy early, the planned analyses are now considered exploratory. Formal testing procedures as well as sensitivity analyses were deleted. In particular, all analyses on weighted net clinical benefit were deleted. In addition,

the time of the decision (19 NOV 2023) will be used as censoring date for the time under risk/censoring date.

5. Sample Size Determination

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Sample size calculations were derived using the software PASS 13.

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 region and country 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 (Screening 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 the variables

- time from randomization to the date of last contact (see Section 4.1.1.5) for participants in the aFAS
- time from first intake of study intervention to the date of last double-blind dose of study intervention for participants in the aSAF

will be summarized using descriptive statistics. The cumulative incidence risk will be estimated using cause-specific Aalen-Johansen estimators and reported via both figures displaying the cumulative incidence curves and tables containing the cumulative probability for the relative days and its 95% CI.

For the time in study follow-up, the competing risks “death” and “loss to follow-up/withdrawal of consent” will be accounted for.
For the time to the date of last double-blind dose of study intervention, the competing risks “death”, “early discontinuation of assigned treatment” and “loss to follow-up/withdrawal of consent” will be accounted for.

In addition, the duration of study intervention (treatment) 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.

6.2 Demography and other baseline characteristics

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

Demographics and baseline characteristics will also be displayed by risk factors for apixaban dosage, current use of single use antiplatelet therapy (vs no current use), and DCT vs. conventional study.

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 to severe renal dysfunction with eGFR 25-50 ml/min/1.73 m^2 (yes/no)
- Time from AF diagnosis to randomization (≤30 days; >30 days to 3 months; > 3 months)
- Chronic Kidney Disease (yes/no)
- Coronary Artery Disease (yes/no)
- Tobacco/nicotine use (never; former; current)
- Baseline ORBIT-AF bleeding score (see Section 4.1.1.7)
- Baseline modified HAS-BLED score (see Section 4.1.1.7)
- Baseline $CHADS_2$ score (see Section 4.1.1.13, will be used for Japanese Eldercare subgroup)

6.3 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) that started before signing of the informed consent 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.

Number and percentages of participants with different AF patterns (Paroxysmal, Persistent, Long-standing persistent, Permanent), and of participants in the apixaban dosage groups (0-1 risk factor vs 2-3 risk factors) will be shown separately. The AF pattern table will be repeated by risk factors for apixaban dosage.

6.4 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 at baseline is defined as medication taken at day of randomization
- 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-Drug,). CCI [redacted]. The number of participants taking prior and concomitant medication will be presented by study intervention arm and overall using ATC classes and subclasses. All tables will be reported for the aSAF only. The concomitant medication table will be repeated for the risk factors for apixaban dosage (0-1, 2-3) and DCT vs conventional model. The concomitant table will be repeated including prohibited medications only.

Tables in similar format to the concomitant medication table will be produced for the aSAF 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 aSAF. These tables will be repeated for ongoing at start of treatment period, started during treatment period and started after treatment period. The anticoagulant/antiplatelet table will be repeated for those medications used during the 7 days prior to an ISTH major or CRNM or minor bleeding.

Drugs will be grouped using standardized drug groupings.

A table of number and percentage of participants on anticoagulants and antiplatelets at specific days during the study will be reported, this table will be for the overall study intervention arm (i.e., not split by intervention group) and only include participants that completed treatment. The study days that will be reported are days 1, 15, 30, 60, 90, 180, and 365.

A participant will be defined being on dual antiplatelet therapy at a day if the participant takes ASA and any other antiplatelet inhibitor as defined by the respective drug grouping at that day. Dosages higher than 325 mg for ASA and routes of administration besides oral administration will not be counted for antiplatelet use. The following medications will not count as antiplatelet therapy: alprostadil, beraprost and limaprost.

6.4.1 Drug groupings

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

CCI [redacted]

7. Document history and changes in the planned statistical analysis

- SAP Version 1.0 completed 01 DEC 2022
- SAP Version 2.0: The following changes have been made:
- Analysis using the SAF will utilize the planned study intervention group.
    - Renal dysfunction with eGFR 25-50 ml/min/1.73 m^2 (yes/no) label has been updated to "moderate to severe renal dysfunction" for demography and other baseline characteristics.
    - HAS-BLED score has been updated to modified HAS-BLED score to include medical history of anemia for Bleeding, Score 1 in addition to prior major bleeding
    - Analyses for change from baseline for Vital Signs deleted as Vital Signs are collected only for Visits 1 and 2 (optionally)
    - "Anemia" subgroup: unit for hemoglobin updated from mg/dL to g/dL
    - Section 4.4.2: On-study CRNM bleeding and minor bleeding events, number of subjects with more than one bleeding event added to exploratory safety endpoints
    - Added section on classification of regions
    - Specific analyses on COVID-19 deleted due to the change of COVID-19 pandemic.
    - Added clarifications on definition of CHA_2DS_2-VASc Score
    - Added rule for Imputation of concomitant medication start dates
    - Removed subgroup cardiac surgery
    - Added primary efficacy outcomes after treatment discontinuation
    - Deleted analyses based on PK; PD and biomarker as they are now done under separate cover
    - Add aFAS and aSAF due to request of Japanese MHLW
    - Changes after decision of study stop:
        - Additional analyses up until decision of study stop
        - Deletion of pre-planned analyses due to study stop, especially all testing procedures and weighted net clinical benefit analyses

8. References

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