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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
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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

Protocol Version: KOR-1

Amendment Number: KOR-1

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

Study Phase: Phase 3

Acronym: **OCEANIC-AF** (Phase 3 program of the **O**ral fa**C**tor **E**leven **A** i**N**hibitor asundex**I**an as novel antithromboti**C** - **A**trial **F**ibrillation study)

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This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

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

Confidential

Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
KOR-1	KOR-1	06 JAN 2023	Updated to fully reflect the changes specific to the Republic of Korea (KOR-1)
KOR-1	KOR-1	19 DEC 2022	Prepared to include changes specific to the Republic of Korea. It was submitted but updated prior to approval
Clinical Study Protocol	1.0	01 SEP 2022	-

Protocol Amendment Summary of Changes Table

KOR-1 (06 JAN 2023)

This amendment is prepared to include country specific changes of the original protocol dated 01 SEP 2022, to meet local requirements valid for the Republic of Korea only. A description of the country-specific changes and a brief rationale is outlined in the Appendix Country/region-Specific Requirements.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Appendix 10.12 Country/region-specific Requirements	Republic of Korea-specific modification listed in Section 10.12.3.1	To follow the request from Ministry of Food and Drug Safety (MFDS)

Table of Contents

Title Page **1**
Document History Table **3**
Protocol Amendment Summary of Changes Table **4**
Table of Contents **5**
Table of Tables **8**
Table of Figures **9**
List of Abbreviations and Definitions of Terms **10**
1. Protocol Summary **17**
1.1 Synopsis 17
1.2 Schema 22
1.3 Schedule of Activities (SoA) 23
2. Introduction **25**
2.1 Study Rationale 26
2.2 Background 26
2.2.1 Disease Background 26
2.2.2 Treatment Guidelines 27
2.2.3 FXIa Inhibition: Mode of Action 27
2.2.4 Asundexian (BAY 2433334) 28
2.3 Benefit/Risk Assessment 29
2.3.1 Risk Assessment 29
2.3.2 Benefit Assessment 32
2.3.3 Overall Benefit/Risk Conclusion 34
3. Objectives, Endpoints, and Estimands **35**
4. Study Design **41**
4.1 Overall Design 41
4.1.1 Decentralized Clinical Trial Model 43
4.2 Scientific Rationale for Study Design 44
4.2.1 Patient Input into Design 44
4.3 Justification for Dose 45
4.4 End of Study Definition 45
5. Study Population **45**
5.1 Inclusion Criteria 45
5.2 Exclusion Criteria 47
5.3 Lifestyle Considerations 48
5.4 Screen Failures 49
5.5 Criteria for Temporarily Delaying Enrollment or Randomization 49
6. Study Intervention(s) and Concomitant Therapy **49**
6.1 Study Intervention(s) Administered 49
6.1.1 Switching to Study Intervention and Back to Open Label Anticoagulant 51
6.1.2 Medical Devices 52
6.2 Preparation, Handling, Storage, and Accountability 52
6.3 Assignment to Study Intervention 53

6.4 Blinding ... 53
6.4.1 Unblinding ... 54
6.5 Study Intervention Compliance ... 55
6.6 Dose Modification ... 55
6.7 Continued Access to Study Intervention after the End of the Study ... 55
6.8 Treatment of Overdose ... 56
6.9 Prior and Concomitant Therapy ... 56
6.9.1 Guidance for Management of Participants who Have Bleeding During the Study ... 58
6.9.2 Guidance for Management of Participants who Have Surgery or Percutaneous/Endoscopic Procedures ... 59
6.9.3 Guidance for Management of Participants who Experience Ischemic Stroke During the Study ... 60
6.9.4 Guidance for Management of Participants who Experience an Acute Coronary Syndrome During the Study ... 61

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal ... 61
7.1 Discontinuation of Study Intervention ... 61
7.1.1 Permanent Discontinuation of Study Intervention ... 61
7.1.2 Temporary Discontinuation of Study Intervention ... 63
7.2 Participant Discontinuation/Withdrawal from the Study ... 64
7.3 Lost to Follow-Up ... 64

8. Study Assessments and Procedures ... 65
8.1 Administrative and Baseline Procedures ... 66
8.2 Efficacy Assessments ... 66
8.2.1 Primary Efficacy Endpoint ... 66
8.2.1.1 Stroke ... 66
8.2.1.2 Systemic Embolism ... 67
8.2.2 Secondary Efficacy Endpoints ... 67
8.2.2.1 Cardiovascular Death ... 67
8.2.2.2 Myocardial Infarction ... 67
8.2.3 Exploratory Efficacy Assessments ... 68
8.2.3.1 EuroQol Group 5-dimension questionnaire (EQ-5D) ... 68
8.3 Safety Assessments ... 68
8.3.1 Primary Safety Endpoint ... 68
8.3.1.1 ISTH Major Bleeding ... 69
8.3.2 Secondary Safety Endpoints ... 69
8.3.2.1 Clinically Relevant Non-Major Bleeding ... 69
8.3.2.2 Minor Bleeding ... 70
8.3.3 Exploratory Safety Endpoints ... 70
8.3.3.1 BARC Bleeding ... 70
8.3.4 Physical Examinations ... 71
8.3.5 Vital Signs ... 71
8.3.6 Electrocardiograms ... 72
8.3.7 Clinical Safety Laboratory Tests ... 72
8.3.8 Pregnancy Testing ... 73
8.4 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting ... 73
8.4.1 Time Period and Frequency for Collecting AE and SAE Information ... 74
8.4.2 Method of Detecting AEs and SAEs ... 74

8.4.3 Follow-up of AEs and SAEs ... 75
8.4.4 Regulatory Reporting Requirements for SAEs ... 75
8.4.5 Pregnancy ... 75
8.4.6 Disease-related Events ... 76
8.5 Pharmacokinetics ... 77
8.6 Pharmacodynamics ... 78
8.7 Genetics ... 79
8.8 Biomarkers ... 79
8.9 Immunogenicity Assessments ... 79
8.10 Medical Resource Utilization and Health Economics ... 79
8.10.1 Healthcare Resource Utilization (HCRU) ... 79

9. Statistical Considerations ... 80
9.1 Statistical Hypotheses ... 80
9.1.1 Multiplicity Adjustment ... 81
9.2 Analysis Sets ... 82
9.3 Statistical Analyses ... 82
9.3.1 General Considerations ... 82
9.3.2 Primary Endpoint(s)/Estimand(s) Analysis ... 85
9.3.2.1 Primary Efficacy Estimands ... 85
9.3.2.2 Primary Safety Estimand ... 86
9.3.2.3 Primary Net Clinical Benefit Estimand ... 87
9.3.3 Secondary Endpoint(s) Analysis ... 88
9.3.4 Exploratory Endpoint Analysis ... 88
9.3.5 Other Safety Analysis ... 88
9.3.6 Other Analysis ... 89
9.4 Interim Analysis ... 90
9.5 Sample Size Determination ... 91

10. Supporting Documentation and Operational Considerations ... 94
10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations ... 94
10.1.1 Regulatory and Ethical Considerations ... 94
10.1.2 Financial Disclosure ... 94
10.1.3 Informed Consent Process ... 95
10.1.4 Recruiting Strategy ... 95
10.1.5 Data Protection ... 96
10.1.6 Committees Structure ... 96
10.1.6.1 Program Leadership Committee (PLC) ... 96
10.1.6.2 Executive Committee (EC) ... 96
10.1.6.3 Steering Committee (SC) ... 96
10.1.6.4 Independent Data Monitoring Committee (IDMC) ... 97
10.1.6.5 Clinical Events Committee (CEC) ... 97
10.1.7 Dissemination of Clinical Study Data ... 97
10.1.8 Data Quality Assurance ... 98
10.1.9 Source Documents ... 99
10.1.10 Study and Site Start and Closure ... 99
10.1.11 Publication Policy ... 100
10.2 Appendix 2: Clinical Laboratory Tests ... 101
10.2.1 Liver Safety: Follow-up Assessments and Suggested Actions ... 102

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 105
10.3.1 Definition of AE 105
10.3.2 Definition of SAE 106
10.3.3 Recording and Follow-Up of AE and/or SAE 107
10.3.4 Reporting of SAEs 108
10.4 Appendix 4: Contraceptive and Barrier Guidance 110
10.4.1 Definitions 110
10.4.2 Contraception Guidance 112
10.5 Appendix 5: Calculating the Child-Pugh Score 113
10.6 Appendix 6: Calculating Glomerular Filtration Rate 114
10.7 Appendix 7: Calculating CHA_2DS_2-VASc Score 115
10.8 Appendix 8: Modified Rankin Scale 116
10.9 Appendix 9: Outcome Events: Data Collection 117
10.10 Appendix 10: DCT Model for DCT Sites Only 118
10.10.1 Recruitment, Onboarding, Training in DCT Model 118
10.10.2 Schedule of Activities for DCT Model (DCT SoA) 120
10.11 Appendix 11: Tokenization 122
10.12 Appendix 12: Country/region-specific Requirements 123
10.12.1 China 123
10.12.1.1 CHN: Country/region-specific Changes Valid for China only 123
10.12.2 Japan 127
10.12.2.1 JPN: Country/region-specific Changes Valid for Japan only 127
10.12.3 Republic of Korea 128
10.12.3.1 KOR-1: Country/region-specific Changes Valid for the Republic of Korea only 128

11. References 134

Table of Tables

Table 1–1: Summary of study objectives and endpoints 18
Table 1–2: PK, PD and Biomarker sampling 25
Table 2–1: Risk assessment 30
Table 3–1: Study objectives and endpoints 35
Table 6–1: Study Interventions Administered 51
Table 6–2: Study Arms 51
Table 8–1: Reporting of events 77
Table 9–1: Analysis sets 82
Table 10–1: Protocol-required Safety Laboratory Tests 101
Table 10–2: Liver Laboratory Monitoring 104
Table 10–3: Grading of severity of liver disease 113
Table 10–4: Child-Pugh score 113
Table 10–5: CHA_2DS_2-VASc score 115
Table 10–6: Modified Rankin Scale (mRS) and Corresponding Sections of a Structured Interview 116

Table of Figures

Figure 1–1: Study design overview 22
Figure 2–1: FXI(a) in the coagulation cascade 27
Figure 9–1: Graphical testing strategy 82

List of Abbreviations and Definitions of Terms

A1AT	Alpha-1 antitrypsin
AE	Adverse Event
ACC	American College of Cardiology
ADL	Activities of daily living
AF	Atrial fibrillation
AG	Joint stock company, *Aktiengesellschaft*
AHA	American Heart Association
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
ANA	Antinuclear antibodies
AP	Alkaline phosphatase
aPCC	Activated prothrombin complex concentrate
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
ASMA	Anti-smooth muscle antibodies
AST	Aspartate aminotransferase
AXIA	Activated Factor XIa activity
BARC	Bleeding Academic Research Consortium
BCRP	Breast Cancer Resistance Protein
BID	Twice a day, *Bis in die*
BMS	Bristol-Myers Squibb
BP	Blood pressure
BUN	Blood urea nitrogen
BYOD	bring your own device
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CEC	Clinical Events Committee
CEOT	Common End of Treatment
CES1	Carboxylesterase 1
CFR	Code of Federal Regulations
CHEST	American College of Chest Physicians
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CHMP	Committee for Medicinal Products for Human Use
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COA	Clinical Outcome Assessment
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CPMP	Committee for Proprietary Medicinal Products
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical study report
csHR	Cause-specific hazard ratio

CV	Cardiovascular
CYP2C8	Cytochrome P450, family 2, subfamily C, polypeptide 8
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
D	Day
DCT	Decentralized clinical trial
DNA	Desoxyribonucleic acid
DRE	Disease-related Event
DtP	Direct-to-participant
e.g.	For example, *exempli gratia*
EC	Executive Committee
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
eICF	Electronic Informed consent form
EMA	European Medicines Agency
ePRO	Electronic Patient Reported Outcomes
EQ-5D	European Quality of Life group 5-Dimension questionnaire
ESC	European Society of Cardiology
ET	Early termination
EU	European Union
EudraCT	European Clinical Trials Database
F	Factor
FAS	Full Analysis Set
FDA	Food and Drug Administration
FeCl	Ferric chloride
FEIBA	Factor eight inhibitor bypass activity
FFP	Fresh frozen plasma
4F-PCC	4-factor Prothrombin complex concentrate
FSH	Follicle stimulating hormone
γGT	Gamma glutamyl transpeptidase
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HA	Health Authority
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
HCM	Hypertrophic cardiomyopathy
HCRU	Healthcare resource utilization
HDPE	High-density polyethylene
HDV	Hepatitis D virus
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HN	Home nurse
HR	Hazard ratio

HRS	Heart Rhythm Society
HRT	Hormonal replacement therapy
i.e.	That is, *id est*
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISTH	International Society on Thrombosis and Hemostasis
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous(ly)
LAA	Left atrial appendage
LAM	Lactational amenorrhea method
LDH	Lactate dehydrogenase
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MD	Medical doctor
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MI	Myocardial infarction
mRS	Modified Rankin Scale
N	Total number of participants
NA	Not applicable
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
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
P-gp	Permeability glycoprotein
PK	Pharmacokinetic(s)
PLC	Program Leadership Committee
PPIs	Proton pump inhibitor
PROs	Patient Reported Outcomes
PT	Prothrombin time
PtP	Pharmacy-to-participant
QC	Quality control

RBC	Red blood cell (count)
RCT	Randomized controlled trial
RHR	Resting heart rate
RNA	Ribonucleic acid
RND	Randomization
ROTEM	Rotational thromboelastometry
SAC	Statistical analysis center
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical analysis software
SC	Steering Committee
SCR	Screening
SD	Single dose
SDLL	Source Data Location List
SFU	Safety follow-up
SI	Study intervention
SoA	Schedule of activities
StP	Site-to-participant
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment Emergent Adverse Event
TIA	Transient ischemic attack
TKA	Total knee arthroplasty
TM	Trademark
TMF	Trial Master File
U	Unit
ULN	Upper limit of normal
US / USA	United States / United States of America
vs.	As compared to, *versus*
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
W	Week
WBC	White blood cell (count)
WOCBP	Woman of Childbearing Potential
WONCBP	Woman of Nonchildbearing Potential

Definitions

BAY 2433334	Sponsor's drug number for asundexian. Throughout this document, the sponsor's investigational intervention will be referred to as asundexian for better readability.
Bring Your Own Device (BYOD)	Participation in the DCT element of the study requires the use of a camera-equipped, web-enabled device which can be provisioned by the site, or participants can use their own – known as "BYOD" – as long as it meets certain minimum hardware requirements.
DCT Platform	Software that acts as the central point for some or all of the digital study components of a DCT. This can be in the form of a web portal (for use on desktop or laptop computers / via web browser on a smartphone or tablet) and / or an app to be used on a smartphone or tablet and depending on the requirements of the study, may be utilized by site teams, remote providers (e.g. home nurses) and the participants themselves. The platform may act as a "hub" to more seamlessly connect other apps or systems used by the study to improve the user experience by reducing the number of interfaces. The DCT platform can host patient engagement or learning content, reminders or provide a route for participants to contact or share information with the site team directly. It can also act as a point for remote source data capture (e.g. for home nursing). The DCT platform may be able to be integrated with other systems such as IRT to allow more efficient transfer of data between them.
Direct-to-participant (DtP)	Delivery of the study intervention to the participant's home. There are 3 possible options for DtP shipments, depot-to-participant, pharmacy-to-participant (PtP) and site-to-participant (StP) and these are chosen based on the needs of the trial and country-specific regulations.
eConsent / eICF	The use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive websites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent. This may also include electronic signature of the consent form. All or parts of the overall process may be conducted

	remotely, dependent on study set up and local regulations (in some countries all or part of the consenting / signature process must be done in person and / or wet ink signatures are mandatory).
eCOA / ePRO	eCOA is an electronic method of collecting data about a patient's experience with his / her disease and treatment. Patient Reported Outcomes (PROs) are diaries and questionnaires that assess the patient's view. COAs can be administered by the site during a clinic visit or at home using mobile devices to capture the data related to the assessment.
Engagement Content	Any content that plays an important role in the engagement of the participant in the study. It could be in the form of reminders to complete activities, surveys regarding certain services, providing educational material, a patient community platform, reminders, and gamification of the components like ePRO.
Home Nurse (HN)	Home nursing enables nurses / phlebotomists to perform study-related procedures such as blood draws, collection of vital signs, ECG or drug administration in the participant's home or other suitable location convenient to the patient. Nurses are able to process biological samples using bench-top devices and can pass processed specimens to a courier or will deliver them themselves to a local courier depot or site. In this protocol, "home nurse" is also referred to as "home health".
Participation Kit	This kit provides the participants in the DCT model with the technology and instruction guide for remote participation. The kit includes an instructional guide, ECG device, and a provisioned smartphone, unless the participants opt to use their own device.
Patient Service Center	A laboratory or network of laboratories separate from (and often independent of) site facilities with a more convenient location and ease of access for patients e.g. location within a pharmacy. The patient service center can be used to facilitate the collection of biological samples such as blood and other measurements such as weight, and vital signs during a clinical study.

Remote Metasite	A site that enrols patients and maintains oversight remotely. The site can be an existing brick and mortar site that offers remote services.
Teleresearch	Technology that allows long-distance contact between a participant and the clinician, using a video call. It can also be used in combination with other modules to deliver training or monitoring, e.g. if the investigator needs to ask certain questions to a participant. In a broader sense this also includes phone calls in case a video interaction is not accomplishable due to technical reasons.
Visit	Scheduled interaction, i.e. site visit, teleresearch, or phone call
Wearables and devices	Digital technologies designed for the monitoring of a participant remotely. This could be a connected device, e.g. an ECG device. The monitoring of participants via digital technologies can also be referred to as “remote monitoring” or “remote patient monitoring”. This is not to be confused with the remote monitoring a clinical research associate does as part of study oversight.

1. Protocol Summary

1.1 Synopsis

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.

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.

Envisaged indications:

Prevention of stroke and systemic embolism in patients with atrial fibrillation (cardioembolic stroke prevention).

Rationale:

Current guidelines recommend long-term oral anticoagulant therapy such as non-Vitamin K oral anticoagulants (NOACs) or Vitamin K antagonists (VKAs) for patients with atrial fibrillation (AF) at risk for stroke. Despite the better benefit-risk profile for NOACs when compared with VKAs, patients receiving NOACs continue to have an important residual risk for experiencing stroke, systemic embolism and cardiovascular (CV) death. In addition, there is still an important risk for bleeding. The inhibition of FXIa with asundexian is expected to have superior yet at least similar efficacy while leading to less bleeding and an overall net clinical benefit when compared with the NOAC apixaban.

Objectives, Endpoints and Estimands:

Table 1–1: Summary of 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*
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*

Abbreviations: CV = cardiovascular, ISTH = International Society on Thrombosis and Hemostasis, mRS = modified Rankin Scale

* 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 primary efficacy **estimand** is the cause-specific hazard ratio of the composite of stroke or systemic embolism comparing the assignment to asundexian with the assignment to apixaban

in adult patients with atrial fibrillation at risk for stroke while alive and including effects of treatment discontinuation or treatment with dual antiplatelet therapy.

The primary safety **estimand** is the cause-specific hazard ratio of ISTH major bleeding when treatment with asundexian is compared to treatment with apixaban in adult patients with atrial fibrillation at risk for stroke who have taken at least one dose of asundexian or apixaban while alive and while exposed to asundexian or apixaban.

The primary net clinical benefit **estimand** is the cause-specific hazard ratio of stroke, systemic embolism, or ISTH major bleeding (excluding hemorrhagic stroke) when treatment with asundexian is compared to treatment with apixaban in adult patients with atrial fibrillation at risk for stroke who have taken at least one dose of asundexian or apixaban while alive and while exposed to asundexian or apixaban.

Overall Design Synopsis:

OCEANIC-AF (study 19767) is a multicenter, international, 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 with atrial fibrillation at risk for stroke, will be randomized to 1 of the 2 arms (approximately 9000 participants per arm), as follows:

- 1 investigational study intervention arm asundexian 50 mg once a day (OD) and
- 1 active comparator arm apixaban 5 mg twice a day (BID) or 2.5 mg BID, according to label (for details see Section 6.1).

A fully remote **decentralized clinical trial (DCT) model** may be implemented in selected countries.

Randomization will be first stratified by participation in the conventional study model vs. in 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 randomly assigned to 1 of the 2 treatment arms in a 1:1 ratio.

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. At the same time approximately the same number of participants are expected to experience a primary safety outcome. The planned individual study duration is expected to be 10-34 months; however the timelines may vary (i.e. longer or shorter than planned). The study will consist of the following study periods:

- **Screening period (from visit 1 until visit 2)**: 2 weeks (participants will be screened and have to be randomized within 2 weeks after screening). If all information is available, a participant can be randomized on the day of screening (visits 1 and 2 are combined). **For participants in the DCT model**, after obtaining informed consent, an additional time interval of up to 2 weeks will be required (refer to Section 10.10).
- **Intervention period (from visit 2 until the common end of treatment [CEOT] visit)**: approximately 9-33 months. The intervention period will end when the required number of primary efficacy endpoint events has accrued. For an individual participant

the CEOT visit marks the end of the intervention period. For participants permanently discontinuing study intervention, see also early termination period.

- **Common End of treatment period (from CEOT visit until CEOT safety follow-up [SFU] visit)**: 2-week period that will end upon completion of the CEOT SFU visit for participants who did continue intake of study intervention as expected.

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

- **Early termination (ET) period (from ET until CEOT visit):** If the study intervention is *permanently* discontinued earlier than expected, the participant will enter the ET period and an ET visit has to be performed as soon as possible. All living participants who permanently discontinued study intervention prior to the CEOT visit are still part of the study and should participate in their visits as scheduled (preferably via telephone) as part of their ET period. In those participants also the above mentioned CEOT visit will need to be performed, that marks the end of the ET period.

  For participants who prematurely discontinue study intervention ≥ 2 weeks prior to the CEOT visit, an ET safety SFU visit will also be conducted 2 weeks after permanent discontinuation of study intervention. In such a case the CEOT visit will represent the last study visit.

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

Short Summary:

The purpose of this study is to investigate the efficacy of the oral FXIa inhibitor asundexian in prevention of stroke and systemic embolism and its safety (bleeding risk) compared with apixaban in adult participants with atrial fibrillation at risk for stroke. The inhibition of FXIa with asundexian is expected to have superior yet at least similar efficacy while leading to less bleeding when compared with the NOAC apixaban.

Study details include:

The study duration for an individual participant is expected to be up to approximately 34 months. This is an estimate, and all participants will be followed until the end of the study.

- The recruitment period of the study is expected to be approximately 24 months.
- The individual treatment duration is expected to be minimum approximately 9 months and maximum approximately 33 months.
- There will be a screening visit followed by a randomization visit within 2 weeks. The visit frequency after randomization will be a first visit after 1 month, the next visit after 3 months and then every 3 months until the common end of treatment (CEOT) visit. A safety follow-up visit will take place 2 weeks after the CEOT visit.

Number of Participants:

Approximately 20000 participants will be screened to achieve 18000 randomized participants for an estimated total of 9000 randomized participants per intervention group. This is an event-driven study. The required target number of study participants who have experienced a primary efficacy event is estimated to be approximately 340. The target number of study

participants with a primary safety event while exposed to study intervention is approximately the same as for primary efficacy. More details are available in Section 9.5.

Study Arms and Duration:

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

- Asundexian 50 mg OD
- Apixaban 5 mg or 2.5 mg BID, according to product label.

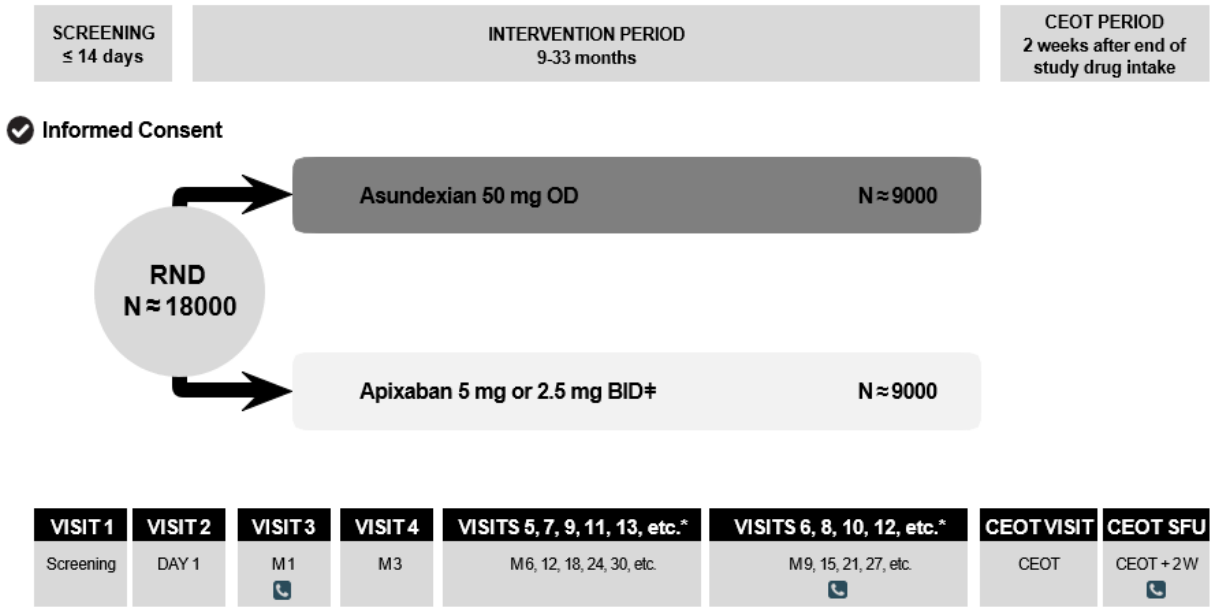
The total duration of study participation, along with the sequence and the duration of study periods, is provided under "Overall Design Synopsis", and in Section 4.1.

Independent Data Monitoring Committee:

An Independent Data Monitoring Committee (IDMC) will be involved in the review of the safety data as well as efficacy data to determine the risk / benefit ratio across the Phase 3 studies with asundexian (Section 10.1.6.4). Detailed information on the roles and responsibilities of the IDMC will be described in the IDMC Charter.

1.2 Schema

Figure 1–1: Study design overview



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

‡ 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.

Participants of the decentralized clinical trial model will have the screening visit split into a “part a” to initiate operational logistics and a “part b” to perform screening procedures.

1.3 Schedule of Activities (SoA)

Study periods Duration	**Screening** **≤2** weeks before **RND**	**Intervention period** **~9 → ~33** months*, from **RND** until **Common End of Treatment (CEOT) visit** / **Early Termination (ET)**											**Early Termination period**** **ET** until **CEOT visit**			**CEOT period** **CEOT visit** until **2** weeks after	
Visit number / acronym	**1**	**2‡**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12***	**13***	**ET visit**	**ET SFU visit**	**≥3 → 13***	**CEOT visit**	**CEOT SFU visit†**
Visit type	site	site	☎	site	site	☎	site	☎	site	☎	site	☎	site	site	☎ (site)	☎ (site)	site (☎)	☎
Visit / Month [M] Day [D] / ± allowed windows Week [W] ± allowed windows	**SCR** D-14 → 1	**RND / M0** D1	**M1** 30±4	**M3** W13±1	**M6** 26±1	**M9** 39±1	**M12** 52±1	**M15** 65±1	**M18** 78±1	**M21** 91±1	**M24** 104±1	**M27** 117±1	**M30** 130±1	**ET** ET	**ET+2W** (ET+2W)+1W	**≥M1 → M30** ≥D30±4 → W130±1	**CEOT** CEOT±~3W	**CEOT visit+2W** (CEOT visit+2W)+1W
Administrative procedures																		
Informed consent	X																	
Inclusion / exclusion criteria	X	X																
Demographics / biometrics	X																	
Medical history	X	X																
Prior / concomitant medication	←==========continuously==========→															AP/AC only	X (AP/AC only)	X
Clinical procedures / assessments																		
ECG	X	(X)																
Vital signs (BP and RHR)	X	(X)																
Adverse events	only procedure related events	←==========continuously==========→															X†	X
Outcome events		←==========continuously==========→																
HCRU		←==========continuously==========→																
EQ-5D		X			X		X		X		X		X	X			X†	
IRT																		
Randomization / Visit registration	X	X		X	X		X		X		X		X	X			X	
Laboratory assessments																		
Safety blood sampling	X	(X)		X	X		X				X			X			X†	
Pregnancy test (if WOCBP)	X	X												X			X†	
PD / Biomarkers (a); PK (b)		a		a, b			a, b											
Study intervention (SI) shipment																		
SI dispensation		X		X	X		X		X		X		X					
SI collection / accountability				X	X		X		X		X		X	X			X†	

Note: SoA for the DCT model can be found in Section 10.10.2.

Annotated Schedule of Activities (Annotated SoA)

Administrative procedures	
Informed consent	informed consent must be obtained before initiation of any study-specific procedures
Inclusion / exclusion criteria	in case SCR and RND are performed on the same calendar day, these criteria need to be assessed only once
Demographics / biometrics	biometrics refers to measurement of height and weight and will only be performed and recorded at screening
Medical history	in case SCR and RND are performed on the same calendar day, this needs to be assessed only once
Prior / concomitant medication	in case SCR and RND are performed on the same calendar day, this needs to be assessed only once; in case a participant pretreated with a NOAC (or another antico-agulant) has already taken the anticoagulant on the planned day of randomization, intake of study intervention should be postponed by one day (Section 6.1.1); if SI is *permanently* discontinued ≥ 2W before CEOT visit, *only* AP / AC need to be reported at scheduled visits, including CEOT visit; otherwise all meds need to be reported
Clinical procedures / assessments	
ECG	to display ≥ 6 leads; can also be used if done as part of routine management and no older than 30 days at RND; no need to be repeated once available (Section 8.3.6)
Vital signs (BP and RHR)	can also be used if done as part of routine management and no older than 14 days at RND; no need to be repeated once available (Section 8.3.5)
Adverse events	(S)AEs will be collected from start of SI intake until SFU visit; only study procedure related events will be reported from signing of ICF onward (Section 8.4.1)
Outcome events	outcome events including all bleeding, death, MI, stroke and systemic embolism, as well as events indicative of a potential outcome (Section 8.4.6) need to be reported continuously from RND until death or last study visit (= CEOT SFU; *only* if SI is *permanently* discontinued ≥ 2 W prior to CEOT visit reporting occurs until CEOT visit)
HCRU	HCRU (within hospitals) in conjunction with SAEs and outcome events needs to be documented, e.g. time points or periods affected (Section 8.10.1)
EQ-5D	participants should complete the questionnaire during the visits at the timepoints reported in the SoA
IRT	
Randomization / Visit registration	SCR and RND can take place on the same calendar day if all information is available (Visits 1 and 2 are combined); study intervention intake will start as soon as possible after randomization (day 1), preferably on the day of randomization, and is expected to continue until the day prior to the CEOT visit
Laboratory assessments	
Safety blood sampling	creatinine and eGFR values must be available at RND; if not available from SCR central lab, respective values should be determined in local lab prior to RND; values obtained as part of routine management can also be used if no older than 14 days at RND (Section 8); in any case, the full set of safety laboratory tests (Table 10–1) needs to be obtained once during the SCR period, at the latest at RND, and at indicated visits thereafter
Pregnancy test (if WOCBP)	a WOCBP must have a negative serum or urine pregnancy test at SCR; a repeat test at RND (before SI intake) is required, unless ≤ 4 days lie between SCR and RND
PD / Biomarkers (a); PK (b)	refer to Table 1–2 regarding further details; pharmacogenetics will be collected in a subset of participants
Study intervention (SI) shipment	
SI dispensation	the term “SI” includes the comparator drug as defined in Section 6.1; at each contact the participants should be instructed regarding SI compliance
SI collection / accountability	at the CEOT visit the final SI collection occurs: no SI intake should take place on the day of this visit anymore; the last intake of SI occurs on the previous day

Abbreviations: AP / AC = antiplatelets / anticoagulants, BP = blood pressure, CEOT = Common End of Treatment, D = day, ECG = electrocardiogram, EQ-5D = European Quality of Life group 5-Dimension questionnaire, ET = early termination, HCRU = healthcare resource utilization, RHR = resting heart rate, ICF = informed consent form, IRT = interactive response technology, M = month, PD, PK = pharmacodynamic(s), -kinetic(s), RND = randomization, SCR = screening, SFU = safety follow-up, SI = study intervention, W = week(s), WOCBP = woman of childbearing potential

‡ procedures and assessments at visit 2 should preferably be conducted prior to RND; SI dispensation / intake will usually be concluding the visit

* if applicable (if the number of efficacy outcome events does not accrue until Month 33 as expected) the visit schedule will continue after Month 30 with the respective labelling, e.g. Visit 14, 15. The duration of the intervention period (~9 to ~33 months) depends on when a participant joins during the course of the study. Displayed timepoints might therefore not be applicable to all participants.

** An **early termination visit** is only applicable to participants who prematurely discontinue intake of SI *permanently*; those should undergo an ET visit as soon as possible after discontinuation of SI. An **ET SFU visit** will occur 2 weeks (+ 7 days window) after the day of the discontinuation of SI (Section 7.1), unless *permanent* discontinuation occurred < 2 W prior to CEOT visit, in which case a **CEOT SFU** will be performed instead. After permanent discontinuation of SI participants should take part in the remaining visits (via phone) as scheduled, until including the CEOT visit (or CEOT SFU).

† if SI *permanently* discontinued: item not applicable; only if discontinued < 2 W before CEOT visit, CEOT SFU will replace ET SFU; if SI is *permanently* discontinued a phone call CEOT visit is expected

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

Table 1–2: PK, PD and Biomarker sampling

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

Abbreviations: PD = Pharmacodynamic(s), PK= Pharmacokinetic(s)

* at all visits: in order to collect pre-dose samples for PK,PD and biomarker plasma / serum, participants should take their study intervention at the site only after blood sampling. The investigator must record the time when the study intervention is taken at the site. A phone call to remind the participants is recommended. Biomarker blood for pharmacogenetics can be collected at any time in relation to study intervention intake.

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

PK samples will be collected in all participants of the conventional study model; PD and biomarkers will be collected in subsets of participants if approved by local IECs / IRBs and competent authorities (refer to Sections 8.5, 8.6 and 8.8). Biomarker blood for pharmacogenetics is generally planned to be collected at the randomization visit (Day 1), however, it can also be collected at a later visit in case it has not yet been taken (refer to Section 8.7).

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

2. Introduction

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

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

OCEANIC-AF (study 19767) will evaluate the efficacy and safety of asundexian versus apixaban, a FXa inhibitor (NOAC), in participants with AF. The study will be an event-driven Phase 3 study with expected treatment duration of 9-33 months (refer to Section 9.5 for more details).

The current clinical development of asundexian (FXIa inhibitor) includes 1 additional Phase 3 study in participants with non-cardioembolic ischemic stroke or high-risk TIA (OCEANIC-STROKE, study 20604). This study is planned to also be event-driven and will be testing asundexian against placebo on top of antiplatelet therapy.

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

Thus, the 2 Phase 3 studies in AF and non-cardioembolic stroke are expected to support that asundexian may offer a uniform therapeutic option for ischemic stroke patients independent of the underlying ischemic stroke's etiology (cardioembolic or non-cardioembolic).

2.1 Study Rationale

This Phase 3 study will explore asundexian 50 mg once daily to determine a lower risk for bleeding as well as an improved efficacy in terms of reduction of thromboembolic events when compared with apixaban (NOAC) in patients with AF at risk for stroke.

Current treatment guidelines recommend the use of long-term oral anticoagulant therapy such as VKAs, or NOACs in patients with AF at risk for stroke (refer to Section 2.2.2).

Despite a better benefit-risk profile for NOACs when compared with VKAs, patients receiving NOACs continue to have an important residual risk for stroke, systemic embolism and CV death. In addition, even though NOACs lead to less intracranial hemorrhage compared with VKAs, there is still an important risk for bleeding, including major bleeding.

Asundexian, as an oral FXIa inhibitor, is expected to show a benefit in reducing the risk for stroke or systemic embolism in patients with AF in Phase 3. This has been demonstrated by predictive animal models with asundexian indicating a potential for additional benefit in terms of thrombus prevention beyond of what has been shown with a therapeutic dose of NOACs. In addition, this is supported by the analysis of genetic data from FXI-deficient individuals. At the same time asundexian is expected to have a low risk for bleeding. This is based on the available preclinical data, data from patients with inherited FXI deficiency and clinical data from 4 Phase 2 proof of concept studies in participants undergoing total knee replacement (see Section 2.3), as well as data from the completed dose finding Phase 2 study comparing the safety of asundexian to apixaban in patients with atrial fibrillation (PACIFIC-AF(Piccini et al. 2022) reported in the Investigator's Brochure (IB).

Asundexian is therefore an attractive candidate to be evaluated as a potential replacement for NOAC therapy in patients with AF.

2.2 Background

2.2.1 Disease Background

AF is the most common sustained cardiac arrhythmia and is associated with increased rates of death, stroke and other thromboembolic events. It has been estimated that about 33.5 million patients worldwide are affected by AF (Chugh et al. 2014). AF is a particularly common disorder in the elderly, with a prevalence of less than 1% in the population under 60 years of age, and with estimates of up to 17% among those over 80 years of age (Wilke et al. 2013). As a consequence of the aging population, the prevalence of AF is predicted to rise (Dai et al. 2021).

Patients who have AF are known to have a markedly increased risk for stroke due to a predisposition to the development of atrial thrombi (Wolf et al. 1991). Full anticoagulation with Vitamin K antagonists was the recommended therapy until the introduction of NOACs.

2.2.2 Treatment Guidelines

Current guidelines AHA / ACC / HRS 2014 (January et al. 2014), CHEST 2018 (Lip et al. 2018), as well as the focused update AHA / ACC / HRS 2019 (January et al. 2019), ESC 2020 (Hindricks et al. 2021) and EHRA 2021 (Steffel et al. 2021) recommend the use of long-term oral anticoagulant therapy such as VKAs or NOACs like Factor Xa- (rivaroxaban, apixaban, edoxaban) or Factor IIa- (dabigatran) inhibitors for patients with AF at risk for stroke.

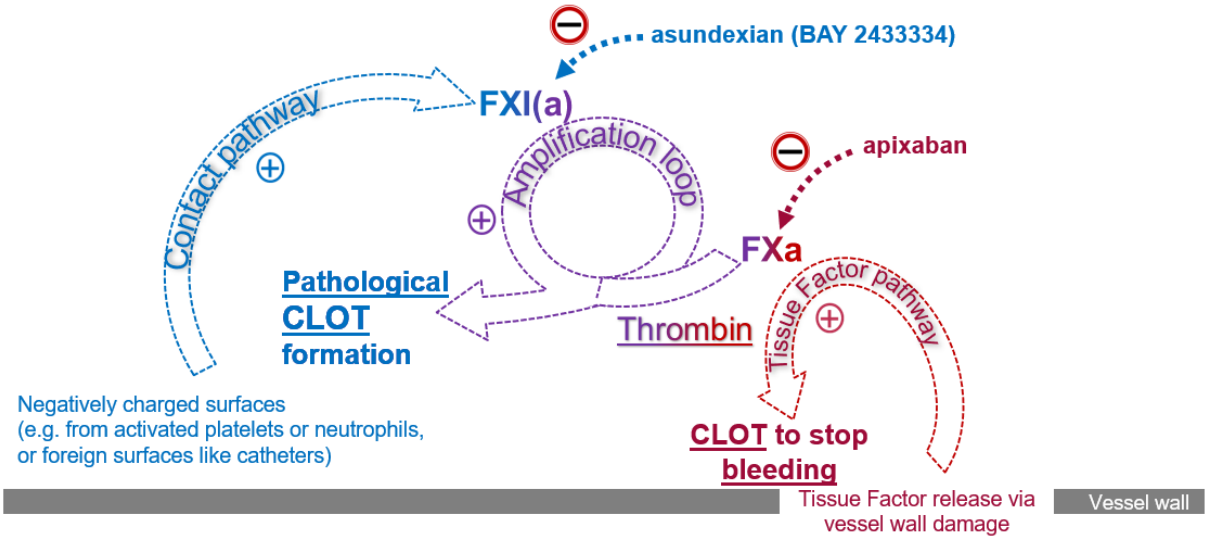
2.2.3 FXIa Inhibition: Mode of Action

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

The plasma serine protease zymogen factor XI (FXI) is activated after initiation of the contact activation pathway via factor XIIa (FXIIa) and during the amplification phase as part of a positive feedback loop through activation by thrombin (Figure 2–1). FXIa is thought to contribute strongly to clot progression, which may potentially lead to vessel occlusion and pathological manifestations of thrombosis but has minor impact on hemostasis due to its limited role in the initiation phase of the extrinsic (tissue factor) pathway (Heitmeier et al. 2022).

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

Figure 2–1: FXI(a) in the coagulation cascade



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

Drafted by Heitmeier S and van Giezen JJJ, 2021.

2.2.4 Asundexian (BAY 2433334)

Preclinical / Toxicology Data

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

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

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

Clinical Data

As of June 2022, the sponsor conducted 20 Phase 1 studies in more than 550 subjects which investigated the safety, tolerability, PK and pharmacodynamic (PD) properties of asundexian. Two additional clinical Phase 1 studies are currently ongoing. Doses of asundexian that were tested in these studies ranged from 5 mg to 150 mg as single doses, and multiple doses up to 100 mg once daily.

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

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

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

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

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

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

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

2.3 Benefit/Risk Assessment

The FXIa inhibitor asundexian is an oral anticoagulant that is planned to be developed for patients with AF as well as non-cardioembolic ischemic stroke or high-risk TIA. Phase 2 studies have been initiated in 2020 in the 2 mentioned indications as well as in AMI and have recently ended (AF in October 2021, AMI and non-cardioembolic stroke in February 2022). The Phase 2 PACIFIC-AF study was the first study investigating asundexian in patients with AF. Once daily doses of 20 mg and 50 mg were tested in the study. Based on analysis of the overall data from the Phase 2 studies, a decision was made to select the 50 mg dosage for the Phase 3. More details on the justification for this can be found under Section 4.3.

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

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

2.3.1 Risk Assessment

Potential risks related to the study investigational intervention, together with a brief description of strategies to mitigate these risks are displayed in Table 2–1.

Table 2–1: Risk assessment

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Study Intervention asundexian		
A risk for bleeding cannot be excluded in participants with AF included in the Phase 3 study and randomized to asundexian or to the comparator apixaban.	Bleeding is the main safety concern related to antithrombotic therapies. For an inhibitor of FXIa a lower bleeding risk is expected than with the comparator drug.	Exclusion criteria are phrased to exclude patients with a higher risk for bleeding (e.g. recent major surgery / active bleeding at randomization). Bleeding will be closely monitored in the study and will be adjudicated by an independent Clinical Events Committee. Furthermore, an IDMC will be installed monitoring unblinded study data on an ongoing basis.
Liver-related adverse effects.	The findings regarding liver-related adverse events were reassuring during the PACIFIC Phase 2 studies. Liver-related adverse effects will continue to be monitored to further characterize the clinical profile of asundexian.	Patients with known significant liver disease or known hepatic insufficiency classified as Child-Pugh B or C will be excluded from Phase 3, liver parameters are part of the safety laboratory panel and follow-up will be required for certain liver events. Furthermore, an IDMC will be installed monitoring unblinded study data on an ongoing basis.
Study Procedures		
Clinical procedures or assessments mandated by the protocol (see SoA) are routine measures from everyday practice. They do not carry a risk of clinical significance to the safety of the participants.	Procedures or assessments do not pose more than minimal additional risk or burden compared with normal clinical practice.	No mitigation strategy is required.
Participation in this study presents minimal risk for SARS-CoV-2 infection during study participation.	As long as the COVID-19 pandemic situation is ongoing, there is a risk of SARS-CoV-2 infections for study participants as for the general population. However, this risk during study participation is not increased compared to the general population.	In order to minimize their infection risk during study participation, the investigators / sites will follow all recommendations issued by local authorities and guidelines aiming to reduce the risk of disease spreading. Details on the measures are specified by the site and agreed with the sponsor. Measures which prioritize participant safety and data validity are implemented. In case these 2 objectives conflict, participant safety always prevails. During the pandemic situation, further measures according to recommendations and requirements from local health authorities may become necessary. These will be followed within the context of this study as far as applicable.

Abbreviations: COVID-19 = Coronavirus Disease 2019, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2

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

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

FXI and risk for bleeding:

- Patients with inherited FXI deficiency are typically identified when presenting with a prolonged activated partial thromboplastin time (aPTT) in routine clinical testing. There is no direct association between FXI activity levels and bleeding risk, though historically and predominantly in the Ashkenazi Jewish population, FXI deficiency has been categorized as having a mild bleeding phenotype that generally only manifests following injury or trauma in tissues with high fibrinolytic activity (Visser et al. 2020).

Nonclinical Evidence:

- FXI-deficient knockout mice do not show a bleeding phenotype. In addition, in rabbits treated with FXIa inhibitors no increase in bleeding time (gum and ear) or blood loss (liver injury model) was reported. Importantly, no further increase in bleeding time was seen when asundexian was given on top of dual antiplatelet agents. In addition, in the toxicology studies no relevant bleeding was reported for up to 31-fold the expected human exposure of the planned 50 mg multiple dose in patients.

Clinical Evidence:

- In the completed and ongoing Phase 1 studies conducted with asundexian, no relevant bleeding events were reported.
- The completed Phase 2 studies showed less bleeding when compared to apixaban in patients with atrial fibrillation and no clinically relevant increase in bleeding when compared to placebo on top of antiplatelet therapy in patients with AMI or non-cardioembolic stroke.

  A risk for bleeding cannot be excluded in participants with AF included in the Phase 3 study, especially also in patients that receive concomitant therapy with antiplatelet therapy. Specific eligibility criteria have been implemented to exclude patients with a higher risk for bleeding (e.g. with a known bleeding disorder or on dual antiplatelet therapy; refer to Section 5.2). Bleeding will be closely monitored in the study and will be adjudicated by an independent and blinded Clinical Events Committee.

2. In toxicology studies, the liver was identified as a target organ in the rat but not in the dog. This included dose-dependent spontaneous, mostly transient increases in liver enzymes in single animals without clear correlation to histopathological findings in the hepatic tissue. Based on this, patients with a > 2.5-fold ALT or AST increase were excluded from the PACIFIC Phase 2 studies and liver findings during the studies were defined as AE of special interest. Analysis of the AEs of special interest as well as laboratory elevations of transaminases from the more than 3000 exposed participants were reassuring, with no cases identified meeting Hy's law criteria (i.e. any elevated ALT or AST > 3 x ULN, AP < 2 x ULN, and associated with an increase in bilirubin ≥ 2 x ULN and no alternative explanation). Nevertheless, patients with known significant liver disease or known hepatic insufficiency classified as Child-Pugh B or C will be excluded in Phase 3, liver parameters

are part of the safety laboratory panel and follow-up will be required for certain liver events (refer to Section 10.2.1).

3. In all completed Phase 1 and 2 studies asundexian was well tolerated and no additional safety signal was identified regarding general safety, laboratory parameters or vital signs and ECGs. The dedicated Phase 1 thorough QT study was negative, i.e. asundexian did not have an influence on the corrected QT interval at single doses of 50 mg and 150 mg. The completed Phase 2 PACIFIC program showed no specific safety concerns regarding laboratory parameters or vital signs. Furthermore, no new or unexpected safety topic has been identified in the Phase 2 studies. In these studies, the characteristics of SAEs (including life-threatening and fatal SAEs) in general are consistent with the corresponding clinical populations.

In order to ensure the safety of the patients enrolled in each of the Phase 3 studies, an IDMC will monitor the safety with a focus on bleeding and general safety during the study conduct for each of the Phase 3 indications. Furthermore, there will be an overarching IDMC assessing the data from all 2 studies together.

In conclusion, asundexian is believed to represent a potentially improved new therapeutic option for thrombosis prevention in life-threatening thrombotic diseases with superior bleeding safety compared to oral anticoagulants and without a significant increase in bleeding risk on top of available antiplatelet therapy. This also could permit treatment of patients at higher risk for bleeding events than current standards of care allow. Moreover, the dose selection was not limited by bleeding in Phase 2, thus choosing the highest dose studied in Phase 2, 50 mg once daily, for further investigation in Phase 3. Ultimately, currently available preclinical and clinical data from the ongoing and completed studies regarding the key risks do not indicate an unfavorable risk profile for asundexian.

2.3.2 Benefit Assessment

At this stage of development there is clinical evidence available suggesting the efficacy benefit of asundexian in the non-cardioembolic-stroke indication. The Phase 2 PACIFIC-AF study was not planned for assessment of efficacy of asundexian versus apixaban due to the limited number of participants with efficacy events within a 3-month intervention period (< 0.5% at 3 months), however, the data supporting that this compound is expected to lead to prevention of thrombosis events in the intended indications are the following:

FXI and risk for thrombotic events:

- In subjects with inherited Factor XI deficiency, a rare coagulation deficiency caused by either reduced production of factor XI or by production of a loss-of-function factor XI molecule, a lower risk for venous thromboembolic events as well as cardiovascular events and especially stroke has been reported. The lower stroke risk was particularly evident in patients with atrial fibrillation (Georgi et al. 2019).
- Increased levels of FXI are reported as a risk factor for venous thromboembolism and myocardial ischemia or stroke. Whether there is a causal relationship is unclear (Schumacher et al. 2010).

Nonclinical evidence:

- FXI-deficient knockout mice are protected from thrombosis (Wang et al. 2005). In addition, in various thrombosis models in rabbits, administration of asundexian

resulted in a dose-dependent thrombus weight reduction compared to control animals, and this was seen when given alone or on top of dual antiplatelet treatment. While clinically relevant doses of NOACs translate into 20-30% thrombus weight reductions in such models, asundexian was able to reduce the thrombus formation by up to ~90% at doses with aPTT prolongations similar to the ones of the 20 and 50 mg doses tested in the PACIFIC Phase 2b program (Heitmeier et al. 2022, Piccini et al. 2022).

Clinical evidence:

- Phase 1 Pharmacodynamics:

  Studies of asundexian in healthy volunteers are not able to assess efficacy. However, after multiple dosing the 50 mg once daily dose in the Phase 1 multiple dose escalation study (also the highest dose being tested in Phase 2) lead to nearly complete inhibition of FXIa during 12 hours of the day as measured in a fluorogenic assay of activated FXIa (AXIA) in plasma. This was combined with a mean prolongation of activated partial thromboplastin time (aPTT) of ~105%. In addition, the compound was shown to be safe and well tolerated (Kubitza et al. 2005).

- Phase 2b Clinical Pharmacodynamics:

  In the PACIFIC studies, concentration-dependent, near complete inhibition of FXIa, measured with the AXIA assay (Heitmeier et al. 2022), was observed across the program. 50 mg OD asundexian led to rapid, sustained and near complete inhibition of FXIa, and this observation was consistent across all Phase 2 studies.

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

- Phase 2b Clinical Efficacy:

  Data from the PACIFIC-STROKE study indicate a benefit in the prevention of ischemic strokes (and TIA) in patients receiving asundexian 50 mg once daily. This trend is further supported by post-hoc characterization of relevant subgroups.

- Clinical Evidence from Other FXI(a)-Targeting Compounds:

  A first proof of concept targeting FXI as anticoagulant had been shown by a FXI Antisense Oligonucleotide (Büller et al. 2015), as well as a FXIa antibody (osocimab) (Weitz et al. 2020). Reducing FXI levels in patients undergoing total knee arthroplasty (TKA) led to an improved prevention of postoperative venous thromboembolism (VTE), when compared with enoxaparin. This was confirmed by 2 more recent studies with a further antibody compound (abelacimab) (Verhamme et al. 2021), as well as a small molecule compound (milvexian) (Weitz et al. 2021), both also tested in TKA patients.

Overall, there is no direct clinical evidence yet in patients with atrial fibrillation available which confirms the benefit of asundexian for stroke prevention in patients with atrial fibrillation. However, based on the clinical, nonclinical, and genetic data presented above, the sponsor expects asundexian to bring at least similar if not superior reduction in the risk for stroke or systemic embolism when compared to apixaban in patients with atrial fibrillation. Significant reduction in stroke in patients with non-cardioembolic stroke or high-risk TIA when compared to placebo on top of standard antiplatelet therapy is also expected and

supported by available data. Therefore, the data continue to support further development of these indications in Phase 3.

2.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with asundexian are justified by the anticipated benefits that may be afforded to participants with atrial fibrillation at risk for stroke. More detailed information about the known and expected benefits and risks and commonly reported AEs of asundexian may be found in the Investigator's Brochure.

In light of all measures implemented in this study to prevent infection of study participants with SARS-CoV-2 during the entire study conduct, the benefit / risk assessment for the conduct of this study is not altered by the COVID-19 pandemic in its current extent. The benefit / risk assessment will be continuously monitored during the conduct of this study and will be updated in accordance to changes of the COVID-19 pandemic situation and related authority regulations and recommendations.

3. Objectives, Endpoints, and Estimands

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

Table 3–1: Study objectives and endpoints

Objectives	Endpoints
Primary	
Efficacy	
To 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*
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	• Gastrointestinal bleeding* • All bleeding* • BARC type 3 and 5 bleeding* • BARC type 2, 3 and 5 bleeding* • BARC type 1 bleeding* • Total number of ISTH major bleeding events
Net clinical benefit	
To further investigate the benefit and risk of the study intervention	• Composite of weighted vascular efficacy and bleeding safety outcomes as defined by formal assessment of patient or physician preference • Total number of hospitalizations due to efficacy or safety outcome events
Other	
To further investigate the study intervention, and drugs with similar, e.g. mode-of-action related effects, and to further investigate pathomechanisms deemed relevant to cardiovascular diseases and associated health problems	• PK 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, 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:

For the 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

the primary efficacy estimand **for non-inferiority** and **for superiority assessment** is described by the following attributes:

- **Population:** Adult individuals with AF at risk for stroke
- **Treatment condition:**
  - Experimental: 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)
- **Endpoint:** time to first occurrence of stroke or systemic embolism
- **Population-level summary:** Cause-specific hazard ratio (i.e. ratio of cause-specific hazard rates of the primary endpoint) comparing the two treatment conditions
- **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 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).

Rationale for the primary efficacy estimand:

The clinical question related to the primary efficacy endpoint has two parts:

1. The first part of the objective is to show non-inferiority
2. The second part of the objective is to demonstrate superiority

of assigning asundexian versus apixaban for preventing stroke or systemic embolism in adult patients with AF at risk for stroke.

Relative to apixaban it is expected that asundexian will reduce the instantaneous risk for experiencing a stroke or systemic embolism in patients with AF over time. To summarize the relative effect of the two treatment conditions over time, the ratio of cause-specific hazard rates of the primary efficacy outcome is considered an appropriate summary measure. It will be supplemented with estimates of the cumulative incidence over time.

In terms of observing a primary efficacy outcome, death of participants after treatment assignment is considered a competing risk because it would preclude the primary efficacy outcome from occurring. Therefore, it is of interest to characterize the treatment effect prior to the death of a study participant, using the "while alive" strategy. In this setting, information on the treatment effect on the competing event "death" itself will complement the understanding of the treatment effects on outcome events other than death.

Further, it is assumed that an early discontinuation of asundexian or apixaban will alter the probability of the occurrence of a primary efficacy outcome event.

The primary clinical question is about the difference between assigning asundexian versus apixaban *including* effects of treatment discontinuation and implicitly, also including subsequent open label treatment with an anticoagulant. Assuming a beneficial effect of asundexian, using the treatment policy strategy is considered to produce a conservative estimate of the average effect that might be seen in clinical practice.

The need of dual antiplatelet therapy after randomization and intercurrent events related to the COVID-19 pandemic are addressed with the "treatment policy strategy", meaning that the effects of these intercurrent events are included into the estimation of the treatment effect. Thus, the estimation of the treatment difference reflects the clinical practice of confounding factors that cannot be controlled for.

The same estimand was defined for both the non-inferiority and the superiority evaluation and is in line with CPMP "Points to consider on switching between superiority and non-inferiority" (Committee for Proprietary Medicinal Products 2001). The trial will be carried out in accordance with the strict requirements (in terms of protocol deviations) of a non-inferiority trial and measurements of protocol deviations as well a premature discontinuation will be monitored during the conduct of the study.

To support decision making a supplemental analysis will be performed for an estimand more specifically targeting the non-inferiority objective to provide additional insights into the understanding of the treatment effect.

For the primary safety objective:

to demonstrate that asundexian is superior to apixaban in participants with atrial fibrillation as assessed by ISTH major bleeding

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

- **Population**: Adult individuals with AF at risk for stroke exposed to at least one dose of treatment
- **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)
- **Endpoint:** time to first occurrence of ISTH major bleeding
- **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
- **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 (here: 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 effect includes the effect of intercurrent events related to COVID-19 (other than the mentioned intercurrent events).

Rationale for the primary safety estimand:

The clinical question related to the primary safety endpoint is about a reduced risk for ISTH major bleeding when treating adult patients with AF at risk for stroke with asundexian as compared to apixaban.

The ratio of cause-specific hazard rates of the primary safety outcome is expected to summarize the relative effect of the two treatment conditions over time. As the hazard rate for asundexian is assumed to be constant over time and the same holds true for apixaban after some time of treatment, the ratio is assumed to be constant. Deviations from that assumption are negligible.

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

An early discontinuation of asundexian or apixaban (or the underlying reasons leading to treatment discontinuation) could alter the probability of the occurrence of a primary safety outcome event. It is of interest to quantify the risk associated with the intake of asundexian, i.e. while patients are exposed to the treatments. A participant is to be assumed exposed to study intervention up to 2 days after the last intake of study intervention. Therefore, the proposed estimand for the safety question addresses early treatment discontinuation using a “while exposed to randomized treatment” strategy (in the past: “on treatment effect”). This decision implies that early treatment discontinuation is considered a (”soft”) competing risk. Information on the treatment effect on the competing event “early treatment discontinuation” itself will complement the understanding of the treatment effects on outcome events.

Similar to the efficacy estimand the intercurrent events “treatment with dual antiplatelet therapy after randomization” and “intercurrent events related to the COVID-19 pandemic” will be addressed with the “treatment policy strategy” with the same rationale as for the efficacy estimand.

Patients who were assigned to a treatment arm (i.e. randomized) but never took a single dose of randomized treatment will be addressed via the population attribute of the estimand, i.e. the population is defined as those patients taking randomized treatment at least once.

For the primary net clinical benefit objective:

to demonstrate that asundexian is superior when compared to apixaban with respect to benefit and risk

the estimand for **net clinical benefit assessment** is described by the following attributes:

- **Population**: Adult individuals with AF at risk for stroke exposed to at least one dose of treatment
- **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)
- **Endpoint**: time to first occurrence of stroke, systemic embolism, or ISTH major bleeding (excluding hemorrhagic stroke)
- **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
- **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 (here: 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. net clinical benefit events and observation time up until death will be used
  - Treatment with dual antiplatelet therapy after randomization: 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)

Rationale for primary net clinical benefit assessment estimand:

The clinical question related to the net clinical benefit endpoint is about a positive net clinical benefit effect of treatment with asundexian as compared with apixaban in adult patients with AF at risk for stroke.

With respect to intercurrent events, it will follow the strategies as described for the primary safety outcome as the objective of the investigation of this endpoint is to describe a broader safety profile including the benefit of prevention of stroke and systemic embolism and the risk of more bleeding.

Further secondary estimand(s)

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

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

4. Study Design

4.1 Overall Design

Study 19767 is a multicenter, randomized, active comparator-controlled, double-blind, double-dummy, parallel-group, 2-arm, 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).

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 at least one of the following enrichment criteria in addition:

- age ≥ 70
- previous stroke, transient ischemic attack, or systemic embolism
- renal dysfunction with eGFR < 50 ml/min 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 model, 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, 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. in 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 1 of the 2 arms, in a 1:1 ratio.

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. At the same time approximately the same number of participants are expected to experience a primary safety outcome. The planned individual study duration is expected to be 10-34 months; however the timelines may vary (i.e. longer or shorter than planned) depending on enrollment rate and incidence rate in the study. The study will consist of the following study periods:

- **Screening period (from visit 1 until visit 2)**: 2 weeks (participants will be screened and have to be randomized within 2 weeks after screening). There will be a screening

visit followed by a randomization visit within 2 weeks. If all information is available, a participant can be randomized on the day of screening (visits 1 and 2 are combined). **For participants in the DCT model**, after obtaining informed consent, an additional time interval of up to 2 weeks will be required, during which operational logistics will be initiated (refer to Section 10.10 for more details).

- **Intervention period (from visit 2 until the CEOT visit)**: approximately 9-33 months.

  The visit frequency after randomization will be a first visit after one month, the next visit after 3 months and then every 3 months. Site visits (remote visits for **DCT model**) will take place after 3 months, 6 months and then every 6 months until the CEOT visit. Phone visits will take place after 1 month, 9 months and then every 6 months in between site visits (remote visits). Safety follow-up visits will take place as phone calls, unless the investigator and the participant agree that those should be preferably done at the site.

  The last day of intake of study intervention will be on the day before the CEOT visit. For an individual participant the CEOT visit marks the end of the intervention period (for participants permanently discontinuing study intervention, refer to "early termination period"). For planning the CEOT visits, the sponsor will notify the sites in advance of 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 9.5 for details). The sites will be informed of the allowed window for the CEOT visits (CEOT date ± 3 weeks approximately).

  If the number of events does not accrue as quickly as expected, visits in the intervention period might need to be continued longer than anticipated (expected individual time in intervention period: 9-33 months). This will be done in the same way as before until the CEOT visit, i.e. site visits and phone visits will be performed in alternating order every 3 months.

- **Common End of treatment period (from CEOT visit until CEOT SFU visit)**: 2 week period that will end upon completion of the CEOT SFU visit for participants who did continue intake of study intervention as expected.

A participant only *temporarily* interrupting study intervention intake and taking the last dose within less than 2 weeks before the CEOT visit will complete the study upon completion of the CEOT SFU visit. A participant temporarily interrupting study intervention with a final dose taken 2 or more weeks before the CEOT will complete the study upon completion of the CEOT, and in such a case no additional SFU telephone call will be required thereafter.

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

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

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

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

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

For participants who permanently discontinue study intervention less than 2 weeks prior to the CEOT visit, the ET SFU visit will be replaced by the CEOT SFU visit, that is to be conducted after the CEOT visit and is the last study visit in those participants. Further details on premature discontinuation of the study intervention are reported in Section 7.1.

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

4.1.1 Decentralized Clinical Trial Model

This fully remote DCT model intends to follow the conventional on-site activity schedule as much as possible. The DCT model will substitute remote visits where on-site visits are conducted in the conventional model, and it will incorporate more patient-centric and convenient methods for obtaining blood samples, vital signs and for dispensation of study investigation. Participants following the DCT model will utilize technology (mobile application and / or web-based platform) to access study-specific applications, including eConsent, ePRO, sensor data (ECG), and a teleresearch visit tool. Participants will be provided with a “participation kit” which, as a standard, will include instructional guide, ECG device and a provisioned smartphone, unless the participants opt to use their own device (BYOD). Participants may be supported by home health or family member / caregiver with the participation kit, if needed.

In the DCT model, remote visits requiring laboratory samples will be divided into 2 parts. For the first part, home nurses will visit the participant at home to complete the designated study procedures (see Section 10.10.2), or the option to visit a patient service center may be possible for collection of lab samples or execution of other procedures in some locations. For the second part of the visit, the investigator, or designee, will conduct the specified study procedures with the participant via teleresearch video call. Remote visits without laboratory sampling will be conducted via teleresearch only. Subsequent to the visit, the relevant IRT transaction will be made, and supply of study intervention requested. Study intervention will be shipped DtP in appropriate shipping containers (see Section 6 for more information). Due to the timelines associated with shipping new study intervention to the participant’s home for remote visits, it is possible that study intervention resupply does not happen within the scheduled visit window. This should be avoided, yet it is not considered a protocol deviation.

Technology will also provide the investigator and authorized site representatives access to a web-based portal via unique credentials to review and perform study activities.

4.2 Scientific Rationale for Study Design

This pivotal Phase 3 study will evaluate the efficacy and safety of asundexian compared with apixaban for the prevention of stroke or systemic embolism in participants with atrial fibrillation. The study aims at showing that the oral FXIa inhibitor asundexian (50 mg once daily dosage) when compared with apixaban (a NOAC, FXa inhibitor, 5 mg / 2.5 mg doses twice daily according to label) leads to a similar or lower cause-specific hazard ratio of the composite of stroke or systemic embolism as well as a lower cause-specific hazard ratio of ISTH major bleeding.

Study 19767 is a randomized, active comparator-controlled, double-blind, double-dummy, parallel-group, 2-arm, Phase 3 study in 18000 participants (9000 participants per arm) with atrial fibrillation. The study will apply the principles of randomization and double-blinding in order to prevent bias in the inclusion of participants or reporting of safety or efficacy events.

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

The study will include participants who have been treated with an oral anticoagulant for no more than 6 consecutive weeks at randomization (labelled “OAC naïve”), e.g. participants newly diagnosed with AF. Furthermore, participants on an OAC for more than 6 consecutive weeks at randomization can participate (labelled “OAC experienced”). Participants on VKA are excluded from the study, unless they have stopped treatment with a Vitamin K antagonist at least 10 days prior to randomization and their INR is < 2, as the switch from VKA to study intervention may otherwise lead to bleeding events related to overlapping PD effects in the period and not to the assigned study intervention itself.

A limited number of sites and participants will execute study activities remotely, following the DCT model (see Section 10.10). DCTs are an operational strategy leveraging technology to enable clinical study activities in settings more local to the participants. This approach centers the clinical study around the participant, allowing individuals more choice in how they participate. There is a growing body of evidence supporting the use of broadband internet access, home computing and smartphones as well as digital health technologies enabling remote interactions and robust monitoring, support, and management of trial participants. DCTs are intended to reduce the burden on clinical study participants and make a study more visible and accessible to patients independently of referring physicians.

4.2.1 Patient Input into Design

Feedback was collected from the AF patient population through patient surveys with the intent to:

- Seek input on the content and visual design of study-related awareness and educational materials
- Gather patient perspective on weighting of different study endpoints
- Gather patient view on the relevance of the DCT approaches
- Identify potential hurdles to recruitment, adherence with the study procedures, and participant retention
- Gather patient perspective on the selection of technologies.

4.3 Justification for Dose

The study will test 50 mg of asundexian once daily.

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

The dose of 50 mg was widely tested among the 3 different indications of the Phase 2 PACIFIC program and demonstrated favorable bleeding safety against apixaban (in the PACIFIC-AF study), as well as no relevant increase in bleeding in participants treated with asundexian compared to placebo (PACIFIC-STROKE and PACIFIC-AMI). Across the Phase 2 studies, the evaluation of the AEs, laboratory parameters, vital signs and ECG did not show any unfavorable safety signals for asundexian. The dose selection was not limited by bleeding in Phase 2, thus choosing the highest dose studied in Phase 2, 50 mg once daily, for further investigation in Phase 3. The PACIFIC-AF Phase 2 study was neither powered nor designed to test for differences in rates of efficacy events, and in consequence those were only described in an exploratory fashion. In PACIFIC-STROKE a favorable trend in benefit for symptomatic ischemic stroke in participants taking asundexian was seen. Based on the available data, asundexian 50 mg leads to a near complete inhibition of FXIa, showing a favorable benefit-risk profile. Taken all together, the current results support further development of asundexian in Phase 3. More detailed information may be found in the Investigator's Brochure.

4.4 End of Study Definition

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

5. Study Population

The study will enroll adult participants with AF at moderate to high risk for future thromboembolic events and who therefore qualify for oral anticoagulant therapy.

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

In order to have a balanced study population across the eligibility criteria, and to avoid overrepresentation of any single entry criterion, recruitment of participants will be monitored on an ongoing basis. If an imbalance is observed (e.g. overrepresentation of CHA_2DS_2-VASc score of 2 if male, or 3 if female), enrolment based on the affected criterion may be restricted.

5.1 Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Atrial fibrillation documented by ECG evidence* with an indication for indefinite treatment with an oral anticoagulant
3. CHA_2DS_2-VASc score ≥ 3 if male *or* ≥ 4 if female,

   OR

   CHA_2DS_2-VASc score of 2 if male *or* 3 if female and at least one of the following enrichment criteria:

   - age ≥ 70
   - previous stroke, transient ischemic attack, or systemic embolism
   - renal dysfunction with eGFR < 50 ml/min 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.

Sex and Contraceptive / Barrier Requirements

4. Male or female

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

   Male participants: there are no measures required for the study

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

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

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

     A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 4 days before the first dose of study intervention, see Section 8.3.8. If a urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. *See country-specific requirements for the Republic of Korea (KOR-1) in Section 10.12.3.1.*
   - Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.8. The investigator is responsible for review of medical

* AF should be documented within the last 12 months prior to randomization, either on a 6 (or more)-lead ECG or otherwise as an episode of AF of at least 30 seconds in case of continuous ECG recording, rhythm strip, pacemaker or implantable cardiac defibrillator interrogation

history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Mechanical heart valve prosthesis (not including transcatheter aortic valve replacement)
2. Moderate-to-severe mitral stenosis at the time of inclusion into the study
3. Atrial fibrillation *only* due to reversible cause (e.g. thyrotoxicosis, endocarditis, pneumonia, pulmonary embolism)
4. Participants after successful ablation therapy without documented recurrent AF or participants after left atrial appendage (LAA) occlusion / exclusion or plan for ablation or LAA occlusion / exclusion within the next 6 months starting from randomization
5. Recent ischemic stroke (within 7 days prior to randomization)
6. Active non-trivial bleeding; known chronic bleeding disorder (e.g. von Willebrand disease or other coagulopathies); history of non-traumatic intracranial hemorrhage (does not include cerebral microbleeds or asymptomatic hemorrhagic transformation of an ischemic stroke)
7. Known significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or known hepatic insufficiency classified as Child-Pugh B or C at randomization. *See country-specific requirements for the Republic of Korea (KOR-1) in Section 10.12.3.1.*
8. Estimated glomerular filtration rate (eGFR) < 25 mL/min/1.73 m^2 within 14 days prior to randomization, calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (see Section 10.6), or on dialysis or expected to be started on dialysis within the next 12 months starting from randomization
9. Major surgery during the last 30 days prior to randomization
10. Known allergy, intolerance or hypersensitivity to either of the study interventions (active substance or excipients)
11. Any contraindication for the use of an anticoagulant or listed in the local labelling for apixaban. *See country-specific requirements for the Republic of Korea (KOR-1) in Section 10.12.3.1.*

Prior / Concomitant Therapy

12. Requirement for chronic anticoagulation for a different indication than AF, e.g. mechanical heart valve or left ventricular cardiac thrombus (atrial thrombus is allowed), or dual antiplatelet therapy (single agent therapy is allowed)

13. Treatment with Vitamin K antagonist (VKA) in the 10 days prior to randomization (International Normalized Ratio [INR] ≥ 2 prior to randomization if VKA was used)
14. Concomitant use of or anticipated need for:
    - daily or near daily (> 5 days per week) therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) for more than 4 weeks during the study period
    - herbal or traditional medicine, and / or supplements with known anticoagulant and / or antiplatelet effect
    - combined P-glycoprotein (P-gp) and strong cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors e.g. human immunodeficiency virus protease inhibitors, systemically used azole antimycotic agents, clarithromycin, nefazodone
    - combined P-gp and strong / moderate CYP3A4 inducers, e.g. phenytoin, carbamazepine, phenobarbital, rifampicin or St. John's wort

    Respective substances (apart from NSAIDs) must be stopped – in case of combined inhibitors / inducers of CYP3A4 and P-gp for at least 14 days (or at least five half-lives of the active substance, whichever is longer) – before randomization and first intake of study intervention.

Prior / Concurrent Clinical Study Experience

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

Other Exclusions

16. Known current alcohol and / or illicit drug abuse that may interfere with the participant's safety and / or compliance at the discretion of the investigator
17. Close affiliation with the investigational site; e.g. a close relative of the investigator, or a dependent person (e.g. employee or student of the investigational site or the sponsor)
18. Any other history, condition or therapy, or uncontrolled intercurrent illness which would make the participant unsuitable for the study (e.g. noncompliance) or otherwise vulnerable (e.g. participant in custody by order of an authority or a court) or life expectancy < 12 months.

For DCT model only

19. Not willing or able to use the smartphone and / or electronic devices to access the web-based platform / app required for the DCT-elements.

For country-specific requirements for the Republic of Korea (KOR-1), please see Section 10.12.3.1.

5.3 Lifestyle Considerations

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

5.4 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once at any time within the recruitment period. This also applies if a participant had successfully passed the screening procedures, but could not be randomized to treatment on schedule (e.g. due to unavailability of study intervention). The investigator has to ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk. In the event of rescreening, participants should be assigned a new participant number. Please refer to Section 10.1.3 for the informed consent process for rescreening.

5.5 Criteria for Temporarily Delaying Enrollment or Randomization

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

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

6.1 Study Intervention(s) Administered

The following study interventions will be administered in the study:

- Asundexian: sponsor's study intervention under investigation
- Placebo to asundexian
- Apixaban: marketed product used as comparator
- Placebo to apixaban

Asundexian is taken orally once a day, if possible in the morning, preferably around the same time each day (for exceptions see Section 8.5). The immediate-release tablets will be provided as pink, oval, film-coated tablets containing 50 mg of asundexian (see Table 6–1).

Apixaban, the active comparator used in this study, is a selective, orally active inhibitor of the coagulation Factor Xa (FXa) developed by Bristol-Myers Squibb (BMS) and Pfizer as an anticoagulant agent. It is supplied as 5 mg and 2.5 mg tablets. Apixaban is taken orally twice a day. The usual dose is 5 mg, reduced to 2.5 mg 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. Participants have to receive the dose of apixaban according to the label and the respective initial dosage of apixaban for the first intake of study intervention will be determined based on the values current at the randomization visit. If a participant will manifest at least 2 of the characteristics requiring dose adjustment while on study intervention, the apixaban (or placebo) dosage regimen may be adjusted at the subsequent study intervention dispensation. In case a participant starts with receiving a dose

of 2.5 mg BID, and later on fewer than 2 of the characteristics apply, adjustment to 5 mg BID at the following study intervention dispensation time point should be considered. In case a participant is affected by a sustained decrease of kidney function (eGFR < 30 ml/min) there is the option to reduce the apixaban dose to 2.5 mg BID – independent of meeting at least 2 of the above mentioned dose reduction criteria – if this is according to the locally applicable apixaban label. In any case, dose modifications will need to be registered within the IRT (including documentation of the applicable justifying criteria leading to the dosage change) as well as in the CRF. *See country-specific requirements for the Republic of Korea (KOR-1) in Section 10.12.3.1.*

The study interventions (tablets) are not to be broken, halved or crushed, and should be swallowed whole with a glass of water. Both asundexian as well as apixaban can be taken irrespective of food intake.

Matching placebos for asundexian and both strengths of apixaban are supplied in the same way.

For apixaban / placebo one tablet in the morning and one tablet in the evening are to be taken from the apixaban bottle. For asundexian / placebo one tablet only is to be taken from the respective bottle, if possible in the morning. At Visits 4 and 7 participants should not take study intervention as usual in the morning at home, as a PK / PD sample will be drawn at the site before intake of study intervention (refer to Table 1–2). Study intervention at those visits should be taken out of the respective bottle that participants receive at their dispensation visit (i.e. at Visit 4 and Visit 7).

The planned double-blind intervention period starts at randomization and ends when study intervention is permanently discontinued. Study intervention intake will start as soon as possible after randomization (day 1), preferably on the day of randomization (unless e.g. medical reasons do not allow for this), and is expected to continue through the end of the planned treatment. **For participants in the DCT model**, please see Section 10.10.

Missed study intervention dose

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

If a dose of apixaban is missed, the dose should be taken as soon as possible on the same day, up until 6 hours after the scheduled intake. After this time point, the dose should be skipped, and the next scheduled dose should be taken. If possible a twice daily administration should be resumed.

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

Table 6–1: Study Interventions Administered

Intervention Arm Label	Asundexian		Apixaban	
Intervention Name	Asundexian	Placebo to apixaban	Apixaban	Placebo to asundexian
Dose Formulation	tablet	tablet	tablet	tablet
Unit Dose Strength(s)	50 mg	NA	5 mg OR 2.5 mg	NA
Dosage Level(s)	50 mg	NA	5 mg OR 2.5 mg	NA
Frequency	Once a day, preferably in the morning	Twice a day	Twice a day	Once a day, preferably in the morning
Route of Administration	oral	oral	oral	oral
Use	Experimental	Placebo (comparator)	Active comparator	Placebo (experimental)
Packaging and Labeling	HDPE bottles. Each bottle will be labeled as per country requirement	HDPE bottles. Each bottle will be labeled as per country requirement	HDPE bottles. Each bottle will be labeled as per country requirement	HDPE bottles. Each bottle will be labeled as per country requirement

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

Table 6–2: Study Arms

Arm Title	Asundexian	Apixaban
Arm Type	Experimental	Active comparator
Arm Description	Participants will receive asundexian	Participants will receive apixaban
Associated Intervention Labels	Asundexian and placebo to apixaban	Apixaban and placebo to asundexian

6.1.1 Switching to Study Intervention and Back to Open Label Anticoagulant

When being enrolled, or in case of the DCT model before the start of the clinical assessments and procedures of the screening phase (Visit 1b), study participants may be treated with a NOAC or may not be treated with any oral anticoagulant.

Participants treated with a VKA are only eligible if the VKA was stopped at least 10 days prior to randomization. Furthermore, INR must not be ≥ 2 prior to randomization. Use of a bridging anticoagulant after stopping a VKA is left to the discretion of the investigator and treating physicians in accordance with local and international guidelines.

After the participant is determined to be eligible for the study during the screening period, he or she should be instructed to take the last dose of the open label NOAC (or non-oral anticoagulant if applicable) on the day prior to study intervention intake. Hence, a participant should not take an open label NOAC (or any other non-oral anticoagulant) on the day of the first dose of study intervention. If a participant has already taken an open label NOAC (or other non-oral anticoagulant) on the planned day of randomization, randomization can be performed but the administration of study intervention should only be started on the next day.

Transition from blinded study intervention to an open label anticoagulant (NOAC or another recommended anticoagulant as deemed appropriate by the investigator) after final discontinuation of study intervention must be done without breaking the study blind. The suggested procedure is to start with an open label anticoagulant on the next day following the last day of intake of the blinded study intervention (i.e. on the day of the CEOT visit, as no study intervention intake should take place on the day of this visit anymore). As all properly enrolled participants will still be at risk for stroke at the end of the study (or after permanent discontinuation of study intervention) they should accordingly be considered for stroke prevention following final discontinuation of study intervention.

Guidelines and practical guides regarding switching, for instance to (open label) NOAC treatment need to be considered in this situation (Chen et al. 2020, Steffel et al. 2021). The same applies in case of switching back and forth between open label anticoagulation and study intervention that might occur during the study period in case of non-permanent discontinuation of study intervention.

6.1.2 Medical Devices

Not applicable.

6.2 Preparation, Handling, Storage, and Accountability

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

1. The investigator or designee must confirm study intervention has been received and, if a temperature data logger has been included, appropriate temperature conditions have been maintained during transit. Any discrepancies are to be reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff, where local regulations permit, may supply or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, institution or the head of the institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

Drug returns, reconciliation and destruction return information will be captured in IRT.

5. Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Site File.

For sites following the DCT model, where DtP distribution of study intervention occurs as part of remote visits, the investigator delegates distribution responsibility to the sponsor. The investigator maintains responsibility and control for dispensing via IRT by confirming whether or not DtP distribution of study intervention can be triggered. Participants who receive study intervention via DtP will return all unused investigational product and empty bottles to their study (meta)site.

6.3 Assignment to Study Intervention

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

Randomization will be first stratified by participation in the conventional study model vs. 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 randomly assigned to 1 of the 2 treatment arms in a 1:1 ratio (see Section 1.1).

Study intervention will be dispensed at the study visit 2 (randomization), as summarized in the SoA, and again at the next visit after 3 months. Subsequently, the Month 6 visit follows, marking the start of 6-monthly on-site visit intervals (on-site visits will be conducted as remote visits for participants in the **DCT model**). From this visit onward, participants will receive study intervention at on-site visits which will last them until the next 6-monthly visit. The Month 6 visit should be scheduled ≤ 14 weeks after the Month 3 visit (even though in theory up to 15 weeks could lie between Visit 4 and Visit 5). Otherwise participants will need to get equipped with additional bottles of each of the study interventions to prevent insufficient supply until the Month 6 visit. At each contact, hence also at the intermittent telephone visits, the participants should be instructed regarding study intervention compliance (refer to Section 6.5).

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

6.4 Blinding

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

Tablets containing 50 mg of asundexian and matching placebo are identical in appearance and packed in bottles labeled with a unique number which will be pre-printed on each bottle. Tablets containing apixaban and corresponding placebo are identical in appearance and packed in bottles labeled with a unique number which will be pre-printed on each bottle. In order to achieve the double-blind, double-dummy design, participants will be provided with bottles either with active drugs (asundexian or apixaban), or placebo depending on the randomization outcome.

6.4.1 Unblinding

Unnecessary unblinding should be avoided and should only be undertaken by the investigator when it is essential for the participant's safety and treatment decision. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a participant's treatment assignment is warranted. If the investigator is unavailable, and a treating physician not associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the study-specific emergency medical advice 24 hours / 7-day service. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should attempt to contact the sponsor prior to unblinding a participant's treatment assignment, unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor should be notified preferably within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

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

The same inadvertent unblinding of the participant or investigator might be applicable to apixaban in case prothrombin time (PT) or its derived measure of the international normalized ratio (INR) are being assessed, as apixaban is known to be associated with a notable increase in those parameters. Hence the measurement of PT or INR after randomization is strongly discouraged and should only be done in case of (emergency) situations where this may help to guide treatment decision, e.g. to assess liver function. Prior to randomization INR measurements might be required as part of local laboratory assessments to determine randomization eligibility in case a participant has been pretreated with a VKA.

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

6.5 Study Intervention Compliance

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

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

To monitor compliance, the investigator will be required to document drug dispensing and return for each participant in the source documents and this record must be reconciled with study intervention and compliance records. An adequate record of receipt, distribution and return / destruction of all study intervention must be captured on the dispensing log and / or in the IRT.

Intervention start and stop dates, including dates for apixaban dose reductions or increases (if applicable) will also be recorded. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

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

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

Participants following the DCT model will be instructed to retain all unused study intervention and empty packages for accountability purposes. At home nurse visits, the nurse may support the investigator site with the compliance assessment by performing a pill count. Participants will be provided shipping materials and instructions to return all unused study intervention and packaging to the investigator site for formal accountability as outlined in the DCT SoA in Section 10.10.2.

6.6 Dose Modification

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

For dosing modifications of the active comparator, refer to Section 6.1.

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

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

Any further therapy at the end of the study is at the discretion of investigator / treating physician (see Section 6.1.1).

6.8 Treatment of Overdose

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

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

For participants receiving comparator treatment, and in line with the apixaban label, administration of activated charcoal may be useful in the management of apixaban overdose (i.e. the accidental or intentional ingestion of any dose of apixaban that is considered both excessive and medically important) by leading to a more rapid fall in apixaban blood levels. For further details the investigator / treating physician should refer to the approved product label of apixaban.

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

In the event of an overdose, the investigator should:

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

6.9 Prior and Concomitant Therapy

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

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

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

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

Single agent antiplatelet therapy is permitted for use any time during the study. Dual antiplatelet therapy (e.g. ASA together with $P2Y_{12}$ inhibitors) in combination with the study interventions is only allowed in exceptional cases, such as an AMI and / or a PCI, symptomatic peripheral artery disease or carotid artery stenting occurring during the study. Such combination treatment with antiplatelet drugs may be administered as per discretion of the investigator, after thorough assessment of the risk / benefit ratio of such a potential combination therapy approach.

Sustained use of anticoagulation during study conduct for a different indication than AF will require at least an interruption of study intervention, if not permanent discontinuation (refer to Section 7.1). In this situation the anticipated duration of anticoagulation treatment and the expected remaining intervention period of the study should be taken into consideration. The assessment on whether to temporary or permanently discontinue the study intervention is left to the investigator's discretion.

Venous thromboembolism prophylaxis with low-molecular-weight heparin or unfractionated heparin for short periods of time while taking study intervention is discouraged due to the potentially increased bleeding risk of combined NOAC and heparin intake (Fujikawa et al. 2020).

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

Proton pump inhibitors (PPIs) may be considered to reduce the risk for gastrointestinal bleeding and accompanying hospitalizations, especially in those with a history of GI bleeding or ulcer and patients requiring concomitant use of (dual) antiplatelet therapy, as recommended by guidelines (Steffel et al. 2021).

Potential for drug-drug interactions:

At supratherapeutic doses asundexian is a weak inhibitor of the cytochrome P450 isoenzyme 2C8 (CYP2C8) and two transporter proteins, i.e. breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp). The risk for clinically relevant drug-drug interactions at a dose of 50 mg asundexian due to inhibition of the respective proteins is regarded as low, but cannot be excluded. If sensitive substrates of the mentioned proteins are taken concomitantly, the pertinent medication labels should be consulted, especially for:

- **rosuvastatin 20 mg daily or higher dose** or **atorvastatin 80 mg daily**, for which additional monitoring may be warranted
- **digoxin** or **paclitaxel**, which should be used with caution and for which additional monitoring may be warranted
- **repaglinide** or **pioglitazone**, for which additional blood glucose monitoring might be warranted.

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

Prohibited concomitant medications:

Concomitant therapy with any of the following drugs is prohibited from 14 days (or at least five half-lives of the active substance, whatever is longer) before randomization and first study intervention administration, until at least 48 hours after last study intervention administration:

- Strong combined inhibitors of CYP3A4 and P-gp, e.g. human immunodeficiency virus protease inhibitors (ritonavir, indinavir, nelfinavir, saquinavir, or telaprevir), systemically used azole antimycotic agents (ketoconazole, itraconazole, or posaconazole), clarithromycin, nefazodone
- Strong / moderate combined inducers of CYP3A4 and P-gp, e.g. phenytoin, carbamazepine, phenobarbital, rifampicin, or St. John's wort

See also country-specific requirements for the Republic of Korea (KOR-1) in Section 10.12.3.1.

A separate, more detailed list with prohibited medications will be provided to the investigator.

For participants who have *permanently* discontinued study intervention after completing their applicable early termination safety follow-up visit, only information on concomitant antiplatelet and anticoagulant medications needs to be collected at the remaining regular study visits until the CEOT visit (those visits are expected to occur as telephone visits during the early termination period; see Section 1.3).

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

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

Participant's bleeding events should be assessed in relation to the last intake of the study intervention, considering that asundexian has a total clearance of about 2.1 L/h and a half-life of approximately 21.5 hours, while apixaban has a total clearance of about 3.3 L/h and a half-life of approximately 12 hours.

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

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

- Investigate other causes of serious bleeding such as coagulopathies, thrombocytopenia, kidney / liver dysfunction, or other concomitant medications.

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

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

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

For those participants treated with apixaban, the following agents may be administered (according to the package insert / label of the respective agent):

- The antidote to apixaban, andexanet alfa, which is a recombinant modified human Factor Xa protein (labelled in the US as ANDEXXA and in the European Union (EU) as Ondexxya) and may be used in case of life-threatening or uncontrolled bleeding (Steffel et al. 2021). However, its availability may be limited.
- 4-factor Prothrombin complex concentrate (4F-PCC) or Activated prothrombin complex concentrate (aPCC) / factor 8 inhibitor bypass activity (FEIBA).

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

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

For urgent or emergent surgery or percutaneous / endoscopic procedures, when waiting for 24 hours is not an option to allow for study intervention washout after temporary discontinuation, the increased risks of procedural bleeding should be assessed against the urgency of the procedure based upon the clinical situation. Peri-procedure management may in part depend on the randomized treatment assignment (asundexian or apixaban) and unblinding of treatment assignment may be necessary. In general, the treatment recommendations should follow the Guidelines for Severe Perioperative Bleeding Management (Kozek-Langenecker et al. 2013). The procedure should be conducted in such a way to minimize the risk for bleeding.

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

anticoagulant / antithrombotic is indicated for the procedure, it should be used with caution and at the lowest therapeutic dose. More detailed information can be found in the Investigator's Brochure.

Depending on the participant's risk for bleeding with the procedure, participants receiving apixaban who require an invasive or surgical procedure within 24 hours of their last dose may be treated with prophylactic peri-procedural FFP (2 units IV every 6 hours) at the discretion of the local physician and investigator. In addition, the label instructions for apixaban should be followed. If treatment with an alternative open label anticoagulant / antithrombotic is indicated for the procedure, it should be used at the lowest therapeutic dose (if at all) in the 12 hours following last dose of study intervention. Interactions between apixaban and other antithrombotics (except for ASA and $P2Y_{12}$ inhibitors) have not been evaluated.

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

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

The treatment assignment may have to be emergently unblinded if necessary (see Section 6.4.1), to facilitate management decisions.

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

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

No high-quality data are available regarding the use of intravenous thrombolysis for acute stroke in participants receiving apixaban. Experienced stroke centers worldwide are using thrombolysis for patients who have taken NOAC therapy within 48 hours by applying different approaches and selection criteria, including therapy guided by NOAC plasma level concentration and reversal of NOAC treatment using specific reversal agents like andexanet alfa (Seiffge 2022); therefore, for participants with acute ischemic stroke who are receiving apixaban, the use of thrombolytic agents will follow local practice. Based on the half-life of apixaban (approximately 12 hours) it may be anticipated that little or no study intervention is present in circulation if the last dose of study intervention was given at least 48 hours before. The anti-Factor Xa chromogenic assay, when used with validated calibrators and controls and where available, may be used to confirm that little or no residual anticoagulant effect is present for participants on apixaban.

For participants who undergo thrombolysis, study intervention should be withheld until at least 24 hours after thrombolysis. Interventional thrombectomy may be an option in participants experiencing an acute ischemic stroke on study intervention.

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

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

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

For participants who are receiving asundexian or apixaban, the risk for bleeding related to the concomitant use of an intravenous fibrinolytic for acute ST-elevation MI is unknown and has not been studied. For participants treated with intravenous fibrinolytics, study intervention should therefore be withheld until at least 24 hours after receiving fibrinolytics.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

7.1.1 Permanent Discontinuation of Study Intervention

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

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

An early termination (ET) visit is only applicable to participants who prematurely discontinue intake of study intervention *permanently*; such participants should undergo the ET visit as

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

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

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

- Pregnancy or breastfeeding of the study participant (see also Section 8.4.5)
- Concomitant treatment with any of the following medications has to be taken *continuously* throughout the expected remaining intervention period of the study:
  - anticoagulation for a different indication than AF (e.g. cardiac ventricular thrombus, pulmonary embolism, superficial or deep venous thromboembolism)
  - antiplatelet therapy other than permitted (single agent therapy is allowed, as well as indicated dual antiplatelet therapy, e.g. in case of a myocardial infarction and / or a PCI, symptomatic peripheral artery disease or carotid artery stenting occurring during the study)
  - strong combined inhibitors or inducers of CYP3A4 *and* P-gp
- abnormal liver function if a participant meets one of the conditions outlined in Section 10.2.1, or if the investigator believes that it is in best interest of the participant.

See country-specific requirements for the Republic of Korea (KOR-1) in Section 10.12.3.1.
See the SoA for data to be collected at the time of premature intervention discontinuation and for any further evaluations that need to be completed.

After permanent discontinuation of the study intervention, the participant is expected to continue the study visits as outlined in the protocol by telephone and will therefore be contacted by the study site at the regular follow-up intervals. The remaining outlined visits may also be done as site visits if preferred by investigator or participant. The same applies to participants of the **DCT model** in case they would prefer video calls over phone calls after discontinuation. *Ad hoc* additional telephone contacts may also be requested and made to the participant themselves or to other contact as provided by the participant.

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

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

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

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

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

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

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

7.1.2 Temporary Discontinuation of Study Intervention

In the event of a temporary interruption of study intervention for any reason, study intervention will be restarted as soon as medically justified in the opinion of the investigator. An example would be concomitant treatment with any of the prohibited medications mentioned above (in Section 7.1), that has to be taken only for a limited, foreseeable timeframe, that is expected to be considerably less than the expected remaining intervention period of the study. In such a case, based on medical judgement, a temporary interruption of study intervention instead of permanent discontinuation should be considered. The need for a temporary interruption might also arise from an adverse event, for instance relating to liver dysfunction (refer to Section 10.2.1). There is no predefined maximum limit for temporary treatment interruption. *See country-specific requirements for the Republic of Korea (KOR-1) in Section 10.12.3.1.*

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

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

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request, for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- At the time of informed consent, participants will be explained all the options to continue in the study after permanent discontinuation of study intervention (see Section 7.1). This will be re-discussed at the time of permanent discontinuation of study intervention and the participant's specific agreement will be documented. Participants will be asked to agree to be contacted to obtain follow-up information should they decide to stop the intervention.
- When a participant withdraws consent from study participation before completing the study, meaning that the participant does not agree to any kind of follow-up and specifically refuses any further contact with the investigator, the reason for consent withdrawal is to be documented in the source document. Public information can be used to obtain vital status for these participants where allowed by local regulations.
- **Participants following the DCT model**: If the participant withdraws consent for continued participation (i.e. follow-up) in the study and if the participant received a provisioned device (participation kit), he / she must return the study devices following provided shipping instructions. The participation kit does not need to be returned until the end of the study, if only study intervention is permanently discontinued, and consent is not withdrawn.

7.3 Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit

schedule, and ascertain whether the participant wishes to and / or should continue in the study.

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Results from procedures conducted as part of the participant's routine clinical management (e.g. creatinine, eGFR, ECG, vital sign measurement) and obtained before signing of the ICF may be utilized for screening and / or baseline purposes, provided the procedures met the protocol specified criteria and were performed within the timeframe defined in the SoA (if no older than 14 days at randomization for eGFR, creatinine and vital signs, or no older than 30 days in case of ECG; refer to annotated SoA in Section 1.3). *See country-specific requirements for the Republic of Korea (KOR-1) in Section 10.12.3.1.*
- Laboratory / analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- In the event of a significant trial-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority / ethics requirements.
- The maximum blood draw volume for each participant over the duration of the study is provided in a separate document (e.g. ICF and laboratory manual).

- If a participant requires an unscheduled visit to perform additional procedures / assessments other than regularly scheduled (e.g. for lab sampling), this should be documented in the CRF accordingly. Unscheduled visits may occur any time during the study conduct.

8.1 Administrative and Baseline Procedures

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

8.2 Efficacy Assessments

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

8.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is assessed as the time from randomization to the first occurrence of the composite of stroke or systemic embolism.

Definitions of the primary efficacy outcome events are provided as follows. Details on the time periods for collecting outcome events information are reported in Section 10.9.

8.2.1.1 Stroke

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

Differentiation is made regarding hemorrhagic stroke and ischemic stroke.

Hemorrhagic stroke is defined as an acute, atraumatic extravasation of blood into the brain parenchyma, intraventricular or subarachnoid space with associated neurological symptoms. This does not include microbleeds or hemorrhagic transformation of an ischemic stroke.

An ischemic stroke is defined as the rapid onset (or present on awakening) of a new focal neurological deficit with clinical (> 24 hours symptoms / signs) or imaging evidence of infarction that is not attributable to a non-ischemic cause (i.e. not associated with infection, tumor, seizure, severe metabolic disease).

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

Participants who suffer a stroke of any type during this study should be assessed for their resulting disability by the modified Rankin Scale (mRS) as follows:

- at day 7 after the event (or at hospital discharge / death, if this occurs before day 7); and
- at the next visit (any type of visit is acceptable), but no less than 2 months after the event (i.e. between 2 and ~5 months after the stroke). If death occurs in the intercurrent period this should be documented according to the scale.

Further details on mRS are available in Section 10.8.

Transient Ischemic Attack (TIA)

Unlike a stroke, a TIA is defined as transient episode of neurologic dysfunction caused by focal brain, spinal cord or retinal ischemia without acute infarction (Easton et al. 2009). Differentiating TIA from other mimicking conditions is important. Symptoms of TIA usually start abruptly, followed by gradual offset, usually over minutes, and are typically associated with a focal neurologic deficit and / or speech disturbance due to underlying cerebrovascular disease. Isolated dizziness / vertigo or isolated numbness do not qualify as classical TIA.

8.2.1.2 Systemic Embolism

Systemic embolism is defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms (this does not include myocardial infarction, thromboembolism of the pulmonary vasculature or venous thrombosis, e.g. pulmonary embolism or deep venous thrombosis).

8.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are assessed as time from randomization to first occurrence of:

- Composite of ischemic stroke or systemic embolism
- All-cause mortality
- Ischemic stroke
- CV death
- Composite of CV death, stroke, or myocardial infarction.

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

8.2.2.1 Cardiovascular Death

Cardiovascular (CV) death includes death due to stroke, myocardial infarction, heart failure or cardiogenic shock, sudden death or any other death due to other cardiovascular causes or CV procedures. In addition, death due to non-traumatic cardiovascular hemorrhage will be included, e.g. non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g. aortic aneurysm), or hemorrhage causing cardiac tamponade (Hicks et al. 2015). Death for which the cause cannot be determined, so called “undetermined death”, will be included in the analysis as cardiovascular death (yet will not be excluded from SAE reporting).

8.2.2.2 Myocardial Infarction

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

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

8.2.3 Exploratory Efficacy Assessments

Exploratory efficacy endpoints are assessed as time from randomization to first occurrence of:

- Composite of CV death, stroke or systemic embolism
- Systemic embolism
- Hemorrhagic stroke
- Disabling stroke (modified Rankin Scale [mRS] ≥ 3).

Another exploratory efficacy endpoint is:

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

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

A health-related quality of life assessment tool, the European Quality of life group 5-Dimension questionnaire (EQ-5D) will be administered at Day 1 (randomization), every 6 months, and at the CEOT visit. This is a standardized instrument for use as a measure of health outcomes primarily designed for self-completion by patients. The questionnaire is to be completed by the participant (questionnaires are provided in local languages). However, if the participant has problems completing the questionnaire, an attempt has to be made to explain the questions in a neutral and unpersuasive manner. The participant will fill in a paper-based version of the questionnaire directly at the site, which is then entered by the study personnel into the CRF. Participants in the **DCT model** will complete an electronic version of the questionnaire.

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

8.3 Safety Assessments

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

8.3.1 Primary Safety Endpoint

The primary safety endpoint is assessed as time from first intake of study intervention to first occurrence of ISTH major bleeding events.

8.3.1.1 ISTH Major Bleeding

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

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

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

8.3.2 Secondary Safety Endpoints

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

- Composite of ISTH major or clinically relevant non-major bleeding
- Clinically relevant non-major bleeding (Section 8.3.2.1)
- Hemorrhagic stroke (Section 8.2.1.1)
- Intracranial hemorrhage (does not include cerebral microbleeds or asymptomatic hemorrhagic transformation of an ischemic stroke)
- Fatal bleeding
- Minor bleeding (Section 8.3.2.2).

8.3.2.1 Clinically Relevant Non-Major Bleeding

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

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

  * overt bleeding requires the identification of the bleeding location.

A visit alone at a healthcare professional (without fulfilling any of the above criteria) does not suffice. Also an assessment of bleeding as part of a healthcare encounter that is primarily for a different health issue does not qualify. Examples of clinically relevant non-major bleeding include, but are not limited to: multiple-source bleeding requiring treatment for bleeding;

macroscopic (gross, visible) hematuria (spontaneous or lasting > 24 hours if associated with an intervention) requiring increased medical care; epistaxis or gingival bleeding that requires tamponade or other medical intervention to stop the bleeding; hemoptysis, hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention.

8.3.2.2 Minor Bleeding

All other overt bleeding episodes not meeting the above criteria for ISTH major or clinically relevant non-major bleeding will be classified as minor bleeding (e.g. bleeding from a minor wound that does not prompt a treatment for the bleeding, for instance with surgical hemostasis, or epistaxis that does not require a medical treatment for bleeding or a change in antithrombotic therapy).

8.3.3 Exploratory Safety Endpoints

Exploratory safety endpoints are assessed as time from first intake of study intervention 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.

Another exploratory safety endpoint is:

- Total number of ISTH major bleeding events.

8.3.3.1 BARC Bleeding

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

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

  Type 3a

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

  Type 3b

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

Type 3c

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

- **Type 5:** fatal bleeding

Type 5a

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

Type 5b

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

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

8.3.4 Physical Examinations

Height and weight (also referred to as "biometrics" in the SoA) will be measured and recorded at screening (see Section 1.3). For participants following the DCT model, height and weight will be measured by the home nurse; alternatively, these values can also be measured by personnel of a patient service center.

8.3.5 Vital Signs

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

Vital signs will be measured in a semi-supine position preceded by 5 minutes rest for the participant in a quiet setting and without distractions (e.g. television, cell phones) and will include systolic and diastolic blood pressure, and pulse (i.e. the resting heart rate).

If appropriately and recently conducted (i.e. no older than 14 days at randomization) vital sign measurements from routine management are available for the participants, those can be used instead of being obtained again at the screening visit. This is not applicable to participants following the **DCT model**. If a previous measurement result for the vital sign parameters is available at the randomization visit, the repetition of this measurement at the randomization study visit is not required.

For participants following the **DCT model,** blood pressure together with resting heart rate will be measured by the home nurse; alternatively, these values can also be measured by personnel of a patient service center.

8.3.6 Electrocardiograms

A single 6 (or more)-lead ECG will be obtained as outlined in the SoA (see Section 1.3), preferably using an ECG machine that automatically calculates the heart rate.

If an appropriately and recently (i.e. no older than 30 days at randomization) conducted ECG as part of routine management is available, this can potentially be used instead of being obtained again at the screening visit. This is not applicable to participants following the **DCT model**. If a previous ECG result is available at the randomization visit, the repetition of the ECG at the randomization study visit is not necessarily required. Both scenarios of not needing to repeat an ECG assessment are only applicable in case the required ECG evidence of atrial fibrillation as requested as part of the inclusion criteria (refer to Section 5.1) is available. In case the ECGs available either from routine management or obtained during the screening and / or randomization visit do not confirm atrial fibrillation, historical proof (within the last 12 months) needs to be available prior to randomization in order for the patient to move forward to getting randomized. For participants following the **DCT model,** the ECG might need to be repeated if not available in sufficient quality in the first place.

8.3.7 Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- Creatinine and eGFR values must be available at randomization; if not available from screening central lab, the respective values should be determined in local lab prior to randomization to be available in time to not delay randomization. Values obtained as part of routine management can also be used for this purpose if no older than 14 days at randomization. In any case, the full set of protocol-required safety laboratory tests for central lab analysis (Table 10–1) needs to be obtained *once* during the 14 day screening period prior to randomization, at the latest at randomization, and at indicated visits thereafter. *See country-specific requirements for the Republic of Korea (KOR-1) in Section 10.12.3.1.*
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor.
- If clinically significant values do not return to normal / baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded.

8.3.8 Pregnancy Testing

A woman of childbearing potential must have a negative highly sensitive pregnancy test within 4 days before the first dose of study intervention. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or Institutional Review Boards (IRB) / Independent Ethics Committees (IEC). *For country-specific requirements for the Republic of Korea (KOR-1), please see Section 10.12.3.1.*

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

Female participants of childbearing potential are scheduled to perform a serum or urine pregnancy test at the screening and randomization visit, unless ≤ 4 days lie between the screening and randomization visit, in which case a negative test at screening is sufficient (refer to SoA).

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

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

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

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

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

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

Sites following the DCT model: Usually, participants will be reporting AEs to the metasite during the scheduled contacts, or *ad hoc* by contacting the metasite directly. During the home nurse (HN) visit or while at the patient service center, the staff (i.e. the home nurse or the responsible personnel at service centers) will not actively enquire about or collect (S)AE information. However, if an (S)AE is self-evident, occurring during a procedure or spontaneously reported by the participant, the staff will capture relevant details which will be made available to the investigator immediately upon conclusion of the visit. In addition, in the case of suspected SAEs, the staff will immediately contact and inform the investigator. If the staff is not able to speak to the investigator or qualified designee directly, he / she is responsible for continuing to attempt this until direct contact is made and should ensure this is done on the same day that the visit took place. In all cases, the investigator is responsible for evaluating potential (S)AEs, ensuring their timely entry into the CRF as well as for SAE reporting to the sponsor within the required timeframe (see Section 8.4.1). The investigator / designee is then responsible for obtaining further information if needed, e.g. contacting the participant, obtaining records from other sources or deciding if an unscheduled follow-up visit or referral to another medical practitioner is required.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

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

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

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

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

8.4.2 Method of Detecting AEs and SAEs

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

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

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

8.4.3 Follow-up of AEs and SAEs

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

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs / IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB / IEC, if appropriate according to local requirements.
- For all studies except those using medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 4 days after the last dose intake.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.
- The female participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information

in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

8.4.6 Disease-related Events

The following disease-related events (DREs) are part of the efficacy outcome events in participants with AF:

a) Ischemic stroke

b) Systemic embolism

c) Myocardial infarction

d) Cardiovascular death

e) Events indicative of those outcome events listed under a) to d) (e.g. TIA or cardiac chest pain requiring hospitalization with increased cardiac enzymes).

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

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

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

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

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

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

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

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

OR

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

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

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

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

Table 8–1: Reporting of events

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

Abbreviations: CRF= case report form; (S)AE= (serious) adverse event

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

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

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

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

8.5 Pharmacokinetics

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

participants of the conventional study model. These analyses will not be performed in participants of the **DCT model**. Details about the collection, processing, storage and shipment of samples will be provided separately (e.g. in the laboratory manual). Study personnel responsible for bioanalytics will be unblinded and will have access to the randomization list. Analysis of samples from participants not treated with asundexian is optional.

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

At Visit 4 and Visit 7 a trough sample for the determination of asundexian plasma concentrations will be collected before intake of study intervention. Study intervention at those visits should be taken out of the respective new bottles that participants receive, preferably at the study site. Ideally, the study personnel should contact the participants prior to Visit 4 and Visit 7 to remind them not to take the study intervention as usual in the morning at home.

The PK data and the relationship of the asundexian exposure parameters with treatment effects might be evaluated using population approaches including potential influence of relevant participant co-variables. Analysis and reporting will be done under a separate cover. This evaluation might be started prior to database lock: if this is applicable, appropriate measures will be taken to maintain blinding of the study team (refer to Section 6.4.1).

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

8.6 Pharmacodynamics

Blood sampling for PD parameters will be done in a subset of countries / regions, in at least (approximately) 5000 of the participants of the conventional study model (not in participants of the **DCT model**), and is scheduled for the time points as given in Table 1–2. PD samples should be drawn before intake of study intervention at the respective visits. The actual date and time of study intervention intake and of blood sampling will be documented in the CRF. All PD parameters will be measured using validated methods.

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

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

The sampling will be done for an exploratory assessment of PD effects and may include but is not limited to, baseline assessments of FXI levels (clotting assay), FXII levels (clotting assay), and von Willebrand factor activity, as well as aPTT at baseline and after study intervention intake.

In addition, blood samples will be taken for exploratory biomarker analyses (see Section 8.8).

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

8.7 Genetics

Genetic as well as non-genetic analyses will be part of the biomarker investigations and collected in the same subset of participants as the biomarkers in this study, if approved by local ECs / IRBs and competent authorities. See Section 8.8 for details. Biomarker blood for pharmacogenetics is generally planned to be collected at the randomization visit (refer to Table 1–2), however, it can also be collected at a later visit in case it has not yet been taken, and can be collected at any time in relation to study intervention intake at the respective visit.

8.8 Biomarkers

Blood sampling for exploratory biomarker analyses will be done only in a subset of countries / regions in approximately 5000 of the participants of the conventional study model (scheduled for the time points as given in Table 1–2). Biomarker plasma / serum samples should be collected before intake of study intervention at the respective visits. The exact biomarkers chosen will depend on the outcome of the Phase 2 biomarker analysis: biomarkers related to the study intervention, its safety or drugs with similar, e.g. mode-of-action related effects may be examined. The same applies to further biomarkers deemed relevant to cardiovascular diseases and associated health problems. These investigations may include e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers.

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

Details on the collection, processing, storage, and shipment of biomarker samples will be provided in separate documents (e.g. sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.

8.9 Immunogenicity Assessments

Not applicable.

8.10 Medical Resource Utilization and Health Economics

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

8.10.1 Healthcare Resource Utilization (HCRU)

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

9. Statistical Considerations

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

9.1 Statistical Hypotheses

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

The proposed study plans to test several null hypotheses.

The aim related to the first part of the primary efficacy objective is to show that assigning asundexian is as least as effective than apixaban in preventing stroke and systemic embolism in patients with AF using a non-inferiority margin of 1.5 for the cause-specific hazard ratio. The one-sided test problem is:

$$H_0: \lambda_{\text{primary efficacy}} \geq 1.5 \text{ versus } H_a: \lambda_{\text{primary efficacy}} < 1.5$$

The aim related to the second part of the primary efficacy objective to show that assigning asundexian versus apixaban is superior in preventing stroke and systemic embolism in patients with AF. The one-sided test problem is:

$$H_0: \lambda_{\text{primary efficacy}} \geq 1 \text{ versus } H_a: \lambda_{\text{primary efficacy}} < 1$$

For the primary safety objective, the aim is to show that treatment with asundexian is associated with less ISTH major bleeding events than treatment with apixaban in patients with AF. The one-sided test problem is:

$$H_0: \lambda_{\text{primary safety}} \geq 1 \text{ versus } H_a: \lambda_{\text{primary safety}} < 1$$

For the net clinical benefit objective, the aim is to show that treatment with asundexian is associated with less events of the net clinical benefit endpoint than treatment with apixaban in patients with AF. The one-sided test problem is:

$$H_0: \lambda_{\text{net clinical benefit}} \geq 1 \text{ versus } H_a: \lambda_{\text{net clinical benefit}} < 1$$

The hypotheses for secondary endpoints follow the same principles as outlined above.

The non-inferiority margin of 1.5 for the primary efficacy composite was chosen to preserve at least 50% of the relative reduction in the risk for stroke or systemic embolism associated with apixaban. As there is no randomized controlled clinical study with a direct comparison of apixaban versus placebo, an indirect comparison was done based on the effect of apixaban over warfarin (HR=0.79 CI=0.66;0.95) as shown in the ARISTOTLE study (Granger et al. 2011) and the effect of placebo over warfarin (HR=2.8 CI=1.88;4.2) as estimated from 6 previous major randomized controlled studies, that was also used in the ARISTOTLE study. Using the extended Bucher method for indirect comparison this provides a lower 95% confidence limit of 2.28 for the relative risk with placebo as compared with apixaban

(HR=3.54 CI=2.28-5.51) (Bucher et al. 1997, Wells et al. 2009). Half of this value on the log scale is 1.509.

9.1.1 Multiplicity Adjustment

The familywise type-I error rate will be controlled at the overall (two-sided) significance level α = 5% using the graphical method of (Bretz et al. 2009). The initial graph of the strategy is shown in Figure 9–1.

The graph will be updated with each null hypothesis that is rejected.

First, the non-inferiority null hypothesis for the primary efficacy outcome will be tested as a gatekeeper at the entire available significance level α. If this null hypothesis is rejected, the significance level will be split and passed on to the superiority null hypothesis for the primary safety outcome (90% of 5% = 4.5%) and to the superiority null hypothesis for the primary efficacy outcome (10% of 5% = 0.5%). The weights, 10% and 90%, were chosen by balancing the prior expectations about efficacy and safety endpoints. In particular, one aim was to ensure that there would be at least 90% power for the testing of the superiority null hypothesis for the primary safety endpoint assuming a 30% relative hazard reduction.

If the superiority null hypothesis for the primary safety outcome is rejected, the local significance level is first propagated to the superiority null hypothesis for the bleeding endpoint ISTH major and clinically relevant non-major bleeding and, if significant, thereafter to the superiority null hypothesis for the primary net clinical benefit outcome. If this null hypothesis is rejected, the local significance level will be propagated to the superiority null hypothesis for the primary efficacy outcome, leading to a local significance level of 5%.

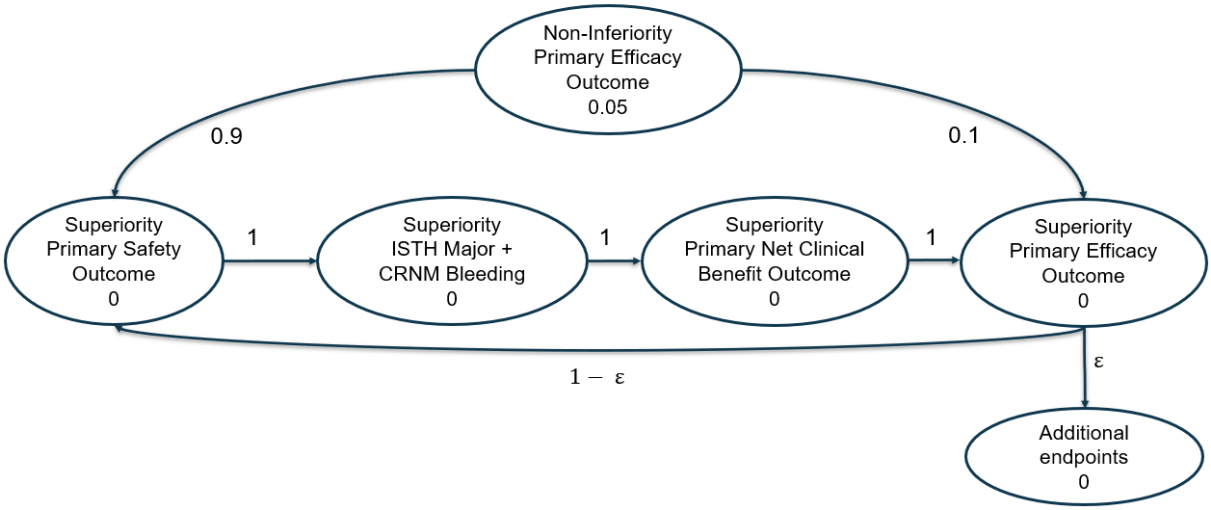
For the primary efficacy outcome, the test for superiority will be performed at a local significance level of either 0.5% or 5%. If the null hypothesis can be rejected, all, except for an infinitesimally small fraction ε, of the local significance level will be propagated to the superiority null hypothesis of the primary safety outcome, if not yet rejected. Further testing of null hypotheses associated with other endpoints will be done in case all 5 key null hypotheses are rejected. This part is not shown in detail in the figure.

The testing of the null hypotheses for other endpoints will be in hierarchical other, i.e. it stops if a null hypothesis cannot be rejected. The following 4 additional hypotheses will be tested in the specified order:

- Composite of ischemic stroke or systemic embolism,
- Composite of ISTH major bleeding, stroke, systemic embolism or all-cause mortality,
- All-cause mortality, and
- Ischemic stroke.

This reflects the priority to show superiority in both efficacy and safety and, in addition, allows testing for the primary net clinical benefit, even in situations where superiority of efficacy cannot be shown. No further formal testing is planned.

Figure 9–1: Graphical testing strategy



Note: The numbers in the bullets are the local significance levels while the numbers on the arrow reflect the proportion of the local significance level transferred to subsequent null hypotheses, once a null hypothesis is rejected.

9.2 Analysis Sets

For purposes of analysis, the following analysis sets are defined as displayed below.

Table 9–1: Analysis sets

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

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

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

9.3 Statistical Analyses

9.3.1 General Considerations

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

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

For the key efficacy and safety events, see Section 9.3.2, the variable is the time to first occurrence of the outcome event of interest, which can be a single outcome or a composite. In general, time-to-event variables will be derived as the number of days from the individual participant's randomization date to the date of onset of the respective endpoint event. The

time-to-event variable for participants who have not experienced the respective endpoint event will be censored on the date of the last follow-up in the following way:

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

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

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

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

- If only the month of the event is known, then the 1st day of this month will be imputed.
- If only the year of the event is known, then the 1st of January will be imputed.
- If year, month and day are unknown, the randomization date will be imputed.

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

Descriptive statistics

Study data will be summarized using methods like frequency tables and other descriptive statistics. Generally, confidence intervals will be presented as two-sided 95% confidence intervals.

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

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

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

Stratification

Regression models or statistical tests for time-to-event outcomes will be stratified (if applicable) by

- participation in conventional study model vs. DCT model

- current use vs. no current use of single agent antiplatelet therapy planned to continue for at least 6 months after randomization.

Stratified analyses will only be conducted if there are at least 5 participants with an event in each stratum and if there is at least 1 participant with an event in each treatment arm.

Missing data

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

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

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

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

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

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

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

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

Unobserved follow-up time will be multiply imputed using hazard rates estimated from those participants who have observed data subsequent to the intercurrent event "treatment discontinuation" but who have not experienced the event of interest prior to "treatment discontinuation". The constant hazard rate assumption will be assessed, and if not satisfied, a piecewise exponential or other distribution will be used for imputing the missing follow-up time. The imputation will include the following steps:

1. Identify participants who have observed follow-up time subsequent to early discontinuation of randomized treatment and who have not experienced the event of interest prior treatment discontinuation. For these participants, estimate the hazard rate for the off-treatment period separately for each treatment group. The off-treatment

period is defined as from the date of last intake of randomized treatment + 2 calendar days to either the outcome event of interest or the date of censoring due to study completion or death.

2. For each participant with incomplete follow-up for the event of interest who was censored without an outcome event of interest, simulate missing follow-up time as follows:

   - Draw (a) parameter(s) [Exponential, Weibull, or other] from the normal distribution using the estimates for the hazard rate in step 1 to incorporate variability in the estimated hazard rates.
   - Simulate a follow-up time from that resulting distribution and add it to the observed censoring date to get the imputed time-to-event for that participant.

   If the imputed time-to-event is before a defined cut-off date, the participant "experienced" the outcome event at the imputed time; if not, the participant would be censored at the cut-off date. The cut-off date will be set to the last CEOT visit date over all participants, reflecting the maximal time under risk for these patients.

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

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

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

9.3.2.1 Primary Efficacy Estimands

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 outcomes are defined in Section 3, the derivation of the time-to-event is described in Section 9.3.1.

Main Analytical Approach

In line with the "while on treatment" (here: "while alive") strategy proposed to address the intercurrent event "death" for the primary efficacy estimand, see Section 3, "death prior to the occurrence of a primary efficacy outcome" will be considered a competing risk in the analysis. Addressing "premature discontinuation of assigned treatment" with the treatment policy strategy means that 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 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".

The primary efficacy non-inferiority null hypothesis, see Section 9.1, will be rejected if the upper limit of the 95% confidence interval for the csHR does not exceed the non-inferiority margin.

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

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

Sensitivity Analyses

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

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

Missing follow-up time will be in general handled as described above. In addition, sensitivity analyses with regard to the missing follow-up time will be done as described in Section 9.3.1. Subgroup analyses will be performed without imputation of missing follow-up time. Details will be described in the SAP.

Supplementary Analyses

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. I.e. the estimand explored in the supplementary analysis is the same as the primary efficacy estimand but the population-level summary is the sub-distribution hazard ratio based on a Fine-Gray model. 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. Gray's test will be used to compare the cumulative incidence functions.

Another supplementary analysis will explore an estimand specifically targeting the non-inferiority objective to provide additional insights into the understanding of the treatment effect. This estimand will use different strategies to address intercurrent events in defining the treatment effect of interest. Details will be described in the SAP.

9.3.2.2 Primary Safety Estimand

Definition of endpoint

The primary safety endpoint is the time from randomization to the first occurrence of ISTH major bleeding. The bleeding outcome is defined in Section 3, the derivation of the time-to-event is described in Section 9.3.1.

Main Analytical Approach

In line with the "while on treatment" strategy proposed to address intercurrent events for the primary safety estimand, see Section 3, both "death prior to the occurrence of a primary safety outcome" and "premature discontinuation of assigned treatment" will be considered

competing risks in the analysis. This also implies that only participants who took at least one dose of study intervention will be included in the analysis, i.e. the analysis will be performed on the SAF.

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

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

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

Sensitivity Analyses

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

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

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

Supplementary Analyses

In a supplementary analysis the objective will be explored from a different angle, comparing the probability for the occurrence of the primary safety outcome as compared to the hazard rates based on a Fine-Gray model and using Gray's test to compare the cumulative incidences. I.e. the estimand explored in the supplementary analysis is the same as the primary safety estimand but the population-level summary is the sub-distribution hazard ratio based on a Fine-Gray model.

9.3.2.3 Primary Net Clinical Benefit Estimand

Definition of endpoint

The primary net clinical benefit endpoint is the time to first occurrence of stroke, systemic embolism, or ISTH major bleeding (excluding hemorrhagic stroke). The outcomes are defined in Section 3, the derivation of the time-to-event is described in Section 9.3.1.

Main Analytical Approach

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

To estimate the relative change in the instantaneous rate of the occurrence of the primary net clinical benefit outcome in participants taking asundexian versus apixaban according to the

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

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

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

Sensitivity Analyses

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

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

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

Supplementary Analyses

In a supplementary analysis the objective will be explored from a different angle, comparing the probability for the occurrence of the primary net clinical benefit outcome as compared to the hazard rates based on a Fine-Gray model and using Gray's test to compare the cumulative incidences. I.e. the estimand explored in the supplementary analysis is the same as the primary net clinical benefit estimand but the population-level summary is the sub-distribution hazard ratio based on a Fine-Gray model.

9.3.3 Secondary Endpoint(s) Analysis

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

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

9.3.4 Exploratory Endpoint Analysis

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

9.3.5 Other Safety Analysis

An overall summary of AEs will be generated by study intervention arm. The number and percentage of participants with treatment emergent AEs (TEAEs; i.e. AEs occurring until 2 days after last study intervention administration), post-treatment AEs (i.e. AEs occurring more than 2 days after last intake of study intervention), treatment emergent SAEs, treatment

emergent study intervention-related AEs, treatment emergent study intervention-related SAEs, TEAEs leading to premature and permanent discontinuation of study intervention, treatment emergent non-serious AEs, TEAEs by maximum intensity, drug-related TEAEs by maximum intensity will be summarized by treatment group using Medical Dictionary for Regulatory Activities (MedDRA) terms grouped by Primary System Organ Class and Preferred Term.

The number of participants with treatment emergent abnormal laboratory values above or below the normal range will be tabulated by the laboratory parameter and study intervention group.

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

9.3.6 Other Analysis

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

Key subgroups

The following subgroup considered to be potentially predictive is planned to be analyzed:

- Apixaban dosage

As described in Section 6.1, 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 apixaban treatment will be blinded, all participants will be assigned to one of the apixaban groups according to their risk factors. As the lower apixaban dosage might decrease the efficacy treatment effect, the “apixaban dosage” factor 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 2 different studies. This holds true since the proportion of participants with 2 or 3 risk factors for apixaban dosage is estimated to be at about 10%.

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

- The stratification factors
  - Participation in conventional study model vs. DCT model.
    Participants in the DCT part might be younger and different compared to participants in the conventional study model.
  - 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 as the most important risk score for stroke
- BMI
- eGFR, reflecting the known higher risks for an event and the recommendation of lowering the apixaban dose for decreased kidney function

- Race, with focus on the known differences in the risk profile for Asian / non-Asian and Black / Non-Black participants.
- Region, as there are different known risk profiles and medical care standards.

If the number of participants is too small within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. For other factors there is no a priori rationale that the treatment effect could possibly be modulated. The definition or categorization of subgroups will be reflected in the final SAP prior to unblinding.

Exploratory subgroups

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

Analytical Approach

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

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

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

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

9.4 Interim Analysis

An interim analysis is planned when about 85 participants with a primary efficacy event have been observed, corresponding to 25% of the target number of participants with a primary efficacy event. The interim analysis is for futility; therefore no adjustment of the type 1 error is needed.

It is recommended to stop the study before its planned completion for ethical reasons if both of the following 2 criteria are fulfilled based on the results of the interim analysis:

- The point estimator of the cause-specific hazard ratio for the primary efficacy outcome is higher or equal to the non-inferiority margin of 1.5.

This guidance corresponds to a setting where based on the results of the interim analysis and assuming the point estimate from the interim analysis governing the remainder of the study, the chance that the trial will reach its success criterion if it continues falls below 1.2%. If the true hazard ratio for the primary efficacy outcome is 1, the probability to estimate a cause-specific hazard ratio of > 1.5 at this stage is only 3.1%.

- The lower bound of the two-sided 95% confidence interval for the cause-specific hazard ratio for all-cause mortality is higher than 1.

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

9.5 Sample Size Determination

A single study with a study-wise type-I error level of 5% is proposed to provide convincing evidence on the effect of asundexian vs. apixaban on prevention of stroke and systemic embolism in participants with atrial fibrillation. Both the number of participants with primary efficacy or safety events and the total sample size must be sufficiently robust to support the intended claims for efficacy and safety, respectively.

To meet these needs approximately 18000 participants will be randomly assigned to study intervention, eventually targeting approximately 333 participants with a primary efficacy event and 343 participants with a primary safety event (while exposed to intervention). The sample size may be increased if planning assumptions are not satisfied. Any decision to extend follow-up or increase sample size will be based upon the review of blinded data.

The target numbers of participants with events were determined based on the primary hypotheses (see Section 9.1), the assumption of constant hazard rates for time from randomization to the events of interest over the total duration of the study, as well as the following assumptions:

- **Efficacy**
  - Non-inferiority margin of 1.5 for the cause-specific hazard ratio of asundexian vs. apixaban for the primary efficacy endpoint
  - Type-I error level of 0.05 for a two-sided log-rank test
  - Power of at least 90% for the non-inferiority test under the assumption that the true cause-specific hazard ratio (including effects of treatment discontinuation) is HR = 1
  - Power of at least 90% for the superiority test under the assumption that the true cause-specific hazard ratio, including effects due to treatment discontinuation, is HR = 0.7 and the non-inferiority for efficacy and superiority for safety can be shown prior to testing of the superiority.
- **Safety**

- Type-I error level of 0.045, reflecting the division for superiority testing for safety and efficacy, for a two-sided log-rank test
- Power of at least 90% for the superiority test under the assumption that the true cause-specific hazard ratio is HR = 0.7.

- **Net Clinical Benefit**
  - Type-I error level of 0.045, reflecting the division for superiority testing for safety and efficacy and assuming that at least bleeding superiority endpoint will be met, for a two-sided log-rank test
  - Power of at least 90% for the superiority test under the assumption that the true cause-specific hazard ratio is HR = 0.7.

Based on the above assumptions, the required target number of study participants who have experienced a primary efficacy event is estimated to be 210 for the non-inferiority test, 333 (rounded to 340) for the superiority test and the required target number of study participants who have experienced a primary safety as well as a net clinical benefit event on treatment is estimated to be 343. If the true hazard ratio (including effects of early treatment discontinuation) for the primary efficacy endpoint is HR = 0.73, the power to detect a treatment difference between asundexian and apixaban is 80% for a target number of 340 participants with a primary efficacy outcome. For an estimated HR $\leq$ 0.80 (including effects of early treatment discontinuation) for an observed target number of 340 participants with a primary efficacy outcome superiority would be achieved at a 5% significance level.

This study will be event-driven, which implies that the study duration depends on when the target numbers of participants have experienced primary efficacy or safety events.

The anticipated incidence rates in the apixaban arm are assumed to be constant over time with

- 1.6 participants with a primary efficacy event per 100–patient years, corresponding to a cumulative incidence of 1.58% participants with a primary efficacy event one year after randomization
- 2.8 participants with a primary safety event per 100–patient years, corresponding to a cumulative incidence of 2.76% participants with a primary safety event one year after randomization
- 4.3 participants with death per 100–patient years, corresponding to a cumulative incidence of 4.21% for all-cause mortality one year after randomization
- 4.0 participants with net clinical benefit outcome per 100–patient years, corresponding to a cumulative incidence of 3.92% for net clinical benefit outcome one year after randomization

Furthermore, the total duration of the accrual period is assumed to be approximately 24 months with a plausible accrual pattern of (0.08%, 0.16%, 0.44%, 0.69%, 1.39%, 1.81%, 2.64%, 3.61%, 4.83%, 4.72%, 5.28%, 5.39%, 4.83%, 5.39%, 5.39%, 5.56%, 6.11%, 6.11%, 5.83%, 5.83%, 6.11%, 6.11%, 6.11%, 5.57%) of the total participants in the respective months.

Under these assumptions, assigning approximately 18000 participants randomly to study intervention an expected study duration of approximately 33 months will be sufficient to achieve the target number of participants with efficacy or safety events. If the pooled incidence rate for the primary safety event is indeed higher than the pooled incidence rate for

primary efficacy events, the study can be stopped when the required number of participants with a primary efficacy outcome is reached. Under the assumptions outlined above, the expected follow-up durations for participants assigned to study intervention are 9 to 33 months after randomization plus safety follow-up. The mean treatment duration is projected as 15.5 months (median observation time 16 months). In addition, > 15600 participants are expected to be followed for at least 9 months, > 12600 participants for 12 months, > 6600 participants for 18 months and > 1700 participants for 24 months.

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

Sample size calculations were derived using the software PASS 13.

10. Supporting Documentation and Operational Considerations

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

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g. advertisements) must be submitted, reviewed and approved in accordance with national legislation and undergo scientific and ethical assessment before the study is initiated.
- Any amendments to the protocol will require IRB / IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB / IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB / IEC
  - Notifying the IRB / IEC of SAEs or other significant safety findings as required by IRB / IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB / IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants or their legally authorized representative and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB / IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participants or their legally authorized representative.
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 7 days from the previous ICF signature date.
- Informed consent must be obtained before initiation of any study-specific procedures. The process of obtaining informed consent must be documented in participant's source documentation.
- Pharmacogenetic samples will be taken in a subset of participants. Eligible participants will be asked to sign a corresponding informed consent.
- As part of the **DCT model**, a secure link will be provided via email to the study participant by the study staff to access the electronic consent web portal, along with unique login credentials.
  - Individuals who agree to take part in the study will be asked to review the consent overview information.
  - Study investigator / designated staff will complete the informed consent process with the participant by telephone / videoconference.
  - Individuals who agree to take part in the study will provide their signature executed to an electronic record as per local requirements on a computer, smartphone, or a tablet in the designated signature block, with the person conducting consent countersigning.
  - Once consented, a DCT participation kit will be sent out to study participants and other operational logistics will be initiated as described in Section 10.10.1.
  - Participants will be instructed to return all study supplies, including any provisioned devices, back to the study site once study participation is completed.

10.1.4 Recruiting Strategy

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

10.1.5 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.1.6 Committees Structure

10.1.6.1 Program Leadership Committee (PLC)

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

10.1.6.2 Executive Committee (EC)

The main task of the Executive Committee for OCEANIC-AF (study 19767), which is composed of a panel of experts in the field cardiology, thrombosis / hematology and neurology, is to be actively engaged in the protocol development and the conduct, interpretation, and reporting of the results of the study. Furthermore it will advise the sponsor on clinical, medical, and scientific questions, and support publications surrounding the study and the overall program. The EC will work collaboratively with other entities (including the sponsor and the Steering Committee) engaged in the relevant clinical study to coordinate communication with sites and site investigators. In addition, the EC will make an effort to engage and train a next generation of diverse clinical study investigators. Details of the Committee will be specified in the Committee charter.

10.1.6.3 Steering Committee (SC)

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

10.1.6.4 Independent Data Monitoring Committee (IDMC)

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

10.1.6.5 Clinical Events Committee (CEC)

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

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

In addition, events that might be indicative of a potential outcome event will be reported as outcome events to ensure that no outcome event is missed. This includes for example 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.

10.1.7 Dissemination of Clinical Study Data

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

Result Summaries of Bayer's sponsored clinical studies in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition results of clinical drug studies will be provided on the publicly funded websites ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

In accordance with the current EU regulation, result summaries will be submitted within one year from the end of the studies in adult populations or within 6 months for studies in a

pediatric population, in **all** participating countries. No preliminary data analysis (e.g. on EU data only) will be performed, as this might compromise data integrity and the scientific validity of the study.

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

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

10.1.8 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF completion guidelines provided to the study sites.
- The investigator must permit study-related monitoring, audits, IRB / IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition to the on-site monitoring, a remote monitoring option is available. All study materials, including but not limited to drug accountability records or electronic source documentation, will be available for remote monitoring with view-only access, with training provided prior to access being granted. Study staff will be available to meet via video conference or over the phone. Study monitors will be able to issue queries and request resolutions which will be completed by the designated study staff.
- Home nurses are expected to record source electronically. The clinical data recorded by home nurses is readily visible to the investigator / authorized site personnel and will

be referenced when making entries into the CRF. Source data collected electronically can also be viewed by study monitors for ongoing source data verification purposes. Where patient service centers are utilized, staff may also record source electronically in a similar fashion.

10.1.9 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data, and its origin can be found in the Source Data Location List (SDLL).
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The site must implement processes to ensure availability of all required source documentation (e.g. participant file, local laboratory report). The monitor will work with the site to collect key data points by completing the SDLL.
- Race and ethnic group may be entered directly into the CRF, without availability of corresponding source documentation. Thus, these CRF data will be the source and no additional source documentation will be available. For all other data, source documentation must be available at the site.

10.1.10 Study and Site Start and Closure

Study Start

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

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

Study / Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB / IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants at study level included earlier than expected.

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

10.1.11 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- Additional information regarding publication policy can be found in the Steering Committee charter.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10–1 will be performed by the central laboratory unless specifically mentioned.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10–1: Protocol-required Safety Laboratory Tests

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

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

Investigators must document their review of each laboratory safety report.

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

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

10.2.1 Liver Safety: Follow-up Assessments and Suggested Actions

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

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

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

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

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

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

Follow-up assessments

- Repeating follow-up samplings for liver enzymes (ALT and AST) and serum total bilirubin tests 2 or 3 times weekly. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize (details see Table 10–2). Follow-up sampling should also include any other relevant abnormal liver parameter observed in prior testing (such as AP, albumin, γGT, CK or LDH), as clinically indicated. Follow-up sampling might be discontinued earlier than when values return to normal or participant baseline levels in case a confirmed clinical diagnosis unrelated to the study intervention has been established that explains the elevated liver enzymes and no further normalization is expected.
- Obtaining additional samples to assess further general chemistry, lipid metabolism and liver function parameters and complete blood count. This is part of the central laboratory sample (see Table 10–2).

Etiological follow-up assessments

- Ruling out acute viral hepatitis, autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis, hypoxic / ischemic hepatitis and biliary tract disease. This may require performing additional procedures, e.g. ultrasound examinations. A sample for further etiology assessment should be obtained from a participant evaluated at a study site as soon

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

- Considering gastroenterology or hepatology consultations.

Additional information

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

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

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

Suggested actions:

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

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

Discontinuation of treatment should be considered if:

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN or INR > 1.5)
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and / or eosinophilia (> 5%).

Table 10–2: Liver Laboratory Monitoring

Sample / Time point	Laboratory Test	Further aspects
Initial confirmatory re-test* within 48-72 hours of the investigator becoming aware of elevation	AST, ALT, AP, Bilirubin (total and fractionated) If not analyzed in prior sample: γGT, CK, LDH	If confirmed: Document (S)AE and additional information in CRF
Follow-up sampling* while ALT or AST are > 3 x or > 4 x ULN#: at least 2-3 times a week	ALT, AST, Bilirubin (total and fractionated)	Continue observation for clinical signs and symptoms
Follow-up sampling* when ALT and AST are ≤ 3 x or ≤ 4 x ULN#: once a week	ALT, AST	Follow-up generally ends earliest when values return to normal or participant baseline levels
Central laboratory sample*/** (after AST or ALT elevation# has been confirmed in a re-test) includes parameters for etiology assessment and should be taken as soon as possible (may be combined with first follow-up sampling)	• ALT, AST, AP, Bilirubin (total and fractionated), γGT, LDH, CK, CRP • PT / INR • Albumin, Cholinesterase • Glucose, HbA1c • Total cholesterol, Triglycerides • Complete blood count including WBC with differentials (absolute and relative values), Hemoglobin **Further etiology assessment** • Anti-hepatitis A virus antibodies (total, IgM) • Hepatitis B virus surface antigen, Anti-hepatitis B virus core IgM antibody; if positive, the following will be evaluated: Anti-hepatitis B virus antibodies (surface, core total, core IgG), Hepatitis B DNA, Anti-hepatitis D virus IgM antibodies • Hepatitis C RNA, Anti-hepatitis C virus IgM antibodies • Hepatitis E RNA, Anti-hepatitis E virus antibodies (IgM and IgG) • IgG • Antinuclear antibodies (ANA) • Anti-smooth muscle antibodies (ASMA) • Cytomegaly virus DNA, Anti-Cytomegaly virus IgM antibodies • Epstein-Barr virus DNA, Anti-Epstein-Barr virus IgM antibodies • Herpes simplex virus DNA, Anti-herpes simplex virus IgM antibodies • Anti-mitochondrial autoantibodies • Ferritin, Iron, Total iron binding capacity, Transferrin saturation • Ceruloplasmin • Anti-neutrophil cytoplasmic antibodies / Anti-neutrophil perinuclear antibodies • Alpha-1 antitrypsin level	Consider update of AE reporting terms in case of relevant findings

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

refer to criteria for comparison to individual baseline value under 1.a) or 1.b) in Section 10.2.1

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

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

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

10.3.1 Definition of AE

AE Definition

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and / or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE / SAE unless it is an intentional overdose taken with possible suicidal / self-harming intent. Such overdoses should be reported regardless of sequelae.
- Sign, symptoms, or the clinical sequelae of suspected medication errors, misuse and abuse of either study intervention or a concomitant medication. Medication errors, misuse and abuse per se will not be reported as an AE / SAE, unless it is resulting in AE / SAE. Such medication errors, misuse and abuse should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and / or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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

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

- The disease / disorder being studied or expected progression, signs, or symptoms of the disease / disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and / or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life threatening**

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

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

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

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

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

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

f. **Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

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

AE and SAE Recording

- When an AE / SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE / SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE / SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and / or other clinical information. Whenever possible, the diagnosis (not the individual signs / symptoms) will be documented as the AE / SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:
    - **Mild**: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
    - **Moderate**: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
    - **Severe**: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE / SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and / or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and / or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE / SAE and document this in the medical notes. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the sponsor.
- The investigator may change his / her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and / or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and / or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form and transmit to the sponsor via PV.CaseProcessing@bayer.com.
- Contacts for SAE reporting can be found in the Investigator Site File.

SAE Reporting to the Sponsor via Paper CRF

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

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are considered WOCBP (fertile)

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below):
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (> 40 IU/L [for US only: FSH levels > 40 mIU/mL and estradiol < 20 pg/mL]) is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

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

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:
    a) Documented hysterectomy
    b) Documented bilateral salpingectomy
    c) Documented bilateral oophorectomy

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

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

2. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (> 40 IU/L [for US only: FSH levels > 40 mIU/mL and estradiol < 20 pg/mL]) is required.
  - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

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

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

10.5 Appendix 5: Calculating the Child-Pugh Score

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

Table 10–3: Grading of severity of liver disease

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

Source: adapted from (Pugh et al. 1973)

Table 10–4: Child-Pugh score

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

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

10.6 Appendix 6: Calculating Glomerular Filtration Rate

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

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

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

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

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

For measurement of renal function in Japan, please refer to Section 10.12.2.

10.7 Appendix 7: Calculating CHA_2DS_2-VASc Score

Table 10–5: CHA_2DS_2-VASc score

Letter	Risk factor	Score
C	**C**ongestive heart failure / LV dysfunction (Clinical HF, or objective evidence of moderate-to-severe LV dysfunction, or HCM)	1
H	**H**ypertension (or on antihypertensive therapy)	1
A_2	**A**ge ≥ 75	2
D	**D**iabetes mellitus (Treatment with oral hypoglycemic drugs and / or insulin or fasting blood glucose > 125 mg/dL [7 mmol/L])	1
S_2	**S**troke / TIA / thromboembolism (Previous stroke, TIA, or thromboembolism)	2
V	**V**ascular disease (Angiographically significant CAD, previous myocardial infarction, PAD, or aortic plaque)	1
A	**A**ge 65-74	1
Sc	**S**ex **c**ategory (i.e. female sex)	1

C Recent decompensated HF irrespective of LVEF (thus incorporating HFrEF or HFpEF), or the presence (even if asymptomatic) of moderate-severe LV systolic impairment (LV ejection fraction ≤ 40%) on cardiac imaging; HCM confers a high stroke risk and OAC is beneficial for stroke reduction.

H History of hypertension may result in vascular changes that predispose to stroke, and a wellcontrolled BP today may not be wellcontrolled over time. Uncontrolled BP - the optimal BP target associated with the lowest risk of ischemic stroke, death, and other cardiovascular outcomes is 120 - 129/< 80 mmHg.

A_2 Age is a powerful driver of stroke risk, and most population cohorts show that the risk rises from age 65 years upwards. Age-related risk is a continuum, but for reasons of simplicity and practicality, 1 point is given for age 65 - 74 years and 2 points for age ≥ 75 years. Age is a powerful driver of stroke risk, and most population cohorts show that the risk rises from age 65 years upwards. Age-related risk is a continuum, but for reasons of simplicity and practicality, 1 point is given for age 65 - 74 years and 2 points for age ≥ 75 years.

D Diabetes mellitus is a well-established risk factor for stroke, and more recently stroke risk has been related to duration of diabetes mellitus (the longer the duration of diabetes mellitus, the higher the risk of thrombo-embolism) and presence of diabetic target organ damage, e.g. retinopathy. Both type 1 and type 2 diabetes mellitus confer broadly similar thromboembolic risk in AF, although the risk may be slightly higher in patients aged < 65 years with type 2 diabetes mellitus compared with patients with type 1 diabetes mellitus.

S_2 Previous stroke, systemic embolism, or TIA confers a particularly high risk of ischemic stroke, hence weighted 2 points. Although excluded from RCTs, AF patients with ICH (including hemorrhagic stroke) are at very high risk of subsequent ischemic stroke, and recent observational studies suggest that such patients would benefit from oral anticoagulation.

V Vascular disease (PAD or myocardial infarction) confers a 17 - 22% excess risk, particularly in Asian patients. Angiographically significant CAD is also an independent risk factor for ischemic stroke among AF patients (adjusted incidence rate ratio 1.29, 95% CI 1.08 - 1.53). Complex aortic plaque on the descending aorta, as an indicator of significant vascular disease, is also a strong predictor of ischemic stroke.

A See above. Recent data from Asia (Chao et al. 2016) suggest that the risk of stroke may rise from age 50 - 55 years upwards and that a modified CHA_2DS_2-VASc ($mCHA_2DS_2$-VASc) score may be used in Asian patients ($mCHA_2DS_2$-VASc assigns 1 point for patients aged 50 - 74 years). This is not applicable to this study.

Sc Recent studies have suggested that female sex, in the absence of other AF risk factors (CHA_2DS_2-VASc score of 0 in males and 1 in females), carries a low stroke risk that is similar to males. The excess risk for females was especially evident among those with ≥ 2 non-sex-related stroke risk factors; thus, female sex is a risk modifier rather than a risk factor.and is age dependent. Adding female sex to the CHA_2DS_2-VASc score matters for age > 65 years or ≥ 2 non-sex-related stroke risk factors (January et al. 2019).

Abbreviations: AF = atrial fibrillation; BP = blood pressure; CAD = coronary artery disease; CI = confidence interval; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICH = intracranial hemorrhage; LV = left ventricular; LVEF = left ventricular ejection fraction; OAC = oral anticoagulant; PAD = peripheral artery disease; RCT = randomized controlled trial; TIA = transient ischemic attack

Sources: adapted from (Hindricks et al. 2021, Lip et al. 2010).

10.8 Appendix 8: Modified Rankin Scale

Table 10–6: Modified Rankin Scale (mRS) and Corresponding Sections of a Structured Interview

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

Abbreviation: ADL = Activities of daily living

Sources: adapted from (Banks and Marotta 2007, van Swieten et al. 1988, Wilson et al. 2002).

10.9 Appendix 9: Outcome Events: Data Collection

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

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

Please also refer to Section 8.4.1 regarding the reporting of AEs.

10.10 Appendix 10: DCT Model for DCT Sites Only

DCTs are intended to reduce the burden on clinical study participants and make studies more visible and accessible to patients independently of referring physicians. There is a growing body of evidence supporting the use of broadband internet access, home computing and smartphones, as well as digital health technologies enabling remote interactions and robust monitoring, support, and management of trial participants.

In this study, approximately 10-20 sites globally are expected to participate as DCT metasites.

10.10.1 Recruitment, Onboarding, Training in DCT Model

Recruitment

Participants in the **DCT model** will be recruited by employing digital advertising on social media (e.g. Facebook, Google, Instagram) and in banners on patient advocacy and other relevant websites. In addition, outreach to the investigator's network should be used to raise awareness of and recruit for the study.

Onboarding and Training

Upon signing informed consent, participants will be onboarded and trained for study-specific procedures during the screening period, including operational logistics. Part of this training will include confirmation that any devices provided to support participation are working appropriately and are fit for use.

Training will be conducted via teleresearch (phone and / or video call as applicable), home nurse, and / or by utilizing remote training methods available via the study application and / or web portal.

DCT study site personnel will be trained for the study during the investigator meeting and / or during the site initiation process.

Training will be conducted on the smartphone application and / or web portal to access, navigate and use the app and / or study platform and on the below listed electronic devices used in the DCT model:

Study applications and devices used in the DCT model:

- **Study app and / or web portal**

  The study application and / or web portal will give participants access to complete the EQ-5D and attend teleresearch visits. Also included are reminders / engagement notifications, and the ability to contact the site directly via the app / portal. Training materials on how to use the app / portal will be provided to participants.

- **Electronic devices**

  Participants are asked to use their own camera-equipped, web-enabled devices for the study. If needed, a smartphone with limited functionality for study use only will be provided to the participants.

- **ECG monitoring device**

  An ECG monitoring device will be utilized during the screening period to evaluate heart rhythm and may be supported by the home nurse.

Further important topics for onboarding and training are:

Pregnancy Testing

- For remote confirmation of the pregnancy test, the pregnancy test results can be reviewed and documented by the home nurse, if applicable. Alternately, the results should be provided to site staff for visual confirmation (e.g. photo, teleresearch visit). The image is not required as source documentation; written confirmation of a negative result in source is sufficient.
- If 4 or more days have elapsed between the negative screening pregnancy test and receipt of study intervention after randomization, a second negative pregnancy test must be obtained prior to the participant starting study intervention.

Direct-to-participant shipments of study intervention

- **First Dose**

  The first intake of study intervention will involve a delay due to the time required for delivery of study intervention to participant. After receipt of the first DtP shipment, but prior to taking the first dose of study medication, site staff will contact the participant to ensure the study medication was received in good condition and to review dosing instructions. Furthermore, study participants should be instructed to take the last dose of their open label NOAC (or non-oral anticoagulant if applicable) on the day prior to starting study intervention intake.

- **Accountability and Compliance**

  The metasite will be responsible for study medication accountability and will facilitate return of the used and unused study medication from the participant via (traceable) courier according to the DCT SoA. While a home nurse may conduct a count of study medication during a visit, this count is considered to be for use in compliance calculations only and is not considered formal accountability.

  Respective documentation of DtP shipments will be maintained by Fisher Clinical Services and will be made available upon request.

10.10.2 Schedule of Activities for DCT Model (DCT SoA)

Study periods Duration	**Screening** **≤4** weeks before **RND**		**Intervention period** **~9 → ~33** months*, from **RND** until **Common End of Treatment (CEOT) visit** / **Early Termination (ET)**												**Early Termination period**** **ET** until **CEOT visit**			**Common End of Treatment period** **CEOT visit** until **2** weeks after	
Visit number / acronym	**1 a**	**1 b**	**2‡**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12***	**13***	**ET visit**	**ET SFU visit**	**≥3 → 13***	**CEOT visit**	**CEOT SFU visit†**
Visit type	☎ / 💻	💻	💻	☎	💻	💻	☎	💻	☎	💻	☎	💻	☎	💻	💻	☎ (💻)	☎ (💻)	💻 (☎)	☎
Visit / Month [M] Day [D] ± window Week [W] ± window	**SCR a** D-28 → D-14	**SCR b** D-14 → D1	**RND / M0** D1 —Δ→ SI intake	**M1** 30±4	**M3** W13±1	**M6** 26±1	**M9** 39±1	**M12** 52±1	**M15** 65±1	**M18** 78±1	**M21** 91±1	**M24** 104±1	**M27** 117±1	**M30** 130±1	**ET** ET	**ET+2W** (ET+2W)+1W	**≥M1 → M30** ≥D30±4 → W130±1	**CEOT** CEOT±~3W	**CEOT visit+2W** (CEOT visit+2W)+1W
Administrative procedures																			
Remote eConsent	X																		
Initiate operational logistics	X																		
Inclusion / exclusion criteria	X	X	X																
Demographics / biometrics		X																	
Medical history		X	X																
Prior / concomitant meds		←==========continuously==========→															AP/AC only	X (AP/AC only)	X
Clinical procedures / assessments																			
ECG		X	(X)																
Vital signs (BP and RHR)		X	(X)																
Adverse events	only procedure related events	←==========continuously==========→																X†	X
Outcome events			←==========continuously==========→																
HCRU			←==========continuously==========→																
EQ-5D			X			X		X		X		X		X	X			X†	
IRT																			
Randomization / Visit registration		X	X		X	X		X		X		X		X	X			X	
Laboratory assessments																			
Safety blood sampling		X	(X)		X	X		X				X			X			X†	
Pregnancy test (if WOCBP)		X	X												X			X†	
Study intervention (SI) shipment (direct-to-participant SI shipment)																			
SI delivery			Δ→X		X	X		X		X		X		X					
SI return / accountability					X	X		X		X		X		X	X			X†	

Annotated Schedule of Activities for DCT Model (DCT Annotated SoA)

Administrative procedures done by remote trial site	
Remote eConsent	this includes use of electronic systems to convey information related to the study and also electronic signature of the consent form
Initiate operational logistics	operational logistics will be initiated during this visit (home health visit scheduling, device shipment, familiarization with app / web portal and communication functionality)
Inclusion / exclusion criteria	in case SCR and RND are performed on the same calendar day, these criteria need to be assessed only once
Demographics / biometrics	biometrics refers to measurement of height and weight and will only be recorded at screening
Medical history	in case SCR and RND are performed on the same calendar day, this needs to be assessed only once
Prior / concomitant medication	in case SCR and RND are performed on the same calendar day, this needs to be assessed only once; in case a participant pretreated with a NOAC (or another anticoagulant) has already taken the anticoagulant on the planned day of intake of study intervention, intake of SI should be postponed by one day (Section 6.1); if SI is *permanently* discontinued ≥ 2W before CEOT visit, *only* AP/AC need to be reported at scheduled visits, including CEOT visit; otherwise all meds need to be reported
Clinical procedures performed by participant or local provider / **assessments** performed by remote trial site or local provider in case of events and HCRU, by participant in case of questionnaire	
ECG	to display ≥ 6 leads; no need to be repeated once available, unless not available in sufficient quality (Section 8.3.6)
Vital signs (BP and RHR)	no need to be repeated once available (Section 8.3.5)
Adverse events	(S)AEs will be collected from start of SI intake until SFU visit; only study procedure related events will be reported from signing of eConsent onward (Section 8.4.1)
Outcome events	outcome events including all bleeding, death, MI, stroke and systemic embolism, as well as events indicative of a potential outcome (Section 8.4.6) need to be reported in the CRF continuously until death or last study visit (= CEOT SFU; *only* if SI is *permanently* discontinued ≥ 2 W prior to CEOT visit reporting occurs until CEOT visit)
HCRU	HCRU (within hospitals) in conjunction with SAEs and outcome events needs to be documented, e.g. time points or periods affected (Section 8.10.1)
EQ-5D	at the respective visits participants should complete the questionnaire via smartphone / electronic device at any time during the visit window, preferably in one attempt
IRT operated by remote trial site	
Randomization / Visit registration	SCR and RND can take place on the same calendar day if all information is available (Visits 1b and 2 are combined); SI intake will start as soon as possible after RND (day 1); this will involve a delay due to time required for delivery of SI to participant; SI intake is expected to continue until the day prior to the CEOT visit
Laboratory assessments done by local provider (home nurse or service center) or potentially participant (pregnancy test)	
Safety blood sampling	creatinine and eGFR values must be available at RND and can be used if done as part of routine management and no older than 14 days at RND (Section 8); in any case, the full set of safety laboratory tests (Table 10–1) needs to be obtained once during the SCR period, at the latest at RND, and at indicated visits thereafter
Pregnancy test (if WOCBP)	a WOCBP must have a negative serum or urine pregnancy test at SCR; a repeat test at RND (before SI intake) is required, unless ≤ 4 days lie between SCR and RND
Study intervention (SI) shipment (direct-to-participant SI shipment)	
SI delivery	at each contact participants should be instructed regarding SI compliance; 1st SI shipment will be initiated after RND, and SI intake will start on the day after arrival of SI at the participant's home; participants need to be instructed on stopping open label anticoagulant; start of SI has to be confirmed with the participant and documented by site
SI return / accountability	at the CEOT visit the final SI collection occurs: no SI intake should take place on the day of this visit anymore; the last intake of SI occurs on the previous day

Abbreviations: AP/AC = antiplatelets/anticoagulants, BP = blood pressure, CEOT = common end of treatment, D = day, ECG = electrocardiogram, EQ-5D = European Quality of Life group 5-Dimension questionnaire, ET = early termination, HCRU = healthcare resource utilization, RHR = resting heart rate, IRT = interactive response technology, M = month, RND = randomization, SCR = screening, SFU = safety follow-up, SI = study intervention; W = week(s), WOCBP = woman of childbearing potential, 💻 = teleresearch visit, ☎ = phone visit, $^{\Delta}$ = time for delivery of SI to participant

‡ procedures and assessments at visit 2 should preferably be conducted prior to RND; SI delivery will be initiated after RND; once participant confirms SI receipt, SI intake will be concluding the visit

* if applicable (if the number of efficacy outcome events does not accrue until Month 33 as expected) the visit schedule will continue after Month 30 with the respective labelling, e.g. Visit 14, 15. The duration of the intervention period (~9 to ~33 months) depends on when a participant joins during the course of the study. Displayed timepoints might therefore not be applicable to all participants.

** An **early termination visit** is only applicable to participants who prematurely discontinue intake of SI *permanently*; those should undergo an ET visit as soon as possible after discontinuation of SI. An **ET SFU visit** will occur 2 weeks (+ 7 days window) after the day of the discontinuation of SI (Section 7.1), unless *permanent* discontinuation occurred < 2 W prior to CEOT visit, in which case a **CEOT SFU** will be performed instead. After permanent discontinuation of SI participants should take part in the remaining visits (via phone) as scheduled, until including the CEOT visit (or CEOT SFU).

† if SI *permanently* discontinued: item not applicable; only if discontinued < 2 W before CEOT visit, CEOT SFU will replace ET SFU; if SI is *permanently* discontinued a phone call CEOT visit is expected

10.11 Appendix 11: Tokenization

Participants at study sites in the United States may be invited to take part in voluntary tokenization that links their de-identified real-world data (e.g. claims, electronic health records, laboratory, pharmacy) to their study data without compromising the privacy of study participants. Approval for tokenization must be obtained from each participant, and a separate ICF will be provided. Tokenization may allow looking into the vital status and potentially cause of death of participants lost to follow-up.

Participation is optional, and participants who decline to take part in tokenization will still be able to participate in the clinical study. Non-participation in tokenization will not affect study conduct or the clinical care of the participants.

Third-party entities will use dedicated software to encrypt the original patient identification information into a new de-identified key (i.e. “token”) that is unique to each participant and will verify privacy compliance. No additional compensation will be provided to participants for participating in tokenization and linking of their data.

10.12 Appendix 12: Country/region-specific Requirements

10.12.1 China

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

Overall Rationale

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

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

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

10.12.1.1.1 Changes to the Protocol Text

Section 1.3 Schedule of Activities

Study periods Duration	**Screening** **≤2** weeks before **RND**	**Intervention period** **~9 → ~33** months*, from **RND** until **Common End of Treatment (CEOT) visit** / **Early Termination (ET)**											**Early Termination period**** **ET** until **CEOT visit**			**CEOT period** **CEOT visit** until **2** weeks after	
Visit number / acronym	**1**	**2‡**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12***	**13***	**ET visit**	**ET SFU visit**	**≥3 → 13***	**CEOT visit**	**CEOT SFU visit†**
Visit type	site	site	☎	site	site	☎	site	☎	site	☎	site	☎	site	site	☎ (site)	☎ (site)	site (☎)	☎
Visit / Month [M] Day [D] / ± allowed windows Week [W] ± allowed windows	**SCR** D-14 → 1	**RND/M0** D1	**M1** 30±4	**M3** W13±1	**M6** 26±1	**M9** 39±1	**M12** 52±1	**M15** 65±1	**M18** 78±1	**M21** 91±1	**M24** 104±1	**M27** 117±1	**M30** 130±1	**ET** ET	**ET+2W** (ET+2W)+1W	**≥M1 → M30** ≥D30±4 → W130±1	**CEOT** CEOT±~3W	**CEOT visit+2W** (CEOT visit+2W)+1W

[……]

Laboratory assessments																		
Safety blood sampling	X	(X)		X	X		X				X			X			X†	
Pregnancy test (if WOCBP)	X	X												X			X†	
PD (a); PK (b) Pharmacogenetics (c)		a, c		a, b			a, b											
Study intervention (SI) shipment																		
SI dispensation / intake		X		X	X		X		X		X		X					
SI collection / accountability				X	X		X		X		X		X	X			X†	

Annotated Schedule of Activities (Annotated SoA)

[……]

Laboratory assessments	
Safety blood sampling	creatinine and eGFR values must be available at RND; if not available from SCR central lab, respective values should be determined in local lab prior to RND; values obtained as part of routine management can also be used if no older than 14 days at RND (Section 8); in any case, the full set of safety laboratory tests (Table 10–1) needs to be obtained once during the SCR period, at the latest at RND, and at indicated visits thereafter
Pregnancy test (if WOCBP)	a WOCBP must have a negative serum or urine pregnancy test at SCR; a repeat test at RND (before SI intake) is required, unless ≤ 4 days lie between SCR and RND
PD (a); PK (b) Pharmacogenetics (c)	refer to Table 1-2 regarding further details. Pharmacogenetics will be limited to CES1 genotyping analysis.

[……]

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

Table 1–2: PK, PD and Pharmacogenetics Sampling

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

Abbreviations: CES1 = Carboxylesterase 1; PD = Pharmacodynamic(s), PK = Pharmacokinetic(s)

* at all visits: in order to collect pre-dose samples for PK and PD, participants should take their study intervention at the site only after blood sampling. The investigator must record the time when the study intervention is taken at the site. A phone call to remind the participants is recommended.

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

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

Blood for pharmacogenetics is generally planned to be collected at randomization (Day 1), however it can also be collected at a later visit in case it has not been taken (refer to Section 8.7).

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

Section 3 Objectives, Endpoints, and Estimands

Table 3–1 Study objectives and endpoints

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

[1] PK and PD analyses in Chinese participants will be performed to investigate ethnicity differences in AF patients. Blood samples for pharmacogenetics (limited to CES1 genotyping analysis) will be collected in China. Other biomarker samples will not be collected in China and therefore, no data from Chinese participants will be available for the analysis of the respective endpoints.

Section 6.5 Study Intervention Compliance

[…]

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

[…]

Section 8 Study Assessments and Procedures

[…]

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

[…].

Section 8.5 Pharmacokinetics

[…]

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

[…]

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

PK analyses in Chinese participants will be performed to investigate ethnicity differences in AF patients.

[…]

Section 8.6 Pharmacodynamics

[…]

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

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

[…]

Section 8.7 Genetics

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

[…]

Section 8.8 Biomarkers

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

10.12.2 Japan

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

Overall Rationale

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

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

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	The name of the formula used for the estimated glomerular filtration rate was modified.	The modified formula has been the standard for the local clinical practice in Japan and frequently used in other clinical studies with the Japanese population. Please note that the eGFR threshold for exclusion of participants from the study remains the same (< 25 mL/min/1.73 m^2).
10.6 Calculating glomerular filtration rate	The formula for calculating the estimated glomerular filtration rate was modified according to the recommendation by Japanese Society of Nephrology for the Japanese population.	

10.12.2.1.1 Changes to the Protocol Text

Section 5.2 Exclusion Criteria

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

Medical Conditions

[…]

8. Estimated glomerular filtration rate (eGFR) < 25 mL/min/1.73 m^2 within 14 days prior to randomization, calculated by Japanese Equation (see Section 10.6), or on dialysis or expected to be started on dialysis within the next 12 months starting from randomization

[…]

Section 10.6 Appendix 6: Calculating glomerular filtration rate

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

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

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

10.12.3 Republic of Korea

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

KOR-1 (06 JAN 2023)

Overall Rationale

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

10.12.3.1.1 Overview of Changes

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

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Inclusion of ALT, AST, total bilirubin, hemoglobin and platelet count assessments	Changes requested by MFDS to account for the safety characteristics of the study interventions
	Only serum pregnancy testing is allowed. It will be performed at all site visits.	
5.1 Inclusion Criteria	Only serum pregnancy testing is allowed	
5.2 Exclusion Criteria	ALT / AST > 2.5 x ULN added to the exclusion criteria	
	Uncontrolled hypertension (e.g. systolic BP > 180 mmHg or diastolic BP > 100 mmHg) added to the exclusion criteria	
	Platelet count ≤ 100000/ mm^3 or hemoglobin < 9 g/dL added to the exclusion criteria	
	Antiphospholipid syndrome and participants who have undergone significant resection of relevant gastrointestinal tract added as examples of contraindications listed in the local label of Apixaban	
6.1 Study Intervention(s) Administered	Inclusion that study intervention should be used with caution in participants with mild hepatic impairment (Child Pugh A) or participants with ALT / AST > 2 x the upper limit of normal (ULN) or total bilirubin ≥ 1.5 x ULN	
6.9 Prior and Concomitant Therapy	Other platelet aggregation inhibitors listed as prohibited medications	
7.1.1 Permanent Discontinuation of Study Intervention	Inclusion of discontinuation rule for severe thrombocytopenia	
7.1.2 Temporary Discontinuation of Study Intervention	Inclusion of further clarification for temporary discontinuation of study intervention	
8 Study Assessments and Procedures	Inclusion of ALT, AST, total bilirubin, hemoglobin and platelet count assessments	
8.3.7 Clinical Safety Laboratory Tests	Inclusion of ALT, AST, total bilirubin, hemoglobin and platelet count assessments	
8.3.8 Pregnancy Testing	Only serum pregnancy testing is allowed.	
10.2.2 Thrombocytopenia: Follow-up Assessments and Suggested Actions	Inclusion of follow-up assessment and suggested actions in case of thrombocytopenia	

10.12.3.1.2 Changes to the Protocol Text

Section 1.3 Schedule of Activities (SoA)

Study periods Duration	**Screening** **≤2** weeks before **RND**	**Intervention period** **~9 → ~33** months*, from **RND** until **Common End of Treatment (CEOT) visit** / **Early Termination (ET)**												**Early Termination period**** **ET** until **CEOT visit**			**CEOT period** **CEOT visit** until **2** weeks after	
Visit number / acronym	**1**	**2‡**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12***	**13***	**ET visit**	**ET SFU visit**	**≥3 → 13***	**CEOT visit**	**CEOT SFU visit†**
Visit type	site	site	☎	site	site	☎	site	☎	site	☎	site	☎	site	site	☎ (site)	☎ (site)	site (☎)	☎
Visit / Month [M]	**SCR**	**RND/M0**	**M1**	**M3**	**M6**	**M9**	**M12**	**M15**	**M18**	**M21**	**M24**	**M27**	**M30**	**ET**	**ET+2W**	**≥M1 → M30**	**CEOT**	**CEOT visit+2W**
Day [D] / ± allowed windows Week [W] ± allowed windows	D-14 → 1	D1	30±4	W13±1	26±1	39±1	52±1	65±1	78±1	91±1	104±1	117±1	130±1	ET	(ET+2W)+1W	≥D30±4 → W130±1	CEOT±~3W	(CEOT visit+2W)+1W
[..]																		
Laboratory assessments																		
Safety blood sampling	X	(X)		X	X		X				X			X			X†	
Pregnancy test (if WOCBP)	X	X		X	X		X		X		X		X	X			X†	

[…]

Annotated Schedule of Activities (Annotated SoA)

[…]

Vital signs (BP§ and RHR)	can also be used if done as part of routine management and no older than 14 days at RND; no need to be repeated once available (Section 8.3.5)
[…]	
Laboratory assessments	
Safety blood sampling	creatinine, eGFR, ALT, AST, total bilirubin, hemoglobin, and platelet count values must be available at RND; if not available from SCR central lab, respective values should be determined in local lab prior to RND; values obtained as part of routine management can also be used if no older than 14 days at RND (Section 8); in any case, the full set of safety laboratory tests (Table 10-1) needs to be obtained once during the SCR period, at the latest at RND, and at indicated visits thereafter
Pregnancy test (if WOCBP)	a WOCBP must have a negative serum pregnancy test at SCR; a repeat test at RND (before SI intake) is required, unless ≤ 4 days lie between SCR and RND
[…]	

Abbreviations: AP/AC = antiplatelets/anticoagulants, BP = blood pressure, CEOT = Common End of Treatment, D = day, ECG = electrocardiogram, EQ-5D = European Quality of Life group 5-Dimension questionnaire, ET = early termination, HCRU = healthcare resource utilization, RHR = resting heart rate, ICF = informed consent form, IRT = interactive response technology, M = month, PD, PK = pharmacodynamic(s), -kinetic(s), RND = randomization, SCR = screening, SFU = safety follow-up, SI = study intervention, W = week(s), WOCBP = woman of childbearing potential

‡ procedures and assessments at visit 2 should preferably be conducted prior to RND; SI dispensation / intake will usually be concluding the visit

* if applicable (if the number of efficacy outcome events does not accrue until Month 33 as expected) the visit schedule will continue after Month 30 with the respective labelling, e.g. Visit 14, 15. The duration of the intervention period (~9 to ~33 months) depends on when a participant joins during the course of the study. Displayed timepoints might therefore not be applicable to all participants.

§ Blood pressure measurements can be repeated if medically justified (e.g. in order to avoid suspected “white-coat hypertension”).

Section 5.1 Inclusion Criteria

[…]

Sex and Contraceptive / Barrier Requirements

4. Male or female

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

Male participants: there are no measures required for the study

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

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

OR

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

A WOCBP must have a negative serum pregnancy test within 4 days before the first dose of study intervention, see Section 8.3.8.

[…]

Section 5.2 Exclusion Criteria

[…]

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

[…]

11. Any contraindication for the use of an anticoagulant or listed in the local labelling for apixaban (e.g. antiphospholipid syndrome or participants who have undergone significant resection of relevant gastrointestinal tract).

[…]

Additional Medical conditions

20. Persistent (confirmed by two measurements, at least 1 hour apart) uncontrolled hypertension (systolic BP > 180 mmHg or diastolic BP > 100 mmHg).

21. Platelet count ≤ 100000/mm^3 or hemoglobin < 9 g/dL.

[…].

Section 6.1 Study Intervention(s) Administered

[…]

Study intervention should be used with caution in participants with mild hepatic impairment (Child Pugh A) or participants with ALT / AST > 2 x the upper limit of normal (ULN) or total bilirubin ≥ 1.5 x ULN.

Matching placebos for asundexian and both strengths of apixaban are supplied in the same way.

[…].

Section 6.9 Prior and Concomitant Therapy

[…]

Prohibited concomitant medications:

Concomitant therapy with any of the following drugs is prohibited from 14 days (or at least five half-lives of the active substance, whatever is longer) before randomization and first study intervention administration, until at least 48 hours after last study intervention administration:

- Strong combined inhibitors of CYP3A4 and P-gp, e.g. human immunodeficiency virus protease inhibitors (ritonavir, indinavir, nelfinavir, saquinavir, or telaprevir), systemically used azole antimycotic agents (ketoconazole, itraconazole, or posaconazole), clarithromycin, nefazodone
- Strong / moderate combined inducers of CYP3A4 and P-gp, e.g. phenytoin, carbamazepine, phenobarbital, rifampicin, or St. John's wort
- Other platelet aggregation inhibitors (e.g. GPIIb/IIIa receptor antagonists, dipyridamole, dextran or sulfinpyrazone).

[…].

Section 7.1.1 Permanent Discontinuation of Study Intervention

[…]

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

- […]
- severe thrombocytopenia (i.e. platelet count < 50000 / mm^3; refer to Section 10.2.2).

[…].

Section 7.1.2 Temporary Discontinuation of Study Intervention

[…]

The need for a temporary interruption might also arise from an adverse event, for instance relating to liver dysfunction or platelet count decrease (refer to Section 10.2.1 and Section 10.2.2). If the investigator believes that for safety reasons it is in the best interest of the participant to interrupt treatment, study intervention can be stopped at any time. There is no predefined maximum limit for temporary discontinuation of study intervention.

[…].

Section 8 Study Assessments and Procedures

- […]
- Results from procedures conducted as part of the participant's routine clinical management (e.g. creatinine, eGFR, ALT, AST, total bilirubin, hemoglobin, platelet count, ECG, vital sign measurement) and obtained before signing of the ICF may be utilized for screening and / or baseline purposes, provided the procedures met the protocol specified criteria and were performed within the timeframe defined in the SoA (if no older than 14 days at randomization for eGFR, creatinine, ALT , AST, total bilirubin, hemoglobin, platelet count, and vital signs, or no older than 30 days in case of ECG; refer to annotated SoA in Section 1.3).
- […].

Section 8.3.7 Clinical Safety Laboratory Tests

- […]
- Creatinine, eGFR, ALT, AST, total bilirubin, hemoglobin, and platelet count values must be available at randomization; if not available from screening central lab, the respective values should be determined in local lab prior to randomization to be available in time to not delay randomization. Values obtained as part of routine management can also be used for this purpose if no older than 14 days at randomization. In any case, the full set of protocol-required safety laboratory tests for central lab analysis (Table 10-1) needs to be obtained *once* during the 14 day screening period prior to randomization, at the latest at randomization, and at indicated visits thereafter.
- […].

Section 8.3.8 Pregnancy Testing

A woman of childbearing potential must have a negative serum pregnancy test within 4 days before the first dose of study intervention.

Female participants of childbearing potential are scheduled to perform a serum pregnancy test at the screening and randomization visit, unless ≤ 4 days lie between the screening and randomization visit, in which case a negative test at screening is sufficient (refer to SoA).

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

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

Section 10.2.2 Thrombocytopenia: Follow-up Assessments and Suggested Actions

Follow-up assessments

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

Suggested actions

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

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

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

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