Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

*Jonathan P Piccini, Valeria Caso, Stuart J Connolly, Keith A A Fox, Jonas Oldgren, W Schuyler Jones, Diana A Gorog, Václav Durdil, Thomas Viethen, Christoph Neumann, Hardi Mundl, Manesh R Patel, on behalf of the PACIFIC-AF Investigators**

Summary

Background Direct-acting oral anticoagulant use for stroke prevention in atrial fibrillation is limited by bleeding concerns. Asundexian, a novel, oral small molecule activated coagulation factor XIa (FXIa) inhibitor, might reduce thrombosis with minimal effect on haemostasis. We aimed to determine the optimal dose of asundexian and to compare the incidence of bleeding with that of apixaban in patients with atrial fibrillation.

Methods In this randomised, double-blind, phase 2 dose-finding study, we compared asundexian 20 mg or 50 mg once daily with apixaban 5 mg twice daily in patients aged 45 years or older with atrial fibrillation, a CHA_2DS_2-VASc score of at least 2 if male or at least 3 if female, and increased bleeding risk. The study was conducted at 93 sites in 14 countries, including 12 European countries, Canada, and Japan. Participants were randomly assigned (1:1:1) to a treatment group using an interactive web response system, with randomisation stratified by whether patients were receiving a direct-acting oral anticoagulant before the study start. Masking was achieved using a double-dummy design, with participants receiving both the assigned treatment and a placebo that resembled the non-assigned treatment. The primary endpoint was the composite of major or clinically relevant non-major bleeding according to International Society on Thrombosis and Haemostasis criteria, assessed in all patients who took at least one dose of study medication. This trial is registered with ClinicalTrials.gov, NCT04218266, and EudraCT, 2019-002365-35.

Findings Between Jan 30, 2020, and June 21, 2021, 862 patients were enrolled. 755 patients were randomly assigned to treatment. Two patients (assigned to asundexian 20 mg) never took any study medication, resulting in 753 patients being included in the analysis (249 received asundexian 20 mg, 254 received asundexian 50 g, and 250 received apixaban). The mean age of participants was 73·7 years (SD 8·3), 309 (41%) were women, 216 (29%) had chronic kidney disease, and mean CHA_2DS_2-VASc score was 3·9 (1·3). Asundexian 20 mg resulted in 81% inhibition of FXIa activity at trough concentrations and 90% inhibition at peak concentrations; asundexian 50 mg resulted in 92% inhibition at trough concentrations and 94% inhibition at peak concentrations. Ratios of incidence proportions for the primary endpoint were 0·50 (90% CI 0·14–1·68) for asundexian 20 mg (three events), 0·16 (0·01–0·99) for asundexian 50 mg (one event), and 0·33 (0·09–0·97) for pooled asundexian (four events) versus apixaban (six events). The rate of any adverse event occurring was similar in the three treatment groups: 118 (47%) with asundexian 20 mg, 120 (47%) with asundexian 50 mg, and 122 (49%) with apixaban.

Interpretation The FXIa inhibitor asundexian at doses of 20 mg and 50 mg once daily resulted in lower rates of bleeding compared with standard dosing of apixaban, with near-complete in-vivo FXIa inhibition, in patients with atrial fibrillation.

Funding Bayer.

Lancet 2022; 399: 1383–90

Published **Online** April 3, 2022 https://doi.org/10.1016/S0140-6736(22)00456-1

See **Comment** page 1360

*The PACIFIC-AF Investigators are listed in full in the appendix (pp 3–10)

Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA (J P Piccini MD, W S Jones MD, Prof M R Patel MD); **Duke University Medical Center, Durham, NC, USA** (J P Piccini, W S Jones, Prof M R Patel); **University of Perugia Stroke Unit, Perugia, Italy** (Prof V Caso MD); **Population Health Research Institute, McMaster University, Hamilton, ON, Canada** (Prof S J Connolly MD); **Hamilton Health Services, Hamilton, ON, Canada** (Prof S J Connolly); **Division of Medical and Radiological Sciences, University of Edinburgh, Edinburgh, UK** (Prof K A A Fox MB ChB); **Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden** (Prof J Oldgren MD); **National Heart and Lung Institute, Imperial College London, London, UK** (Prof D A Gorog MD); **University of Hertfordshire, Hatfield, UK** (Prof D A Gorog); **University Hospital Motol, Prague, Czech Republic** (V Durdil MD); **Bayer, Wuppertal, Germany** (T Viethen MD, C Neumann PhD, H Mundl MD)

Correspondence to: Dr Jonathan P Piccini, Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC 27705, USA **jonathan.piccini@duke.edu**

See **Online** for appendix

Introduction

Atrial fibrillation, the most common sustained cardiac arrhythmia, affects more than 33 million people worldwide and is associated with increased rates of death, stroke, and other thromboembolic events.[1] Patients with atrial fibrillation 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 atrial fibrillation, 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 h 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

Research in context

Evidence before this study

Patients with atrial fibrillation are known to have an increased risk of stroke due to a predisposition to the development of atrial thrombi. Current treatment guidelines recommend the use of oral anticoagulant therapy in patients with atrial fibrillation, preferably with direct-acting oral anticoagulants due to their improved safety and efficacy over vitamin K antagonists. Based on the results of preclinical testing, observational data from patients with inherited factor XI deficiency, and phase 1 data, we hypothesised that treatment with asundexian would lead to less bleeding compared with apixaban.

Added value of this study

Asundexian at 20 mg and 50 mg doses lead to reliable suppression of activated coagulation factor XI (FXIa) with once-daily dosing. Asundexian treatment results in significantly lower rates of bleeding compared with apixaban and is well tolerated; only one in 20 participants discontinued the drug due to an adverse event.

Implications of all the available evidence

The FXIa inhibitor asundexian at 20 mg and 50 mg resulted in lower rates of bleeding compared with apixaban, with near-complete in-vivo FXIa inhibition. These findings add to increasing evidence around FXIa as a therapeutic target, and specifically provide rationale for larger clinical outcome studies with asundexian.

the amplification phase as part of a positive feedback loop through activation by thrombin. FXIa is thought to contribute to clot progression, which might lead to vessel occlusion and pathological manifestations of thrombosis, but, in contrast to factor IX and factor VIII, has only a minor effect on clot consolidation during haemostasis. Consistent with this hypothesis, most people with factor XI (FXI) deficiency do not experience spontaneous bleeding, haemarthroses, or haematomas, and data suggest that they have lower rates of cardiovascular events, including cardioembolic stroke.[8,9]

FXIa inhibition with asundexian might offer an opportunity to prevent thromboembolism without interfering with haemostasis, 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 to assess whether treatment with asundexian leads to a lower incidence of bleeding when compared with apixaban in patients with atrial fibrillation.

Methods

Study design

PACIFIC-AF was a multicentre, randomised, double-blind, double-dummy phase 2 trial comparing two doses of asundexian with standard dosing of apixaban. The study was conducted at 93 sites in 14 countries, including 12 European countries, Canada, and Japan. The study design is shown in the appendix (p 16). All appropriate national regulatory authorities and ethics committees at the participating centres approved the study. The trial protocol and statistical analysis plan are available in the appendix (pp 20–122).

Participants

Eligible patients had atrial fibrillation, as documented by electrocardiography at baseline or within the previous 12 months; a CHA_2DS_2-VASc score of 2 or higher if male or 3 or higher 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 at least one bleeding risk feature (history of previous bleeding requiring medical attention within 12 months, estimated glomerular filtration rate of 30–50 mL/min, or current indication for aspirin). In addition, patients needed to be aged 45 years or older and able to provide informed consent. The full eligibility criteria are included in the appendix (pp 11–13). All participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned centrally to one of two doses of asundexian or standard dosing of apixaban (1:1:1) using an interactive web response system. Randomisation was stratified based on whether patients received a DOAC before study start or had not been receiving an oral anticoagulant. To achieve a double-dummy trial design, matching placebos that were identical in appearance to either asundexian and apixaban were supplied. Participants were provided with either asundexian and a placebo that matched apixaban or apixaban and a placebo that matched asundexian, depending on the randomisation outcome. Investigators and participants were masked to assigned interventions throughout the course of the study. A double-blind design was chosen to minimise bias in the evaluation and reporting of clinical events.

Procedures

Eligible patients were screened and randomly assigned within 2 weeks of screening. The blinded treatment period was 12 weeks, and a safety follow-up visit was done at 14–21 days after the end of the treatment period.

Participants were randomly assigned to asundexian 20 mg once daily, asundexian 50 mg once daily, or standard dosing with apixaban (5 mg twice daily with dose reduction to 2·5 mg twice daily in patients with two or more of the following: age 80 years or older, bodyweight 60 kg or more, or serum creatinine 1·5 mg/dL [133 µmol/L] or higher). All treatments were provided as oral tablets. The protocol required that all randomly assigned patients be seen at screening, randomisation, week 4, and week 12. Telephone visits were scheduled at 2 weeks, 8 weeks, and the safety follow-up visit at 14–21 days after last treatment. Adherence 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 because this has been shown to increase the risk of gastrointestinal bleeding. Aspirin, at doses of 100 g per day or less, was permitted. Higher doses of aspirin or thienopyridines were only allowed in instances of an acute myocardial infarction or after percutaneous coronary or vascular intervention.

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 randomisation and at weeks 4 and 12. Activated FXIa activity was analysed using a kaolin trigger and a fluorogenic substrate readout.[10]

Outcomes

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 (appendix p 14).[11] Secondary safety endpoints were all bleeding, ISTH major bleeding, ISTH clinically relevant non-major bleeding, and ISTH minor bleeding. Additionally, Bleeding Academic Research Consortium and Thrombolysis in Myocardial Infarction bleeding classifications were assessed as exploratory endpoints. Given the anticipated size of the phase 2 study, no primary or secondary thrombotic endpoints were formally analysed. The thrombotic endpoints were entirely exploratory and underpowered and included analysis of the composite of ischaemic stroke, systemic embolism, myocardial infarction, or cardiovascular death, as well as the individual components (appendix pp 14–15). An independent clinical events committee, whose members were blinded to treatment assignment, applied the protocol definitions, and adjudicated all strokes, myocardial infarctions, deaths, and bleeding events.

Statistical analysis

To determine whether asundexian led to lower rates of bleeding compared with apixaban, the primary analysis assessed the ratio of proportions 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 atrial fibrillation who had taken at least one dose of study medication. A 12-week follow-up period was considered adequate on the basis of: guidance from the European Medicines Agency;[12] the phase 2 nature of the study; the fact that bleeding event rates are highest immediately after drug initiation; and the anticipated event projections. Exploratory thrombotic events and adverse events were analysed using descriptive statistics. All adverse events 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 two dose groups of asundexian was assumed to be similar, such that pooling of the asundexian groups was done for the bleeding comparison. Assuming an incidence risk for the primary endpoint of 4% at week 12 in the apixaban control group and an observed relative risk reduction of 50% for both doses of asundexian, sample sizes of 250 (apixaban) and 500 (pooled asundexian groups) participants were required to yield a two-sided 90% CI for the ratio of incidence proportions with a length of 0·77 (0·25–1·02). The 90% CIs were calculated as exact intervals using Farrington-Manning score statistics. The 90% CI was chosen because this was a phase 2 study with short follow-up used to support dose selection in concert with FXIa activity. Statistical analyses were performed using SAS version 9.4.

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. The trial is registered with ClinicalTrials.gov, NCT04218266, and EudraCT, 2019-002365-35.

Role of the funding source

The study sponsor conducted the statistical analysis and participated in the decision to publish the results. The sponsor had no role in the interpretation of the data nor the writing of the report. The sponsor had the opportunity to review and comment on the manuscript.

Results

Between Jan 30, 2020, and June 21, 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 randomly assigned, and two patients never took any study medication (both were randomly assigned to asundexian 20 mg), resulting in 753 patients starting the treatment phase and being included in the analysis (249 received asundexian 20 mg, 254 received asundexian 50 g, and 250 received apixaban; appendix p 17). Overall, 82 patients did

	Asundexian 20 mg (n=251)	Asundexian 50 mg (n=254)	Apixaban (n=250)	Asundexian total (n=505)	Total (n=755)
Age, years	73·6 (8·0)	73·1 (8·5)	74·3 (8·3)	73·4 (8·2)	73·7 (8·3)
Age group, years					
<65	33 (13%)	43 (17%)	34 (13%)	76 (15%)	110 (15%)
65–75	100 (40%)	99 (39%)	95 (38%)	199 (39%)	294 (39%)
>75	118 (47%)	112 (44%)	121 (48%)	230 (46%)	351 (46%)
Sex					
Female	103 (41%)	97 (38%)	109 (44%)	200 (40%)	309 (41%)
Male	148 (59%)	157 (62%)	141 (56%)	305 (60%)	446 (59%)
Race					
White	211 (84%)	212 (83%)	209 (84%)	423 (84%)	632 (84%)
Asian	39 (16%)	40 (16%)	40 (16%)	79 (16%)	119 (16%)
Black	1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)
Missing	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Previous DOAC use	109 (43%)	116 (46%)	111 (44%)	225 (45%)	336 (45%)
Aspirin ≤100 mg	35 (14%)	33 (13%)	39 (16%)	68 (13%)	107 (14%)
Moderate renal dysfunction*	63 (25%)	76 (30%)	69 (28%)	139 (28%)	208 (28%)
Bleed within 12 months requiring medical attention	20 (8%)	24 (9%)	23 (9%)	44 (9%)	67 (9%)
CHA_2DS_2-VASc score	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 (men) or ≤4 (women)	133 (53%)	138 (54%)	127 (51%)	271 (54%)	398 (53%)
Type of atrial fibrillation					
Paroxysmal	122 (49%)	115 (45%)	117 (47%)	237 (47%)	354 (47%)
Persistent	69 (27%)	70 (28%)	57 (23%)	139 (28%)	196 (26%)
Long-standing persistent	5 (2%)	3 (1%)	8 (3%)	8 (2%)	16 (2%)
Comorbidities					
Hypertension	226 (90%)	227 (89%)	220 (88%)	453 (90%)	673 (89%)
Hyperlipidaemia	142 (57%)	153 (60%)	152 (61%)	295 (58%)	447 (59%)
Heart failure	108 (43%)	107 (42%)	117 (47%)	215 (43%)	332 (44%)
Coronary artery disease	76 (30%)	71 (28%)	85 (34%)	147 (29%)	232 (31%)
Diabetes	83 (33%)	74 (29%)	87 (35%)	157 (31%)	244 (32%)
Chronic kidney disease	55 (22%)	84 (33%)	77 (31%)	139 (28%)	216 (29%)
Percutaneous coronary intervention	38 (15%)	46 (18%)	43 (17%)	84 (17%)	127 (17%)
Myocardial infarction	26 (10%)	41 (16%)	36 (14%)	67 (13%)	103 (14%)
Anaemia	26 (10%)	38 (15%)	26 (10%)	64 (13%)	90 (12%)
Stroke or transient ischaemic attack	22 (9%)	18 (7%)	25 (10%)	40 (8%)	65 (9%)
CABG surgery	22 (9%)	16 (6%)	17 (7%)	38 (8%)	55 (7%)

Data are presented as mean (SD) or n (%). DOAC=direct-acting oral anticoagulant. CABG=coronary-artery bypass graft. *Estimated glomerular filtration rate of 30–50 mL/min per 1·73 m^2.

Table 1: **Baseline characteristics according to treatment assignment**

not complete the treatment phase due to adverse events (n=38), death (n=6), physician decision (n=6), withdrawal by participant (n=6), non-adherence with study drug (n=1), and other reasons (n=25). 671 patients completed the treatment phase.

Baseline characteristics of patients according to treatment assignment are shown in table 1. The mean age was 73·7 years (SD 8·3); 351 (46%) were older than 75 years, 309 (41%) were women, 336 (45%) were previously on DOACs, 216 (28·6%) had chronic kidney disease, and the mean CHA_2DS_2-VASc score was 3·9 (1·3). Other comorbidities were frequent and included heart failure (n=332, 44%), hypertension (n=673, 89%), and diabetes (n=244, 32%).

Figure 1 shows FXIa 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 FXIa at trough concentrations and 90% at peak concentrations. Asundexian 50 mg resulted in a 92% reduction in FXIa at trough concentrations and 94% reduction at peak concentrations.

The rates of the primary endpoint, the composite of ISTH major or clinically relevant non-major bleeding, are shown in figure 2. Three composite primary endpoint events occurred in the asundexian 20 mg arm, one in the asundexian 50 mg arm, and six in the apixaban arm. Overall, there were no episodes of ISTH

major bleeding. Ten patients experienced a non-major clinically relevant bleeding event and 48 had any bleeding event. In general, bleeding rates were lower in those treated with asundexian compared with apixaban. The ratio of incidence proportions for the primary endpoint for asundexian once daily versus apixaban twice daily was 0·33 (90% CI 0·09–0·97) for pooled asundexian, 0·50 (0·14–1·68) for asundexian 20 mg, and 0·16 (0·01–0·99) for asundexian 50 mg. The ratio of incidence proportions for all bleeding events for asundexian once daily versus apixaban twice daily was 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 the appendix (p 18).

The rates of thrombotic and cardiovascular events are shown in table 2. For the exploratory thrombotic composite endpoint of cardiovascular death, myocardial infarction, ischaemic stroke, or systemic embolism, two events occurred in those treated with asundexian 20 mg, four in those treated with asundexian 50 mg, and three in those treated with apixaban. Two ischaemic strokes occurred in those treated with asundexian 20 mg, one in those treated with asundexian 50 mg, and none in those treated with apixaban.

The rate of any adverse event occurring was similar in the three treatment groups: 118 (47%) with asundexian 20 mg, 120 (47%) with asundexian 50 mg, and 122 (49%) with apixaban (table 3). The rates of adverse events leading to discontinuation of the study drug were also similar in the three treatment groups: 15 (6%) with asundexian 20 mg, 16 (6%) with asundexian 50 mg, and 13 (5%) with apixaban. There was one death in those treated with asundexian 20 mg, three in those treated with asundexian 50 mg, and two in those treated with apixaban.

Discussion

This randomised dose-finding study in patients with atrial fibrillation showed that FXIa inhibition with asundexian had lower rates of bleeding events compared with inhibition with apixaban.

The trial had three major findings. First, asundexian at 20 mg and 50 mg doses led to similar reliable suppression of FXIa with once daily dosing. Second, asundexian treatment resulted in significantly lower rates of bleeding compared with apixaban. Finally, similar to apixaban, asundexian is well tolerated; only 1 in 20 participants discontinued the drug due to an adverse event. Taken together, these findings add to increasing evidence around FXIa as a therapeutic target, and specifically provide rationale for larger clinical outcome studies with asundexian. Bleeding remains an important limitation of oral anticoagulation. Although DOACs provide safer and more reliable stroke prevention compared with vitamin K antagonism, the

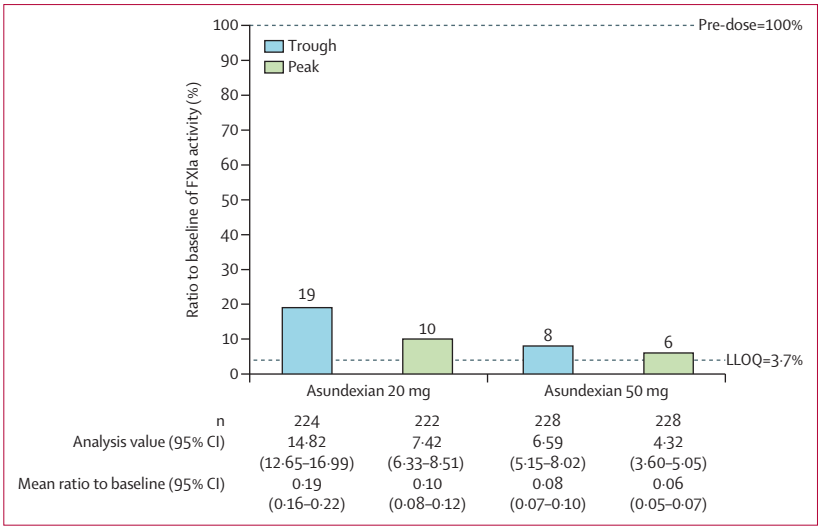

Figure 1: **FXIa activity at steady state after 4 weeks of treatment with asundexian**
Vertical bars indicate the percent reduction in FXIa activity when compared with baseline. FXIa=activated coagulation factor XI. LLOQ=lower level of quantification.

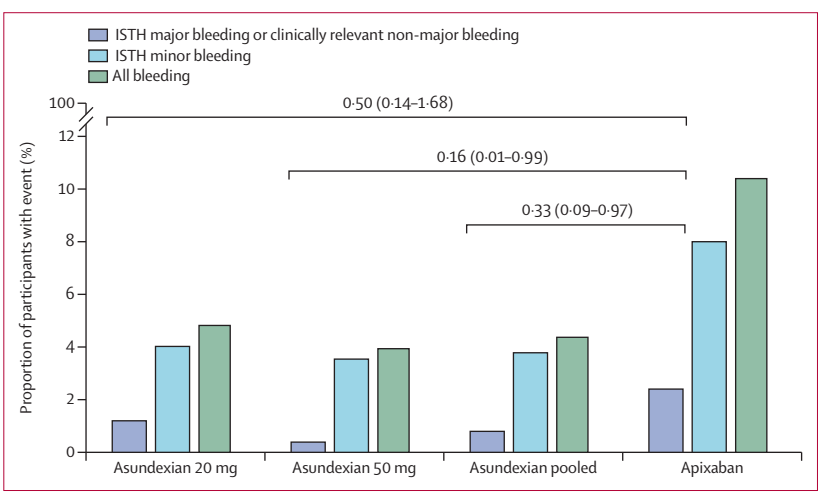

Figure 2: **Safety endpoints according to treatment assignment**
Horizontal bars show the ratio of incidence proportions (90% CIs) between asundexian and apixaban for the primary endpoint, ISTH major bleeding or clinically relevant non-major bleeding. No ISTH major bleeding events occurred in any treatment group. ISTH=International Society on Thrombosis and Haemostasis.

	Asundexian 20 mg (n=251)	Asundexian 50 mg (n=254)	Apixaban (n=250)	Total (n=755)
Cardiovascular death, myocardial infarction, ischaemic stroke, or systemic embolism	2	4	3	9
Cardiovascular death	1	3	3	7
Myocardial infarction	0	1	0	1
Ischaemic stroke	2	1	0	3
Systemic embolism	0	0	0	0
All-cause mortality	2	4	4	10

Data are numbers of participants.

Table 2: **Exploratory thrombotic endpoints**

	Asundexian 20 mg (n=249)*	Asundexian 50 mg (n=254)	Apixaban (n=250)	Asundexian total (n=503)	Total (n=753)
Any AE	118 (47%)	120 (47%)	122 (49%)	238 (47%)	360 (48%)
Any study drug-related AE	29 (12%)	26 (10%)	37 (15%)	55 (11%)	92 (12%)
Any AE leading to discontinuation of study drug	15 (6%)	16 (6%)	13 (5%)	31 (6%)	44 (6%)
AE of special interest	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Any SAE	22 (9%)	20 (8%)	20 (8%)	42 (8%)	62 (8%)
Any study drug-related SAE	4 (2%)	0	0	4 (1%)	4 (1%)
Any SAE leading to discontinuation of study drug	4 (2%)	4 (2%)	4 (2%)	8 (2%)	12 (2%)
AE with outcome of death	1 (<1%)	3 (1%)	2 (1%)	4 (1%)	6 (1%)
Deaths	1 (<1%)	3 (1%)	2 (1%)	4 (1%)	6 (1%)
Heart failure	0	0	1 (<1%)	0	1 (<1%)
Coronary artery disease	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Sudden cardiac death	0	0	1 (<1%)	0	1 (<1%)
Cerebrovascular accident	1 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)
Completed suicide	0	1 (<1%)	0	1 (<1%)	1 (<1%)

Data are presented as n (%), unless otherwise indicated. AE=adverse event. SAE=serious adverse event. *Table includes only patients who took at least one dose of study drug (two patients did not take study drug).

Table 3: **AEs according to treatment assignment**

risk of bleeding is a persistent and troubling clinical problem. The risk of bleeding often dissuades use of oral anticoagulation, bleeding events lead to discontinuation, discontinuation of oral anticoagulation leads to stroke, and some bleeding events are fatal.

There are several lines of evidence that indicate FXIa inhibition might provide a safer method of anticoagulation. Most people with FXI deficiency (Rosenthal syndrome or haemophilia C) do not have spontaneous bleeding, haemarthroses, or haematomas.[13,14] Life-threatening bleeds, including intracranial and gastrointestinal bleeding, are typically not part of the phenotype of severe (even total) congenital FXIa deficiency in humans. Among 52 people with severe FXI deficiency, the mean number of spontaneous bleeding events was 0·6.[13] When bleeding does occur, it is usually after trauma or surgery, consistent with FXI's role in amplification (thrombus growth) but not initiation of clotting (haemostasis).[9,14] Moreover, population studies have shown that reduced FXI levels are protective against cardiovascular thrombotic events such as stroke or venous thromboembolism.[8,15] For example, individuals with moderate to severe FXIa deficiency had a lower risk of cardiovascular events (hazard ratio 0·57, 95% CI 0·35–0·93) when compared with those with normal FXIa.[8]

FXIa inhibition with subcutaneous antisense oligonucleotides, human monoclonal antibodies, or orally administered inhibitors has been shown to prevent venous thromboembolism with a low risk of bleeding after total knee arthroplasty when compared with low molecular weight heparin.[16–18] However, to date, no trials have compared oral anticoagulation with FXIa inhibitors versus factor Xa inhibition with DOACs in patients with atrial fibrillation at risk for stroke. The advantages of reducing thrombosis without reducing haemostasis might be even more salient in the context of lifelong therapy that is often required for stroke prevention in patients with atrial fibrillation.

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 randomised study of patients at moderate-to-high risk for stroke and bleeding, asundexian led to an apparent 90% reduction or more in FXIa (approximately 10% of pretreatment levels). PACIFIC-AF is the first randomised 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.[19] When compared with apixaban, treatment with asundexian led to at least a 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.[20] The lower rate of bleeding is also notable given the lower than expected rates of bleeding despite enrichment criteria for bleeding risk factors in the trial population. Therefore, the potential reduction in bleeding with asundexian might be even greater in general clinical practice, where bleeding rates are higher outside of the controlled setting of a clinical trial. Once-daily asundexian was also well tolerated; approximately 95% of individuals were able to continue the drug without difficulty.

If effective, asundexian could have significant safety advantages in reducing bleeding over contemporary oral anticoagulants for stroke prevention. Bleeding risk

remains a strong barrier to improving rates of stroke prevention in those with atrial fibrillation.[21,22] Moreover, even minor bleeding can compromise adherence to oral anticoagulation.[23] Asundexian might also be particularly beneficial and useful early after an ischaemic stroke related to atrial fibrillation. Because atrial fibrillation-related strokes often involve a large territory of brain compared with other stroke subtypes, the risk of haemorrhagic transformation is higher and leads to greater disability than other stroke subtypes. Therefore, having a medication with a lower risk of bleeding to use very soon after the initial stroke would be valuable. The findings in PACIFIC-AF provide reasonable rationale and safety for participant enrolment in a pivotal phase 3 study to determine whether asundexian is superior to current therapy for patient-centred stroke prevention and net clinical benefit.

This trial was designed as a dose-finding phase 2 clinical study, and was not powered to discern or test differences in the rates of thrombotic events. Moreover, the short follow-up period of 12 weeks limits the ability to ascertain both bleeding and thrombotic events. The observed incidence of bleeding was lower than predicted (ten observed *vs* 20 predicted composite primary outcome events) and there were no ISTH major bleeding events. Although minor bleeding events are not surrogates for major bleeding events, there is a strong correlation between reductions in minor bleeding and major bleeding.[24] Although it appears that asundexian leads to less bleeding than apixaban, the magnitude of this effect cannot be defined due to the low event rates.

In summary, in this randomised 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 atrial fibrillation.

Contributors

The initial draft of the manuscript was written by JPP and MRP, who had full access to and verified all the data underlying the study. CN performed the statistical analysis. All authors had access to the data and contributed to critical interpretation of the data and revision of the manuscript. All authors agreed to submit for publication, and vouch for the integrity, accuracy, and completeness of the data and for the fidelity of the trial to the protocol.

Declaration of interests

JPP is supported by R01AG074185 from the National Institute on Aging. He also receives grants for clinical research from Abbott, the American Heart Association, the Association for the Advancement of Medical Instrumentation, Bayer, Boston Scientific, iRhythm, and Philips, and serves as a consultant to Abbott, AbbVie, Ablacon, Altathera, Biotronik, Boston Scientific, Bristol Myers Squibb, LivaNova, Medtronic, Milestone, ElectroPhysiology Frontiers, Pfizer, Sanofi, Philips, and Up-to-Date. VC has research grants from Boehringer Ingelheim and is an advisory board member or consultant to Bayer, Boehringer Ingelheim, and Bristol Myers Squibb/Pfizer. SJC has received consulting honoraria and is involved in research grants related to atrial fibrillation, anticoagulation, bleeding, or stroke prevention with the following: Abbott, AstraZeneca, Alexion, Atricure, Bayer, Boston Scientific, Bristol Myers Squibb, Daiichi Sankyo, Javelin, and Pfizer. MRP has research grants from Bayer, Janssen, Novartis, Heartflow, the National Heart, Lung, and Blood Institute, the Moore Foundation, and Idorsia, and serves as an advisory board member or consultant to Bayer, Janssen, Novartis, and Medscape. All other authors declare no competing interests.

Data sharing

The de-identified, individual participant-level data will be used and made available for secondary analyses proposed by investigators after review by the PACIFIC-AF steering committee. Requests should be addressed to the corresponding author (jonathan.piccini@duke.edu) or the sponsor representative (pacificsmes@bayer.com). Requesters will be given a study question form. All requests will be evaluated by the trial's steering committee.

Acknowledgments

PACIFIC-AF was funded by Bayer, Leverkusen, Germany.

References

1 Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014; **129:** 837–47.

2 January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019; **74:** 104–32.

3 January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; **64:** e1–76.

4 Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; **42:** 373–498.

5 Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest* 2018; **154:** 1121–201.

6 Kubitza D, Heckmann M, Distler J, Koechel A, Schwers S, Kanefendt F. Pharmacokinetics, pharmacodynamics and safety of BAY 2433334, a novel activated factor XI inhibitor, in healthy volunteers: a randomized phase 1 multiple-dose study. *Br J Clin Pharmacol* 2022; published online Jan 10. https://doi.org/10.1111/bcp.15230.

7 Thomas D, Kanefendt F, Schwers S, Unger S, Yassen A, Boxnick S. First evaluation of the safety, pharmacokinetics, and pharmacodynamics of BAY 2433334, a small molecule targeting coagulation factor XIa. *J Thromb Haemost* 2021; **19:** 2407–16.

8 Preis M, Hirsch J, Kotler A, et al. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. *Blood* 2017; **129:** 1210–15.

9 Gailani D, Gruber A. Factor XI as a therapeutic target. *Arterioscler Thromb Vasc Biol* 2016; **36:** 1316–22.

10 Heitmeier S, Visser M, Tersteegen A, et al. Pharmacological profile of asundexian, a novel, orally bioavailable inhibitor of factor XIa. *J Thromb Haemost* 2022; published online March 15. https://doi.org/10.1111/jth.15700.

11 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3:** 692–94.

12 European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation. June 26, 2014. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-prevention-stroke-systemic-embolic-events_en.pdf (accessed Feb 24, 2022).

13 Asakai R, Chung DW, Davie EW, Seligsohn U. Factor XI deficiency in Ashkenazi Jews in Israel. *N Engl J Med* 1991; **325:** 153–58.

14 Santoro C, Di Mauro R, Baldacci E, et al. Bleeding phenotype and correlation with factor XI (FXI) activity in congenital FXI deficiency: results of a retrospective study from a single centre. *Haemophilia* 2015; **21:** 496–501.

15 Georgi B, Mielke J, Chaffin M, et al. Leveraging human genetics to estimate clinical risk reductions achievable by inhibiting factor XI. *Stroke* 2019; **50:** 3004–12.

16 Weitz JI, Strony J, Ageno W, et al. Milvexian for the prevention of venous thromboembolism. *N Engl J Med* 2021; **385:** 2161–72.

17 Büller HR, Bethune C, Bhanot S, et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med* 2015; **372:** 232–40.

18 Weitz JI, Bauersachs R, Becker B, et al. Effect of osocimab in preventing venous thromboembolism among patients undergoing knee arthroplasty: the FOXTROT randomized clinical trial. *JAMA* 2020; **323:** 130–39.

19 Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ* 2018; **362:** k2505.

20 Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365:** 981–92.

21 O'Brien EC, Holmes DN, Ansell JE, et al. Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Am Heart J* 2014; **167:** 601–609.e1.

22 Savarese G, Sartipy U, Friberg L, Dahlström U, Lund LH. Reasons for and consequences of oral anticoagulant underuse in atrial fibrillation with heart failure. *Heart* 2018; **104:** 1093–100.

23 O'Brien EC, Holmes DN, Thomas L, et al. Therapeutic strategies following major, clinically relevant nonmajor, and nuisance bleeding in atrial fibrillation: findings from ORBIT-AF. *J Am Heart Assoc* 2018; **7:** e006391.

24 Bahit MC, Lopes RD, Wojdyla DM, et al. Non-major bleeding with apixaban versus warfarin in patients with atrial fibrillation. *Heart* 2017; **103:** 623–28.