Original Investigation

Multicenter, Randomized, Active Comparator-Controlled, Double-Blind, Double-Dummy, Parallel Group, Dose-Finding Phase 2 Study Comparing the Safety of the Oral FXIa Inhibitor Asundexian with Apixaban in Patients with Atrial Fibrillation: PACIFIC-AF

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Abstract

Background: Direct-acting oral anticoagulant use for stroke prevention in atrial fibrillation (AF) is limited due to bleeding concerns. Asundexian, a novel, oral small molecule activated factor XIa (FXIa) inhibitor, may prevent thrombosis with minimal effect on hemostasis.

Methods: In this randomized, double-blind phase 2 dose-finding study, we compared asundexian 20 mg or 50 mg once daily with apixaban twice daily in patients with AF and a CHA_2DS_2-VASc score ≥2 if male or ≥3 if female with increased bleeding risk. The primary endpoint was the composite of major or clinically relevant non-major (CRNM) bleeding. Cardiovascular events were captured as exploratory and FXIa inhibition was measured.

Results: Among 755 patients, mean age was 73.7 (8.3) years, 309 (40.9%) were women, 216 (28.6%) had chronic kidney disease, and mean CHA_2DS_2-VASc score was 3.9 (±1.4). Asundexian 20 mg and 50 mg resulted in 81–90% and 92–94% reduction in factor XI activity. Incidence proportions for the primary endpoint were 0.50 (90% CI 0.14–1.68) for asundexian 20 mg, 0.16 (0.01–0.99) for asundexian 50 mg, and 0.33 (0.09–0.97) pooled asundexian versus apixaban. The exploratory thrombotic composite endpoint of cardiovascular death, myocardial infarction, ischemic stroke, or systemic embolism occurred in 2 patients receiving asundexian 20 mg, 4 receiving asundexian 50 mg, and 3 receiving apixaban.

Conclusions: The FXIa inhibitor asundexian at 20 mg and 50 mg resulted in lower rates of major or CRNM bleeding compared with apixaban, with near complete in-vivo FXIa inhibition.

Trial Registration: ClinicalTrials.gov (NCT04218266); EudraCT (2019-002365-35).

Keywords: atrial fibrillation, factor XIa, factor X, asundexian, apixaban, stroke, randomized controlled trial, bleeding.

INTRODUCTION

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, affects over 33 million people worldwide and is associated with increased rates of death, stroke, and other thromboembolic events.[1] Patients with AF are known to have an increased risk of stroke due to a predisposition to the development of atrial thrombi. Current treatment guidelines[2-5] recommend the use of oral anticoagulant therapy in patients with AF, preferably with direct-acting oral anticoagulants (DOACs) due to their improved safety and efficacy over vitamin K antagonists.

Asundexian (BAY 2433334) is a direct, potent inhibitor of activated coagulation factor XI (FXIa). It is dosed once daily and has a mean terminal half-life of 15.8–17.8 hours with less than 15% renal elimination.[6,7] The plasma serine protease zymogen factor XI is activated after initiation of the contact activation pathway via factor XIIa and during the amplification phase as part of a positive feedback loop through activation by thrombin. FXIa is thought to contribute to clot progression, which may 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 pathway. Consistent with this hypothesis, most people with factor XI deficiency do not experience spontaneous bleeding, hemarthroses, or hematomas and data suggest they have lower rates of cardiovascular events, especially cardioembolic stroke.[8,9]

FXIa inhibition with asundexian may offer the opportunity to prevent thromboembolism without interfering with hemostasis, thus leading to a lower risk of bleeding when compared with DOAC therapy. The primary objective of PACIFIC-AF was to determine the optimal dose of asundexian and if treatment with asundexian leads to a lower incidence of bleeding when compared with apixaban in patients with AF.

METHODS

Trial Design

The Dose-Finding Phase 2 Study Comparing the Safety of the Oral FXIa Inhibitor Asundexian with Apixaban in Patients with Atrial Fibrillation (PACIFIC-AF) was a multicenter, randomized (1:1:1),

double-blind, double-dummy, trial comparing asundexian 20 mg once daily, asundexian 50 mg once daily, to standard dosing with apixaban (5 mg twice daily with dose reduction to 2.5 mg twice daily in patients with ≥2 of the following: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL [133 μmol/L]). The study design is shown in **Figure S1**. A double-blind design was chosen to minimize bias in the evaluation and reporting of clinical events. Eligible patients were screened and randomized within 2 weeks of screening. The blinded treatment period was 12 weeks, and a safety follow-up visit was conducted at 14 + 7 days after the end of the treatment period. The trial protocol and statistical analysis plan are available in the Supplementary Appendix.

Study Participants

Eligible patients had non-valvular AF, as documented by electrocardiography at baseline or within the previous 12 months; a CHA_2DS_2-VASc score ≥2 if male or ≥3 if female; an indication for treatment with an oral anticoagulant in those currently not treated with an oral anticoagulant or those treated with a DOAC with ≥1bleeding risk feature (history of prior bleeding within 12 months, and/or estimated glomerular filtration rate 30–50 mL/min, and/or current indication for aspirin). In addition, patients needed to be age ≥45 years and able to provide informed consent. The full eligibility criteria are included in the **Supplementary Appendix**.

Study Procedures

Participants were centrally assigned to randomized study drug using an interactive web response system. Randomization was stratified based on (1) whether patients received a DOAC before study start or (2) whether they had not been receiving an oral anticoagulant. Matching placebos for both asundexian and apixaban were supplied in the same way. The protocol required that all randomized patients be seen at screening, randomization, week 4, and week 12. Phone visits were scheduled at 2 weeks, 8 weeks, and the safety follow-up visit at 14 days after last treatment. Compliance was monitored via drug dispensing and return for each participant. The concomitant use of non-steroidal anti-inflammatory drugs during the study was strongly discouraged since this has been shown to

increase the risk of gastrointestinal bleeding. Aspirin, at doses of ≤100 grams/day, was permitted. Higher doses of aspirin or thienopyridines were only allowed in instances of an acute myocardial infarction and/or after percutaneous coronary intervention.

Endpoints

The primary endpoint was the composite of major bleeding or clinically relevant non-major bleeding, according to International Society on Thrombosis and Haemostasis (ISTH) criteria (**Supplementary Appendix**).[10] Secondary safety endpoints included all bleeding, ISTH major bleeding, ISTH clinically relevant non-major bleeding, and minor bleeding. Bleeding Academic Research Consortium and Thrombolysis In Myocardial Infarction bleeding classifications were included as exploratory endpoints. Given the anticipated size of the phase 2 study, no primary or secondary thrombotic endpoints were formally analyzed. The thrombotic endpoints were entirely exploratory and underpowered and included analysis of the composite of ischemic stroke, systemic embolism, myocardial infarction, or cardiovascular death, as well as the individual components (**Supplementary Appendix**). An independent clinical events committee (CEC), whose members were blinded to treatment assignment, applied the protocol definitions and adjudicated all strokes, myocardial infarctions, deaths, and bleeding events.

Pharmacokinetics & Pharmacodynamics

Blood sampling for pharmacokinetic analysis was performed at weeks 4 and 12. At week 4 a trough sample for the determination of asundexian plasma concentrations was drawn before intake of study intervention. Blood sampling for pharmacodynamic analysis was performed at randomization and weeks 4 and 12 and evaluated via activated FXIa activity assay. The activated Factor XI activity assay is based on the determination of enzymatic Factor XIa activity in citrated plasma samples by measuring the specific cleavage of a fluorogenic peptide FXIa substrate after contact activation with Cephalin/Kaolin over time. FXI is activated to FXIa by FXIIa, which is formed in the cause of the contact activation reaction.

Statistical Analysis

To determine if asundexian led to lower rates of bleeding compared with apixaban, the primary analysis assessed the ratio of proportion of participants experiencing the composite of ISTH major or clinically relevant non-major bleeding within 12 weeks by comparing pooled doses of asundexian with apixaban in patients with AF who had taken at least 1 dose of study medication. Exploratory thrombotic events and adverse events (AEs) were analyzed using descriptive statistics. All AEs were tabulated according to the affected system organ class and preferred term, as coded by the Medical Dictionary for Regulatory Activities.

The study was powered to assess the risk of bleeding with asundexian compared with apixaban. The bleeding risk for the 2 dose groups of asundexian was assumed to be similar, such that pooling of the asundexian arms was done for the bleeding comparison. Assuming an incidence risk for the primary endpoint of 4% at week 12 in the apixaban control arm and an observed relative risk reduction of 50% for both (mid and high) doses of asundexian, sample sizes of 250 (apixaban) and 500 (pooled asundexian arms) participants were required to yield a 2-sided 90% confidence interval for the ratio of incidence proportions with a length of 0.77 (0.25–1.02).

PACIFIC-AF was funded by Bayer HealthCare AG (Berlin, Germany). All appropriate national regulatory authorities and ethics committees at the participating centers approved the study. An independent data safety monitoring board periodically reviewed unblinded study data. An international executive committee was responsible for oversight of the trial and reporting of results, and the authors take responsibility for the accuracy and completeness of the data analyses.

RESULTS

Patient Recruitment and Follow-up

From January 2020 through July 2021, 862 patients were enrolled at 93 sites in 14 countries in Europe, North America, and Japan. There were 107 screening failures, 755 patients were randomized, and 2 patients never took any study medication, resulting in 753 patients starting the treatment phase (**Figure S2**). Overall, 82 patients did not complete the treatment phase due to AEs

(n=38), death (n=6), physician decision (n=6), withdrawal by participant (n=6), noncompliance with study drug, and other reasons (n=25). A total of 671 patients completed the treatment phase.

Baseline Characteristics

Baseline characteristics of patients randomized according to treatment assignment are shown in **Table 1**. The mean age was 73.7 (±8.3) years, 351 (46.5%) were 75 years or older, 309 (40.9%) were women, 336 (44.5%) were previously on NOACs, 216 (28.6%) had chronic kidney disease, and the mean CHA_2DS_2-VASc score was 3.9 (±1.4). Other comorbidities were frequent and included heart failure (44%), hypertension (89%), and diabetes (32%).

Factor XIa Inhibition

Figure 1 illustrates the factor XI activity at steady state including peak and trough concentrations after 4 weeks of treatment with asundexian. Asundexian 20 mg resulted in an 81% reduction in baseline factor XI activity at trough concentrations and 90% at peak concentrations. Asundexian 50 mg resulted in a 92% reduction in factor XI activity at trough and 94% reduction at peak concentrations.

Primary & Secondary Endpoints

The rates of the primary endpoint, the composite of ISTH major or clinically relevant non-major bleeding, are shown in **Figure 2**. Overall, there were no episodes of ISTH major bleeding. Ten patients experienced a clinically relevant non-major event and 48 had any bleeding event. In general, bleeding rates were lower in those treated with asundexian compared with apixaban. The ratio of the incidence proportions for the primary endpoint for asundexian once daily versus apixaban twice daily were 0.33 (0.09–0.97) for pooled asundexian, 0.50 (90% CI 0.14–1.68) for asundexian 20 mg, and 0.16 (0.01–0.99) for asundexian 50 mg. The ratio of the incidence proportions for all bleeding events for asundexian once daily versus apixaban twice daily were 0.42 (0.26–0.67) for pooled asundexian, 0.46 (0.23–0.83) for asundexian 20 mg, and 0.38 (0.16–0.68) for asundexian 50 mg. Additional data including rates of alternative bleeding classification events are shown in **Table S1**.

Exploratory Thrombotic Events

Table 2 illustrates the rates of thrombotic and cardiovascular events. The exploratory thrombotic composite endpoint of cardiovascular death, myocardial infarction, ischemic stroke, or systemic embolism was as follows: 2 events in those treated with asundexian 20 mg, 4 in those treated with asundexian 50 mg, and 3 in those treated with apixaban. There were 2 ischemic strokes in those treated with asundexian 20 mg, 1 in those treated with asundexian 50 mg, and no strokes in those treated with apixaban.

Adverse Events

As shown in **Table 3**, the rates of any AE were similar in the 3 treatment groups: 118 (47.4%) with asundexian 20 mg, 120 (47.2%) with asundexian 50 mg, and 122 (48.8%) with apixaban. Rates of AEs leading to discontinuation of study drug were also similar in the 3 treatment groups: 15 (6.0%) with asundexian 20 mg, 16 (6.3%) with asundexian 50 mg, and 13 (5.2%) with apixaban. There was 1 death in those treated with asundexian 20 mg, 3 in those treated with asundexian 50 mg, and 2 in those treated with apixaban.

DISCUSSION

This randomized dose-finding study in patients with atrial fibrillation demonstrated that FXIa inhibition with asundexian was associated with lower rates of bleeding events compared with guideline-recommended factor Xa inhibition with apixaban.

There are 3 major findings from this trial. First, asundexian at 20 mg and 50 mg doses led to reliable suppression of factor XI activity with once daily dosing. Second, asundexian treatment resulted in substantially lower rates of bleeding compared with apixaban. Finally, asundexian is well-tolerated; only 1 in 20 participants discontinued drug due to an AE. Taken together, these findings broadly add to increasing evidence around FXIa as a therapeutic target, and specifically provide rationale for larger clinical outcome studies with asundexian.

Bleeding remains the Achilles' heel of oral anticoagulation. While DOACs provide safer and more reliable stroke prevention compared with vitamin K antagonism, the risk of bleeding remains a persistent and troubling clinical problem. Risk of bleeding often dissuades use of oral anticoagulation, bleeding events lead to discontinuation, discontinuation of oral anticoagulation can lead to stroke, and some bleeding events are fatal.

There are several lines of evidence that indicate factor XI or factor XIa inhibition may provide a safer method of anticoagulation. Most people with factor XI deficiency (Rosenthal Syndrome or Hemophilia C) do not have spontaneous bleeding, hemarthroses, or hematomas.[11,12] When bleeding does occur, it is usually after trauma or surgery, consistent with factor XI's role in amplification (thrombus growth) but not initiation of clotting (hemostasis).[9,12] Moreover, population studies have shown that reduced factor XI levels are protective against cardiovascular thrombotic events like stroke or venous thromboembolism.[8,13]

Factor XIa inhibition has been shown to prevent venous thromboembolism with a low risk of bleeding after total knee arthroplasty when compared with low molecular weight heparin, both with subcutaneous antisense oligonucleotides, human monoclonal antibodies, or orally administered inhibitors.[14-16] However, there are no trials to date that compare oral anticoagulation with factor XIa inhibitors versus factor Xa inhibition with direct-acting oral anticoagulants in patients with atrial fibrillation at risk for stroke. The advantages of reducing thrombosis without reducing hemostasis may be even more salient in the context of life-long therapy that is often required for stroke prevention in patients with AF.

Phase 1 data in human volunteers have shown that asundexian leads to dose-dependent FXIa inhibition and an increase in activated partial thromboplastin time without an increase in bleeding time compared with placebo.[7] In this randomized study of patients at moderate-to-high risk for stroke and bleeding, asundexian led to a reduction of FXIa by approximately 90% to approximately 10% of pre-treatment levels. PACIFIC-AF is the first randomized study to identify a lower bleeding risk with a novel oral anticoagulant compared with apixaban. Apixaban exhibits the lowest risk of bleeding across all available oral anticoagulants.[17] When compared with apixaban, treatment with asundexian led to

≥50% reduction in bleeding events over 3 months of therapy. The lower risk of bleeding observed with asundexian is notable, given that apixaban has a 30% lower risk of major bleeding when compared with vitamin K antagonism.[18] Once daily asundexian was well-tolerated, as approximately 95% of individuals were able to continue the drug without difficulty.

If effective, asundexian may have significant safety advantages in reducing bleeding over contemporary oral anticoagulants for stroke prevention. Alternatively, asundexian may also have value as a means to target residual stroke risk in people treated with non-pharmacologic measures for stroke prevention, like left atrial appendage closure. Bleeding risk remains a strong barrier to improving rates of stroke prevention in those with AF.[19,20] Moreover, even minor bleeding can compromise adherence to oral anticoagulation.[21] The findings in PACIFIC-AF provide reasonable rationale and safety for participant enrollment in a pivotal phase 3 study to determine if asundexian is superior to current therapy for patient-centered stroke prevention and net clinical benefit.

Limitations

This trial was designed as a dose-finding phase 2 clinical study, it was not powered to discern or test differences in the rates of thrombotic events. The observed incidence of bleeding was lower than predicted and there were no ISTH major bleeding events. However, there is a strong correlation between reductions in minor bleeding and major bleeding.[22] While it appears asundexian leads to less bleeding, the magnitude of this effect cannot be defined due to the low event rates.

Conclusion

In this randomized blinded trial in patients with atrial fibrillation, the FXIa inhibitor asundexian at 20 mg and 50 mg daily had lower observed rates of bleeding compared with apixaban. This was achieved despite near complete in-vivo FXIa inhibition. These findings warrant clinical outcome studies with asundexian in patients with AF.

Disclosures

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Figure Legends

Figure 1. Factor XIa activity at steady state after 4 weeks of treatment with asundexian. Vertical bars indicate the percent reduction in factor XI activity when compared with baseline.

Figure 2. Rates of the primary endpoint according to treatment assignment. Vertical bars identify percentage of participants with bleeding outcomes for the primary endpoint (composite of ISTH major or clinically relevant non-major bleeding) and all bleeding. The bars and numbers provide the ratio of incidence proportions for comparisons between asundexian and apixaban. There were no ISTH major bleeding events in any treatment arm.

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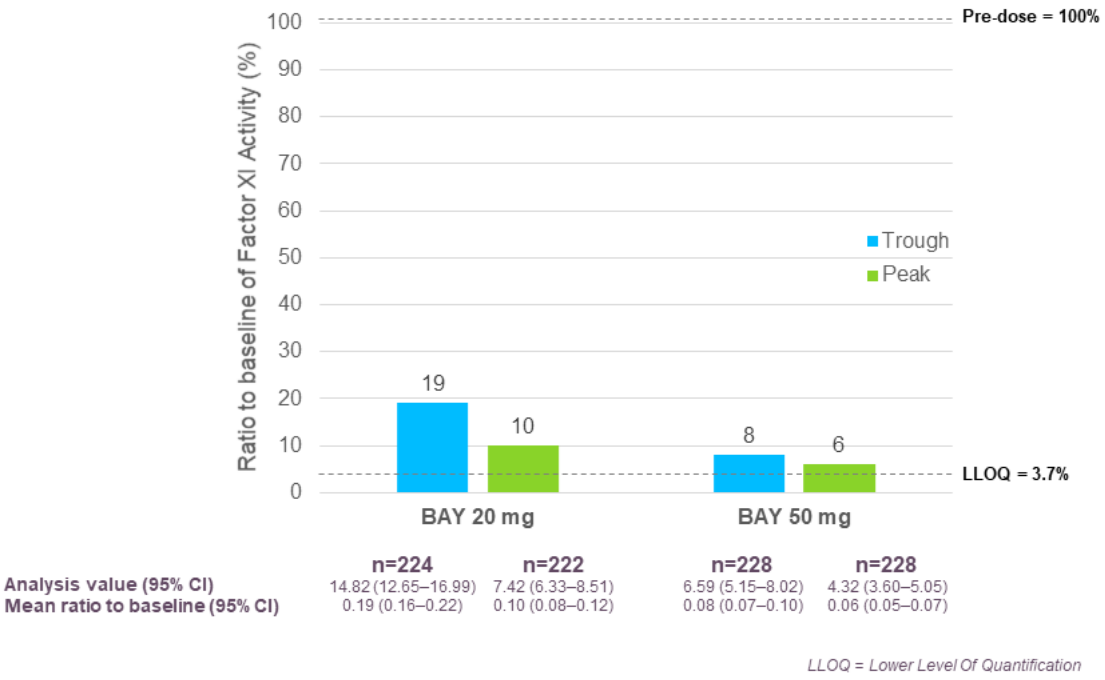

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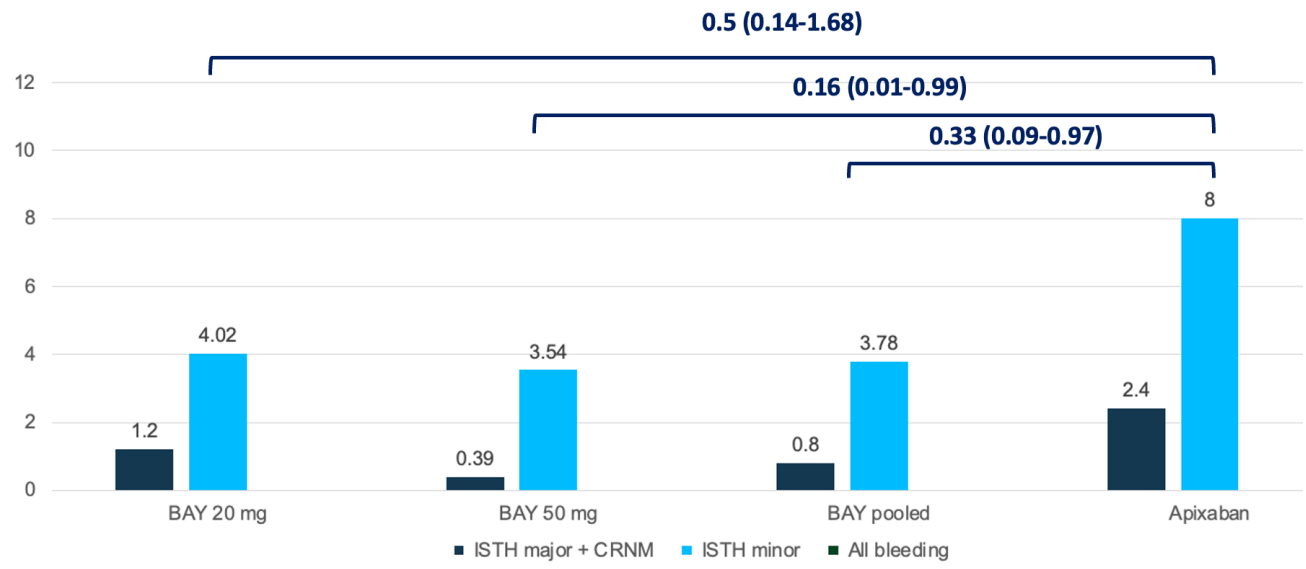

Table 1. Baseline Characteristics According to Treatment Assignment

	Asundexian 20 mg (N=251)	Asundexian 50 mg (N=254)	Apixaban (N=250)	Asundexian Total (N=505)	Total (N=755)
Age, mean (SD), yrs	73.6 (8.0)	73.1 (8.5)	74.3 (8.3)	73.4 (8.2)	73.7 (8.3)
Age, yrs					
<65	33 (13.1%)	43 (16.9%)	34 (13.6%)	76 (15.0%)	110 (14.6%)
65–75	100 (39.8%)	99 (39.0%)	95 (38.0%)	199 (39.4%)	294 (38.9%)
>75	118 (47.0%)	112 (44.1%)	121 (48.4%)	230 (45.5%)	351 (46.5%)
Female	103 (41.0%)	97 (38.2%)	109 (43.6%)	200 (39.6%)	309 (40.9%)
Race					
White	211 (84.1%)	212 (83.5%)	209 (83.6%)	423 (83.8%)	632 (83.7%)
Asian	39 (15.5%)	40 (15.7%)	40 (16.0%)	79 (15.6%)	119 (15.8%)
Black	1 (0.4%)	1 (0.4%)	1 (0.4%)	2 (0.4%)	3 (0.4%)
Missing	0	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Prior DOAC use	109 (43.4%)	116 (45.7%)	111 (44.4%)	225 (44.6%)	336 (44.5%)
Aspirin ≤100 mg	35 (13.9%)	33 (13.0%)	39 (15.6%)	68 (13.5%)	107 (14.2%)
Moderate renal dysfunction*	63 (25.1%)	76 (29.9%)	69 (27.6%)	139 (27.5%)	208 (27.5%)
Bleed within 12 months requiring medical attention	20 (8.0%)	24 (9.4%)	23 (9.2%)	44 (8.7%)	67 (8.9%)
CHA_2DS_2-VASc score (SD)	3.9 (1.4)	3.8 (1.3)	4.1 (1.4)	3.9 (1.3)	3.9(1.3)
CHA_2DS_2-VASc score ≤3 (m) / 4 (f)	133 (52.9%)	138 (54.3%)	127 (50.8%)	271 (53.7%)	398 (52.7%)
Type of AF					
Paroxysmal	122 (48.6%)	115 (45.3%)	117 (46.8%)	237 (46.9%)	354 (46.9%)
Persistent	69 (27.5%)	70 (27.6%)	57 (22.8%)	139 (27.5%)	196 (26.0%)
Long-standing persistent	5 (2.0%)	3 (1.2%)	8 (3.2%)	8 (1.6%)	16 (2.1%)
Comorbidities					
Hypertension	226 (90.0%)	227 (89.4%)	220 (88.0%)	673 (89.1%)	673 (89.1%)
Hyperlipidemia	142 (56.6%)	153 (60.2%)	152 (60.8%)	447 (59.2%)	447 (59.2%)
Heart failure	108 (43.0%)	107 (42.1%)	117 (46.8%)	332 (44.0%)	332 (44.0%)
CAD	76 (30.3%)	71 (28.0%)	85 (34.0%)	232 (30.7%)	232 (30.7%)
Diabetes mellitus	83 (33.1%)	74 (29.1%)	87 (34.8%)	244 (32.3%)	244 (32.3%)
CKD	55 (21.9%)	84 (33.1%)	77 (30.8%)	139 (27.5%)	216 (28.6%)
PCI	38 (15.1%)	46 (18.1%)	43 (17.2%)	84 (16.6%)	127 (16.8%)
Myocardial infarction	26 (10.4%)	41 (16.1%)	36 (14.4%)	67 (13.2%)	103 (13.6%)
Anemia	26 (10.4%)	38 (15.0%)	26 (10.4%)	64 (12.7%)	90 (11.9%)
Stroke or TIA	22 (8.8%)	18 (7.1%)	25 (10.0%)	40 (7.9%)	65 (8.6%)
CABG surgery	22 (8.8%)	16 (6.3%)	17 (6.8%)	38 (7.5%)	55 (7.3%)

Data presented as no. (%), unless otherwise indicated.

AF indicates atrial fibrillation; CABG, coronary-artery bypass graft; CAD, coronary artery disease; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female); CKD, chronic kidney disease; DOAC, direct-acting oral anticoagulant; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

*eGFR 30-50 mL/min/1.73 m^2

Table 2. Exploratory Thrombotic Endpoints

	Asundexian 20 mg (N=251)	**Asundexian 50 mg (N=254)**	**Apixaban (N=250)**	**Total (N=755)**
CV death, MI, ischemic stroke, or systemic embolism	2	4	3	9
CV death	1	3	3	7
MI	0	1	0	1
Ischemic stroke	2	1	0	3
Systemic embolism	0	0	0	0
All-cause mortality	2	4	4	10

CV, cardiovascular; MI, myocardial infarction.

Table 3. Adverse Events According to Treatment Assignment

	Asundexian 20 mg (N=249)* (100%)	**Asundexian 50 mg (N=254) (100%)**	**Apixaban (N=250) (100%)**	**Asundexian Total (N=503) (100%)**	**Total (N=753) (100%)**
Any AE	118 (47.4%)	120 (47.2%)	122 (48.8%)	238 (47.3%)	360 (47.8%)
Any study drug-related AE	29 (11.6%)	26 (10.2%)	37 (14.8%)	55 (10.9%)	92 (12.2%)
Any AE leading to discontinuation of study drug	15 (6.0%)	16 (6.3%)	13 (5.2%)	31 (6.2%)	44 (5.8%)
Adverse event of special interest	0	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Any SAE	22 (8.8%)	20 (7.9%)	20 (8.0%)	42 (8.3%)	62 (8.2%)
Any study drug-related SAE	4 (1.6%)	0	0	4 (0.8%)	4 (0.5%)
Any SAE leading to discontinuation of study drug	4 (1.6%)	4 (1.6%)	4 (1.6%)	8 (1.6%)	12 (1.6%)
AE with outcome death	1 (0.4%)	3 (1.2%)	2 (0.8%)	4 (0.8%)	6 (0.8%)
Deaths	1 (0.4%)	3 (1.2%)	2 (0.8%)	4 (0.8%)	6 (0.8%)
Heart failure	0	0	1 (0.4%)	0	1 (0.1%)
Coronary artery disease	0	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Sudden cardiac death	0	0	1 (0.4%)	0	1 (0.1%)
Cerebrovascular accident	1 (0.4%)	1 (0.4%)	0	2 (0.4%)	2 (0.3%)
Completed suicide	0	1 (0.4%)	0	1 (0.2%)	1 (0.1%)

Data presented as no. (%), unless otherwise indicated.
AE indicates adverse event; SAE, serious adverse event.
*Table includes only patients who took one dose of study drug (2 patients did not take study drug)