Circulation

ORIGINAL RESEARCH ARTICLE

A Multicenter, Phase 2, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Dose-Finding Trial of the Oral Factor XIa Inhibitor Asundexian to Prevent Adverse Cardiovascular Outcomes After Acute Myocardial Infarction

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BACKGROUND: Oral activated factor XI (FXIa) inhibitors may modulate coagulation to prevent thromboembolic events without substantially increasing bleeding. We explored the pharmacodynamics, safety, and efficacy of the oral FXIa inhibitor asundexian for secondary prevention after acute myocardial infarction (MI).

METHODS: We randomized 1601 patients with recent acute MI to oral asundexian 10, 20, or 50 mg or placebo once daily for 6 to 12 months in a double-blind, placebo-controlled, phase 2, dose-ranging trial. Patients were randomized within 5 days of their qualifying MI and received dual antiplatelet therapy with aspirin plus a P2Y12 inhibitor. The effect of asundexian on FXIa inhibition was assessed at 4 weeks. The prespecified main safety outcome was Bleeding Academic Research Consortium type 2, 3, or 5 bleeding comparing all pooled asundexian doses with placebo. The prespecified efficacy outcome was a composite of cardiovascular death, MI, stroke, or stent thrombosis comparing pooled asundexian 20 and 50 mg doses with placebo.

RESULTS: The median age was 68 years, 23% of participants were women, 51% had ST-segment–elevation MI, 80% were treated with aspirin plus ticagrelor or prasugrel, and 99% underwent percutaneous coronary intervention before randomization. Asundexian caused dose-related inhibition of FXIa activity, with 50 mg resulting in >90% inhibition. Over a median follow-up of 368 days, the main safety outcome occurred in 30 (7.6%), 32 (8.1%), 42 (10.5%), and 36 (9.0%) patients receiving asundexian 10 mg, 20 mg, or 50 mg, or placebo, respectively (pooled asundexian versus placebo: hazard ratio, 0.98 [90% CI, 0.71–1.35]). The efficacy outcome occurred in 27 (6.8%), 24 (6.0%), 22 (5.5%), and 22 (5.5%) patients assigned asundexian 10 mg, 20 mg, or 50 mg, or placebo, respectively (pooled asundexian 20 and 50 mg versus placebo: hazard ratio, 1.05 [90% CI, 0.69–1.61]).

CONCLUSIONS: In patients with recent acute MI, 3 doses of asundexian, when added to aspirin plus a P2Y12 inhibitor, resulted in dose-dependent, near-complete inhibition of FXIa activity without a significant increase in bleeding and a low rate of ischemic events. These data support the investigation of asundexian at a dose of 50 mg daily in an adequately powered clinical trial of patients who experienced acute MI.

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Editorial, see p 1207

ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- PACIFIC-AMI (Study to Gather Information About the Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following an Acute Heart Attack), an international, randomized, double-blind, placebo-controlled, phase 2, dose-ranging trial, explored the pharmacodynamics, safety, and efficacy of 3 doses of the oral FXIa inhibitor asundexian for secondary prevention after acute myocardial infarction.
- Asundexian, when used in addition to aspirin plus a P2Y12 inhibitor, resulted in dose-dependent, near-complete inhibition of FXIa without a significant increase in bleeding and with a low rate of ischemic events.
- These phase 2 data support the investigation of asundexian at a dose of 50 mg daily in an adequately powered clinical trial in patients after an acute myocardial infarction.

What Are the Clinical Implications?

- These data suggest that asundexian 50 mg daily will nearly completely inhibit FXIa without increasing bleeding.
- Whether inhibiting FXIa with asundexian will reduce recurrent ischemic events in patients with a recent acute myocardial infarction will require further testing in a larger clinical trial.

Nonstandard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
FXI	factor XI
FXIa	activated factor XI
HR	hazard ratio
MI	myocardial infarction
NSTEMI	non–ST-segment–elevation myocardial infarction
PACIFIC-AF	Study to Gather Information About the Proper Dosing of the Oral FXIa Inhibitor BAY 2433334 and to Compare the Safety of the Study Drug to Apixaban, a Non-Vitamin K Oral Anticoagulant (NOAC) in Patients With Irregular Heartbeat (Atrial Fibrillation) That Can Lead to Heart-Related Complications
PACIFIC-AMI	Study to Gather Information About the Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following an Acute Heart Attack
PACIFIC-STROKE	Study to Gather Information About Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following a Recent Noncardioembolic Ischemic Stroke Which Occurs When a Blood Clot Has Formed Somewhere in the Human Body (But Not in the Heart) Travelled to the Brain
PCI	percutaneous coronary intervention
STEMI	ST-segment–elevation myocardial infarction

After acute myocardial infarction (MI), patients experience hypercoagulability and are at risk for recurrent atherothrombotic events. Guidelines recommend dual antiplatelet therapy with aspirin plus a P2Y12 inhibitor for 12 months after an acute MI, for most patients, irrespective of whether percutaneous coronary intervention (PCI) is performed.[1–4] Despite the use of dual antiplatelet therapy, patients remain at risk for recurrent MI, stroke, and death. The addition of an anticoagulant to dual antiplatelet therapy has been studied after acute MI and in patients with stable coronary or peripheral artery disease; however, its clinical use is limited because the bleeding risk associated with the combination of 2 antiplatelet agents (aspirin + P2Y12 inhibitor) and an anticoagulant is thought to outweigh the ischemic benefit.[5–11] In this context, targeted modulation of coagulation through inhibition of the contact pathway inhibiting activated factor XI (FXIa) may provide a more favorable balance between ischemia and bleeding risk.

The plasma serine protease FXIa plays a key role in amplification of thrombin generation after plaque rupture but is thought to be less important in hemostasis. This

conclusion is supported by the results of experimental and animal studies as well as experience in patients with congenital FXI deficiency who appear to be protected against ischemic events but have little or no increased risk of bleeding.[12] The potential for dissociating the risks of thrombosis and bleeding is supported by the results of phase 2 and 3 trials involving the use of antisense oligonucleotides, monoclonal antibodies, and a small molecule that targets FXIa.[13–16]

Asundexian is a highly bioavailable oral direct selective FXIa inhibitor with a terminal half-life of 14 to 17 hours, supporting once-daily dosing.[17,18] We conducted a phase 2, randomized, double-blind trial assessing the pharmacodynamics, safety, and efficacy of 3 doses of asundexian compared with placebo in patients treated with dual antiplatelet therapy after an acute MI.

METHODS

Deidentified individual participant-level data will be made available for secondary analyses proposed by investigators after review by the PACIFIC-AMI (Study to Gather Information About the Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following an Acute Heart Attack) steering committee. Requests should be addressed to the corresponding author (at sunil.rao@nyulangone.org), the senior author (at john.h.alexander@duke.edu), or the sponsor representative (at rosa.coppolecchia@bayer.com). Requesters will be required to complete a study questionnaire. All requests will be evaluated by the Steering Committee, which may request to review and comment on any potential publication of data from the trial.

Trial Design

We used a randomized, double-blind, parallel-group design to compare 3 different doses of asundexian with placebo (Figure S1). Using an interactive web response system, enrolled patients were randomized (1:1:1:1) to receive asundexian 10 mg once daily, 20 mg once daily, or 50 mg once daily, or placebo. Both study drug and placebo were supplied as tablets that were indistinguishable from each other. Randomization was stratified on the basis of intended use of ticagrelor/prasugrel or clopidogrel. Participant compliance with study drug was assessed at each visit by direct questioning. At each dispensing visit and the final study visit, compliance was assessed by counting returned tablets. Other therapies, including choice and duration of the P2Y12 inhibitor prescribed at discharge, were at the discretion of the investigator; however, it was recommended that investigators follow professional society guidelines for the management of patients after acute MI. All patients were followed for 6 to 12 months after randomization. Institutional review boards at participating sites approved the protocol and all participants provided written informed consent before participation.

Patients

Patients admitted with a diagnosis of acute MI were eligible if they were ≥45 years of age, were hospitalized with acute MI that did not occur in the context of revascularization (PCI or coronary artery bypass graft surgery), and planned to be treated with dual antiplatelet therapy after hospital discharge. Patients could be randomized up to 5 days after hospital admission and randomization occurred after patients were stabilized and after any planned PCI. The proportion of patients with ST-segment–elevation MI (STEMI) enrolled in the study was limited to no more than 50%. Main exclusion criteria were hemodynamic instability at the time of randomization, active bleeding or bleeding diathesis, severe renal dysfunction (estimated glomerular filtration rate <30), or planned use of full-dose anticoagulation. The complete eligibility criteria are available in the Supplemental Material.

Management of Study Drug for Procedures

Elective noncardiac surgery and noncardiac percutaneous or endoscopic procedures after randomization were delayed for at least 24 hours after the last dose of study drug. If noncardiac surgery or noncardiac percutaneous or endoscopic procedures were required on an urgent or emergent basis, the increased risks of procedural bleeding were assessed against the urgency of the procedure. For emergent procedures, the protocol recommended considering the use of FXI concentrate, tranexamic acid, or ε-amino caproic acid to mitigate the risk of procedural bleeding.

For patients who underwent elective coronary angiography (with or without elective PCI after randomization or in cases of a staged PCI procedure for the index event), continuation of blinded study drug and concomitant periprocedural use of standard parenteral or subcutaneous anticoagulants (unfractionated heparin, bivalirudin, or low molecular weight heparin) during PCI was recommended. For patients who underwent elective coronary artery bypass graft surgery, study drug was temporarily discontinued for at least 24 hours before surgery. Study drug was restarted no earlier than 24 hours after the postsurgical drains (chest tubes) were removed.

Pharmacodynamics

Blood sampling for pharmacodynamic analysis was performed at randomization and weeks 4 and 26 and evaluated by means of FXIa activity assay. FXIa activity was analyzed using a kaolin trigger and a fluorogenic substrate readout.[12]

Outcomes

The main safety outcome was the composite of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. Secondary safety outcomes included all bleeding and the individual components of the main safety outcome. The efficacy outcome was the composite of cardiovascular death, recurrent MI, ischemic or hemorrhagic stroke, or stent thrombosis. Secondary efficacy outcomes were the individual components of the composite outcome. Detailed definitions of the outcomes are listed in the Supplemental Material.[19,20]

Statistical Analysis

The trial was designed to focus on safety. As prespecified in the protocol, no formal hypothesis testing was planned. Power calculations were performed using PASS software package version 13 for noninferiority log-rank test using the power calculation function according to Jung et al.[21] With a sample size of 400 participants per treatment arm, a projected risk for a main safety outcome of 4.5% at 6 months for all treatment arms, and a projected 5% of randomized participants being lost

to follow-up for the main safety outcome, it was expected that ≈70 participants will have a main safety outcome through 6 months. With 70 participants with a main safety outcome and an observed hazard ratio (HR) of 1.0 for the comparison of asundexian (all doses pooled) with placebo, the upper bound of the 2-sided 90% CI for the HR was expected to be <1.44 with 50% power and <1.82 with 80% power.

Safety and efficacy outcomes were analyzed on the basis of time to their first occurrence. The prespecified safety estimand was the HR of BARC type 2, 3, or 5 bleeding comparing all pooled asundexian groups with placebo in patients with an acute MI treated with dual antiplatelet therapy who have taken at least 1 dose of study drug while the patient is alive and exposed to study drug. We chose to compare all pooled doses of asundexian with placebo for bleeding with the rationale that even a low dose of an anticoagulant might increase bleeding compared with placebo. Safety analyses used the treatment-emergent data counting all events from first intake of study drug until 2 days after the last intake of study drug. The prespecified efficacy estimand was the HR of the composite of cardiovascular death, MI, stroke, or stent thrombosis comparing the pooled asundexian 20 and 50 mg groups with placebo in patients with an acute MI treated with dual antiplatelet therapy while alive and regardless of treatment discontinuation. We chose to compare the pooled 20 and 50 mg doses of asundexian with placebo for ischemic events with the rationale that the higher doses of asundexian might be more effective at reducing ischemic events than the lowest dose. Efficacy analyses used the intention-to-treat data counting all events from randomization until the scheduled end of treatment visit. The time-to-first-event analyses accounted for competing events using Aalen-Johansen estimates for the cause-specific cumulative risk. The difference between the classic Kaplan-Meier method and the Aalen-Johansen method is that the latter accounts for competing events, including death or study drug discontinuation, for safety analyses and death or noncardiovascular death for efficacy analyses. For the Aalen-Johansen estimator, the cumulative hazard calculated by the cause-specific Nelson-Aalen estimator was needed. The calculation estimated the relative change in the instantaneous rate of the occurrence of the outcome in patients taking asundexian versus placebo according to the defined estimand.[22] A cause-specific HR and associated 2-sided 90% CI were derived from a stratified cause-specific Cox proportional hazards model.

Rates of the main safety and efficacy outcomes were also assessed comparing the 50 mg group and all pooled asundexian groups with placebo for the main safety outcome and the asundexian 50 mg group and the pooled asundexian 20 and 50 mg groups with placebo for the efficacy outcome in the following prespecified subgroups: age, sex, region, body weight, estimated glomerular filtration rate, diabetes, presenting MI type (STEMI versus non-STEMI [NSTEMI]), and intended P2Y12 inhibitor (clopidogrel versus ticagrelor/prasugrel).

All analyses were performed using SAS software version 9.4 (SAS Institute Inc.).

Role of the Funding Source

An academic steering committee was responsible for the design and oversight of the trial in collaboration with the trial's sponsor (Bayer AG; Supplemental Material). With input from the steering committee, the sponsor was responsible for conduct of the trial, data collection, and statistical analysis. The first and last authors wrote the first draft of the manuscript. All authors, including members of the sponsor, had the opportunity to review and comment on the manuscript and approved the final version. An independent clinical events classification committee (Duke Clinical Research Institute; Supplemental Material) developed a systematic process to adjudicate all outcome events included in the primary efficacy and safety analysis without knowledge of treatment assignment. An independent data monitoring committee (Supplemental Material) reviewed accumulating data from the trial. The same data monitoring committee reviewed data from PACIFIC-AF (Study to Gather Information About the Proper Dosing of the Oral FXIa Inhibitor BAY 2433334 and to Compare the Safety of the Study Drug to Apixaban, a Non-Vitamin K Oral Anticoagulant [NOAC] in Patients With Irregular Heartbeat [Atrial Fibrillation] That Can Lead to Heart-Related Complications; URL: https://www.clinicaltrials.gov; Unique identifier: NCT04218266)[23] and PACIFIC-STROKE (Study to Gather Information About Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following a Recent Noncardioembolic Ischemic Stroke Which Occurs When a Blood Clot Has Formed Somewhere in the Human Body [But Not in the Heart] Travelled to the Brain; URL: https://www.clinicaltrials.gov; Unique identifier: NCT04304508).

RESULTS

Patients

A total of 1601 patients were randomized at 157 centers in 14 countries between June 2020 and July 2021. Figure 1 shows the flow of patients through the trial. Table 1 lists the baseline characteristics of the patients across treatment groups. Patients were randomized a median (25th, 75th percentile) of 4.0 (3.0, 5.0) days after the qualifying MI. Most patients were enrolled in Europe. The median age was 68 years and 23% of patients were women. Treatment groups were balanced with respect to demographics, body weight, renal function, and medical comorbidities. As planned, approximately half of patients presented with STEMI and half with NSTEMI. Nearly all patients underwent PCI during their index hospitalization. The median (25th, 75th percentile) time from PCI to randomization was 3 (2, 5) days overall, 4 (3, 5) days among patients with STEMI, and 3 (2, 4) days among patients with NSTEMI. In addition to aspirin, more patients were treated with the P2Y12 inhibitors ticagrelor (53%) or prasugrel (27%) than clopidogrel (20%). The baseline characteristics of the patients treated with clopidogrel or ticagrelor/prasugrel are shown in Table S1. Patients treated with clopidogrel were more frequently from Eastern Europe and North America and patients treated with ticagrelor/prasugrel were more frequently from Western Europe.

The median (25th, 75th percentile) duration of P2Y12 inhibitor use was 361 (295, 361) days. The median (25th, 75th percentile) duration of study drug was 335 (238, 364) days and was similar for patients

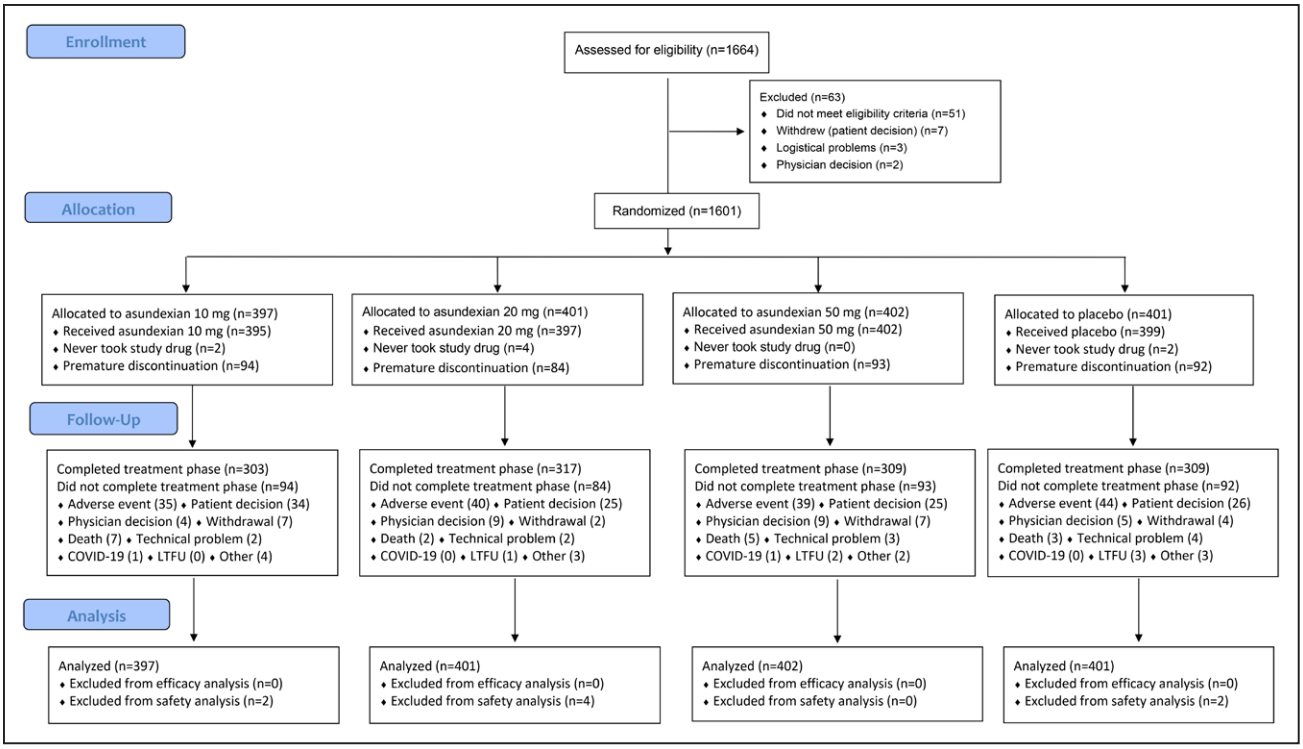

Figure 1. Consolidated Standards of Reporting Trials diagram.
LTFU indicates long-term follow-up.

assigned to asundexian 10 mg (328 days), asundexian 20 mg (341 days), asundexian 50 mg (334 days), and placebo (335 days). While patients were on study drug, median study drug compliance was >99% across all study groups. Of patients remaining in the study, 1227 (79%) were on both study drug (including placebo) and dual antiplatelet therapy with aspirin and a P2Y12 inhibitor at 6 months and 581 (63%) at 12 months. The median (25th, 75th percentile) duration of follow-up was 368 (315, 380) days.

Pharmacodynamics

Figure 2 displays the effect of asundexian on FXIa activity across the 10 mg, 20 mg, and 50 mg doses at week 4 postrandomization. There was a dose-related decrease in both predose (trough) and 2- to 4-hour postdose (peak) FXIa activity. The mean predose level of FXIa activity was 35% of baseline in the 10 mg group, 21% of baseline in the 20 mg group, and 9% of baseline in the 50 mg group. At both predose and 2 to 4 hours postdose, 50 mg of asundexian resulted in >90% inhibition of baseline FXIa activity.

Bleeding and Subgroups

Rates of the main and secondary bleeding outcomes are presented in Table 2. There were numerically higher rates of BARC types 2, 3, or 5 bleeding as the dose of asundexian increased; however, the bleeding rate with placebo was higher than that with asundexian 10 mg or 20 mg. In the prespecified primary safety analysis comparing the combined asundexian groups with placebo, there was no difference in BARC types 2, 3, or 5 bleeding, with wide CIs (HR, 0.98 [90% CI, 0.71 to 1.35]). There was also no difference in the primary safety outcome between patients assigned the highest dose of asundexian (50 mg) and placebo (HR, 1.20 [90% CI, 0.83 to 1.75]). There was no difference in any bleeding between patients assigned any dose of asundexian and placebo (HR, 0.90 [90% CI, 0.73 to 1.11]) or between patients assigned the highest dose of asundexian (50 mg) and placebo (HR, 0.99 [90% CI, 0.77 to 1.28]). One patient receiving asundexian 50 mg and 1 patient receiving placebo experienced an intracranial hemorrhage. There were no BARC 5 (fatal) bleeding events. The main safety outcome comparing the asundexian 50 mg group with placebo across selected subgroups is shown in Figure 3. The main safety outcome comparing all combined asundexian groups with placebo across the same selected subgroups is shown in Figure S2.

Efficacy and Subgroups

The rate of the primary efficacy outcome and its components across treatment groups are also presented in Table 2. There was a numerically lower rate of cardiovas-

Table 1. Baseline Characteristics

Characteristics	Asundexian 10 mg (n=397)	Asundexian 20 mg (n=401)	Asundexian 50 mg (n=402)	Asundexian total (n=1200)	Placebo (n=401)	Total (n=1601)
Age, y	67.0 (62.0, 73.0)	68.0 (61.0, 73.0)	68.0 (63.0, 73.0)	68.0 (62.0, 73.0)	68.0 (60.0, 73.0)	68.0 (62.0, 73.0)
Female sex	93 (23.4)	87 (21.7)	100 (24.9)	280 (23.3)	90 (22.4)	370 (23.1)
Race/ethnicity						
White	334 (84.1)	345 (86.0)	347 (86.3)	1026 (85.5)	339 (84.5)	1365 (85.3)
Asian	53 (13.4)	50 (12.5)	50 (12.4)	153 (12.8)	50 (12.5)	203 (12.7)
Black or African American	3 (0.8)	2 (0.5)	2 (0.5)	7 (0.6)	1 (0.2)	8 (0.5)
American Indian or Alaska Native	1 (0.3)	2 (0.5)	0	3 (0.3)	0	3 (0.2)
Multiple races	1 (0.3)	0	2 (0.5)	3 (0.3)	2 (0.5)	5 (0.3)
Not reported	5 (1.3)	2 (0.5)	1 (0.2)	8 (0.7)	9 (2.2)	17 (1.1)
Region						
Western Europe	222 (55.9)	225 (56.1)	228 (56.7)	675 (56.3)	230 (57.4)	905 (56.5)
Eastern Europe	111 (28.0)	112 (27.9)	111 (27.6)	334 (27.8)	109 (27.2)	443 (27.7)
Asia	49 (12.3)	49 (12.2)	48 (11.9)	146 (12.2)	48 (12.0)	194 (12.1)
North America	15 (3.8)	15 (3.7)	15 (3.7)	45 (3.8)	14 (3.5)	59 (3.7)
Weight, kg	80.0 (70.0, 91.0)	80.0 (70.0, 91.6)	80.0 (72.0, 94.0)	80.0 (70.0, 92.0)	80.5 (70.0, 92.0)	80.0 (70.0, 92.0)
Time from index MI to randomization, d	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)
Previous MI	108 (27.2)	131 (32.7)	100 (24.9)	339 (28.3)	108 (26.9)	447 (27.9)
Previous stroke	23 (5.8)	18 (4.5)	26 (6.5)	67 (5.6)	20 (5.0)	87 (5.4)
Type of MI						
STEMI	215 (54.2)	215 (53.6)	201 (50.0)	631 (52.6)	183 (45.6)	814 (50.8)
NSTEMI	182 (45.8)	186 (46.4)	201 (50.0)	569 (47.4)	218 (54.4)	787 (49.2)
PCI for index event	395 (99.5)	398 (99.3)	400 (99.5)	1193 (99.4)	396 (98.8)	1589 (99.3)
CABG for index event	0	0	0	0	2 (0.5)	2 (0.1)
eGFR, mL/min						
<60	101 (25.4)	109 (27.2)	113 (28.1)	323 (26.9)	103 (25.7)	426 (26.6)
60–90	211 (53.1)	216 (53.9)	223 (55.5)	650 (54.2)	213 (53.1)	863 (53.9)
>90	71 (17.9)	61 (15.2)	56 (13.9)	188 (15.7)	69 (17.2)	257 (16.1)
Missing	14 (3.5)	15 (3.7)	10 (2.5)	39 (3.3)	16 (4.0)	55 (3.4)
Hypertension	275 (69.3)	278 (69.3)	282 (70.1)	835 (69.6)	292 (72.8)	1127 (70.4)
Coronary artery disease	172 (43.3)	174 (43.4)	160 (39.8)	506 (42.2)	163 (40.6)	669 (41.8)
Diabetes	166 (41.8)	154 (38.4)	158 (39.3)	478 (39.8)	170 (42.4)	648 (40.5)
Peripheral artery disease	31 (7.8)	29 (7.2)	22 (5.5)	82 (6.8)	29 (7.2)	111 (6.9)
Chronic kidney disease	28 (7.1)	13 (3.2)	25 (6.2)	66 (5.5)	32 (8.0)	98 (6.1)
P2Y12 inhibitor						
Ticagrelor/prasugrel	319 (80.4)	320 (79.8)	320 (79.6)	959 (79.9)	322 (80.3)	1281 (80.0)
Clopidogrel	78 (19.6)	81 (20.2)	82 (20.4)	241 (20.1)	79 (19.7)	320 (20.0)

Values are median (25th, 75th percentile) or n (%). CABG indicates coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST–segment-elevation myocardial infarction.

cular death, MI, stroke, or stent thrombosis as asundexian dose increased; however, none of the asundexian groups had event rates lower than placebo. In the prespecified primary efficacy analysis comparing the combined asundexian 20 mg and 50 mg groups with placebo, there was no difference in the primary efficacy outcome, with wide CIs (HR, 1.05 [90% CI, 0.69 to 1.61]). There was also no difference in the primary efficacy outcome between patients assigned the highest dose of asundexian (50 mg) and placebo (HR, 1.01 [90% CI, 0.61 to 1.66]). An Aalen-Johansen plot of the primary efficacy outcome over time is shown in Figure S3. The number of patients with cardiovascular death was higher with asundexian 10 mg (7 [1.8%]), 20 mg (4 [1.0%]), and 50 mg (5 [1.2%]) than

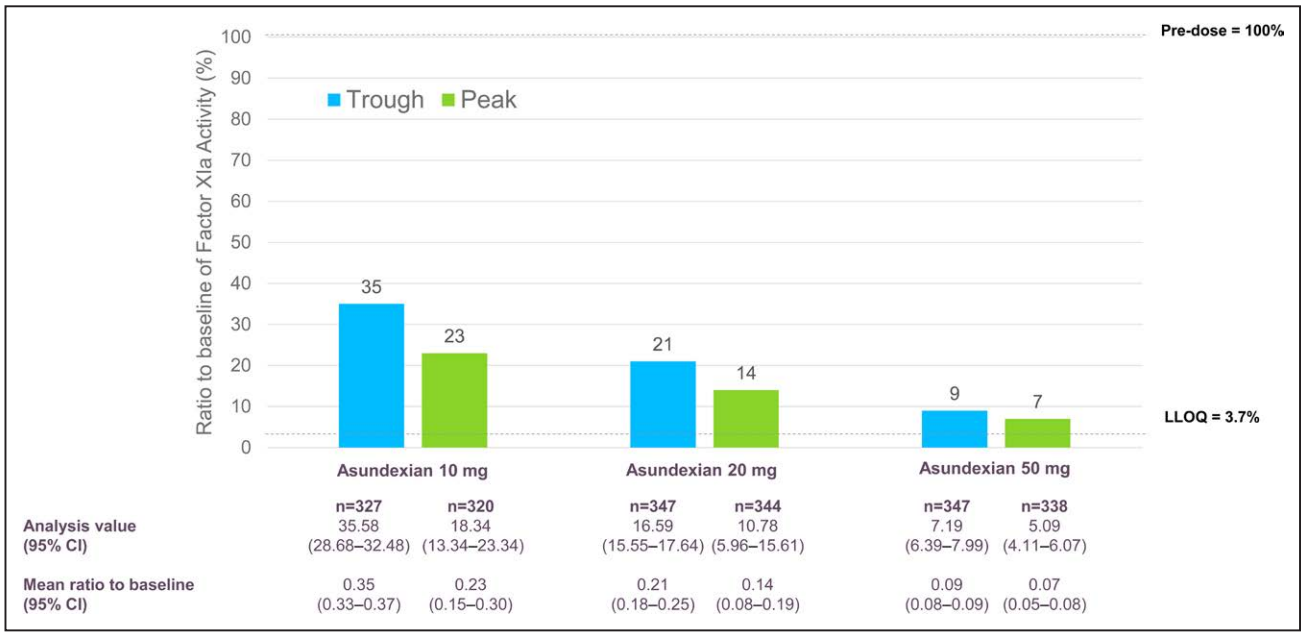

Figure 2. Factor XIa activity at steady state after 4 weeks of treatment with asundexian.
Vertical bars indicate the mean percent reduction in factor XIa activity when compared with baseline. LLOQ indicates lower level of quantification.

with placebo (2 [0.5%]). There were 17 patients with stent thrombosis overall, with no difference between the groups. The overall median (25th, 75th percentile) time from randomization to stent thrombosis was 47 (7, 134) days.

The primary efficacy outcome comparing the asundexian 50 mg group with placebo across selected subgroups is shown in Figure 4. There was a numerically greater reduction in the primary efficacy outcome with asundexian among patients presenting with STEMI than NSTEMI and among those treated with ticagrelor or prasugrel than clopidogrel. The primary efficacy outcome comparing the combined asundexian 20 and 50 mg groups with placebo across the same selected subgroups is shown in Figure S4.

Table 2. Efficacy and Safety Outcomes by Treatment Group

	Asundexian 10 mg (n=395)	Asundexian 20 mg (n=397)	Asundexian 50 mg (n=402)	Asundexian total (n=1194)	Placebo (n=399)	Total (n=1593)
Safety outcomes						
BARC bleeding, type 2, 3, or 5	30 (7.59)	32 (8.06)	42 (10.45)	104 (8.71)	36 (9.02)	140 (8.79)
Type 2	27 (6.84)	29 (7.30)	39 (9.70)	95 (7.96)	31 (7.77)	126 (7.91)
Type 3	5 (1.27)	3 (0.76)	3 (0.75)	11 (0.92)	5 (1.25)	16 (1.00)
Type 5	0	0	0	0	0	0
All bleeding	70 (17.72)	75 (18.89)	82 (20.40)	227 (19.01)	85 (21.30)	312 (19.59)
	Asundexian 10 mg (n=397)	Asundexian 20 mg (n=401)	Asundexian 50 mg (n=402)	Asundexian 20 mg + 50 mg (n=803)	Placebo (n=401)	Total (n=1601)
Efficacy outcomes						
Cardiovascular death, MI, stroke, or stent thrombosis	27 (6.80)	24 (5.99)	22 (5.47)	46 (5.73)	22 (5.49)	95 (5.93)
Cardiovascular death	7 (1.76)	4 (1.00)	5 (1.24)	9 (1.12)	2 (0.50)	18 (1.12)
MI	18 (4.53)	20 (4.99)	18 (4.48)	38 (4.73)	17 (4.24)	73 (4.56)
Stroke	4 (1.01)	3 (0.75)	0	3 (0.37)	2 (0.50)	9 (0.56)
Ischemic stroke	4 (1.01)	2 (0.50)	0	2 (0.25)	2 (0.50)	8 (0.50)
Hemorrhagic stroke	0	1 (0.25)	0	1 (0.12)	0	1 (0.06)
Stent thrombosis	4 (1.01)	5 (1.25)	4 (1.00)	9 (1.12)	4 (1.00)	17 (1.06)
All-cause mortality	10 (2.52)	7 (1.75)	10 (2.49)	17 (2.12)	7 (1.75)	34 (2.12)

Values are n (%). BARC indicates Bleeding Academic Research Consortium; and MI, myocardial infarction.

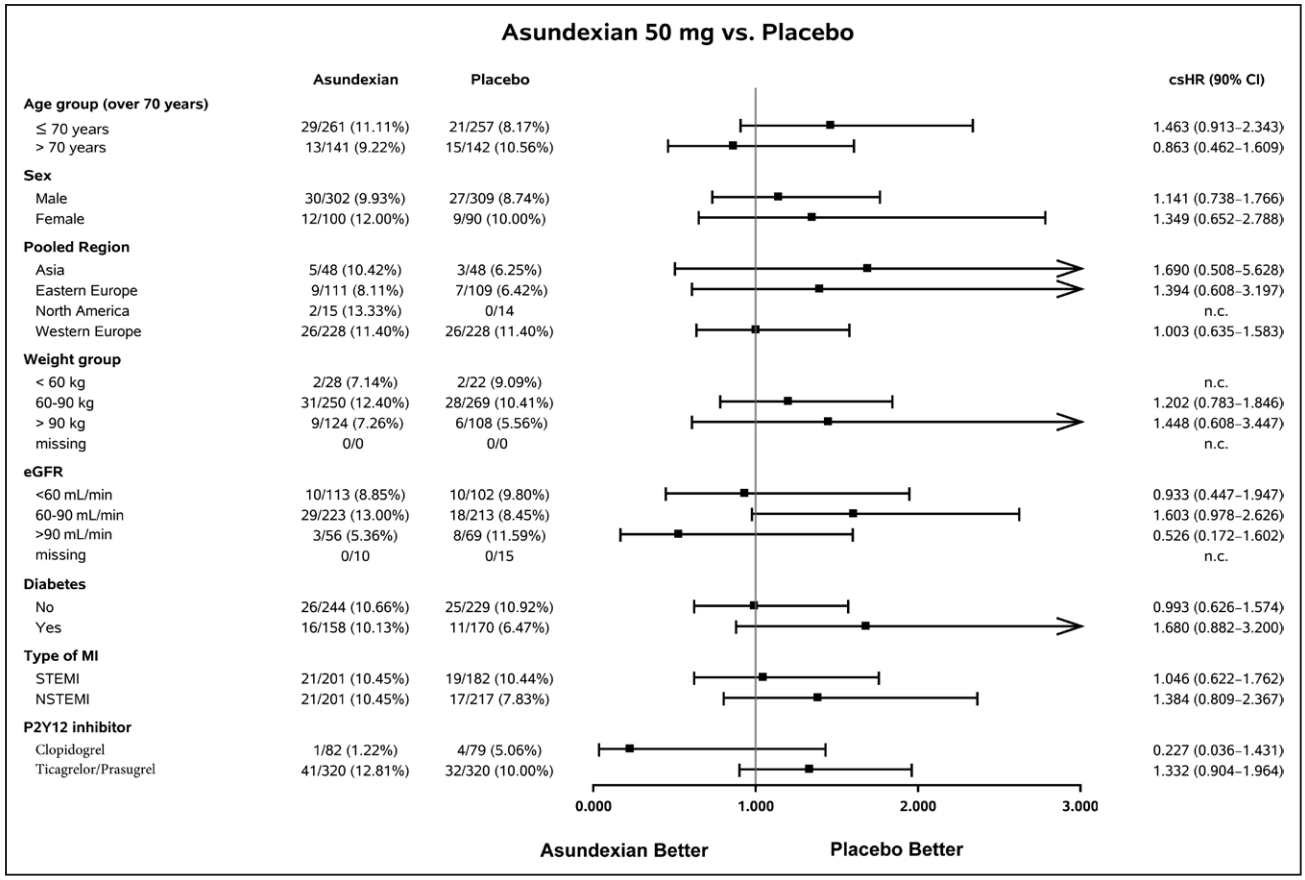

Figure 3. Main safety outcome (Bleeding Academic Research Consortium 2, 3, or 5 bleeding) comparing asundexian 50 mg with placebo in selected subgroups.

$P_{interaction}$ values for all subgroups were nonsignificant (>0.10). csHR indicates cause-specific hazard ratio; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; and NSTEMI, non–ST-segment–elevation myocardial infarction.

Other Safety Outcomes

Rates of other adverse event outcomes, including adverse events that occurred in >5% of participants, are listed by treatment group in Table S2. Adverse events leading to study drug discontinuation occurred in 35 (8.9%) patients taking asundexian 10 mg, 40 (10.1%) patients taking asundexian 20 mg, 39 (9.7%) patients taking asundexian 50 mg, and 44 (11.0%) patients taking placebo. Serious adverse events occurred in 79 (20.0%) patients taking asundexian 10 mg, 84 (21.2%) patients taking asundexian 20 mg, 71 (17.7%) patients taking asundexian 50 mg, and 85 (21.3%) patients taking placebo. There were no clinically or statistically significant imbalances of any adverse event between patients receiving asundexian or placebo.

DISCUSSION

In this phase 2 trial of the FXIa inhibitor asundexian on top of dual antiplatelet therapy in patients after an acute MI, we observed a dose-dependent reduction in FXIa activity with asundexian, with the 50 mg dose resulting in >90% inhibition of FXIa activity at peak and trough. Even at near-complete FXIa inhibition, there was no significant increase in bleeding. PACIFIC-AMI enrolled a selected population after MI, excluding many patients at increased risk of bleeding. Given the encouraging absence of a bleeding signal with asundexian in PACIFIC-AMI, future studies should include these patients. Whereas there was no observed reduction in ischemic events with asundexian, the study was underpowered to exclude a clinically meaningful benefit. Although the number of cardiovascular deaths was higher in the asundexian arms than with placebo, the trial was not statistically powered for this outcome and the extremely small number of cardiovascular deaths in the trial limit the interpretation of this outcome. These data provide a foundation for conducting a larger, definitive phase 3 trial of coagulation modulation with the FXIa inhibitor asundexian in a broader population of patients after acute MI.

FXIa represents an attractive target for antithrombotic therapy because it is involved intimately in thrombus progression and much less in hemostatic mechanisms. Thus, targeting FXIa has the potential to reduce ischemic events without increasing bleeding. Agents directed against FXIa have been studied in venous thromboembolism, atrial fibrillation, and hemo-

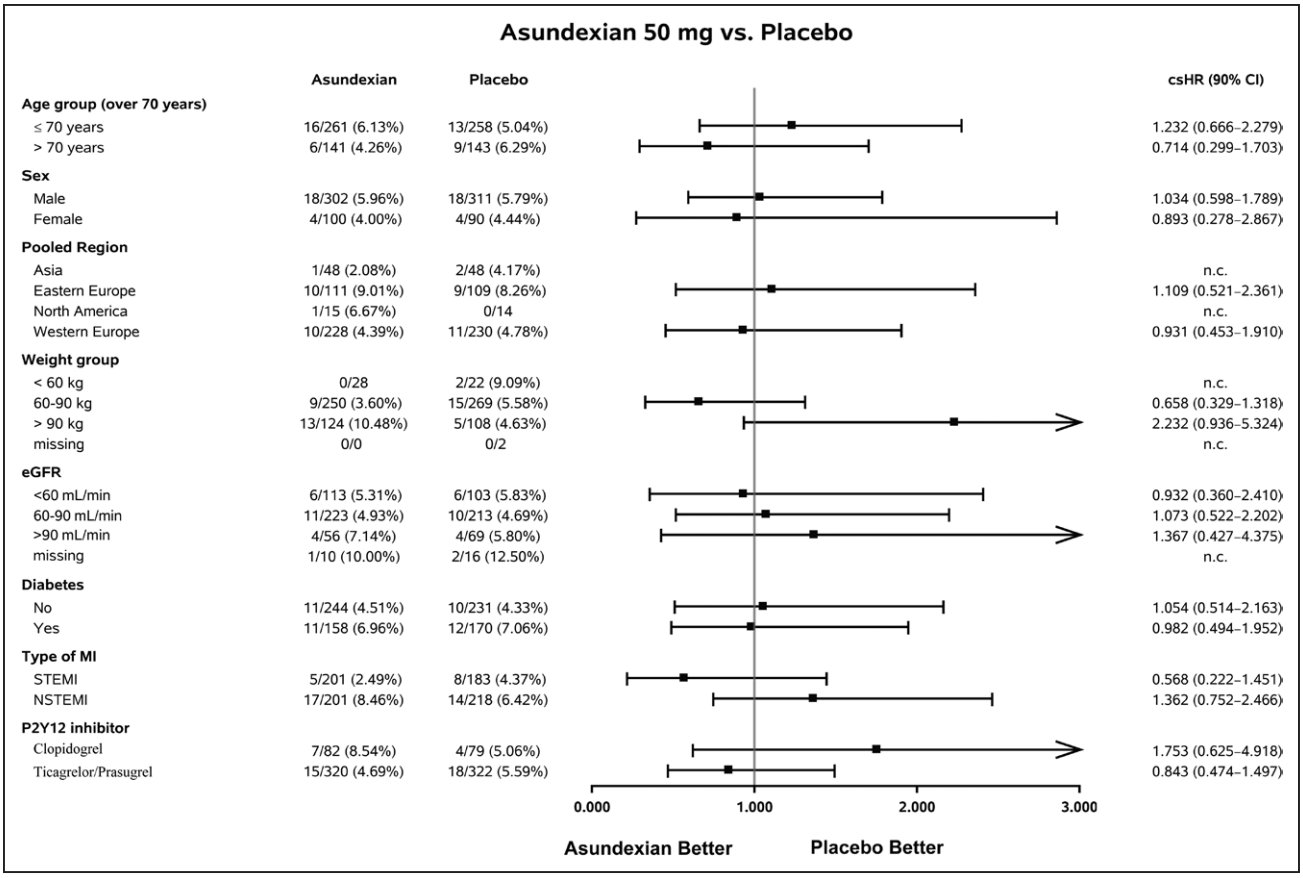

Figure 4. Primary efficacy outcome (cardiovascular death, myocardial infarction, stroke, or stent thrombosis) comparing asundexian 50 mg with placebo in selected subgroups.

$P_{interaction}$ values for all subgroups were nonsignificant (>0.10). csHR indicates cause-specific hazard ratio; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; and NSTEMI, non–ST-segment–elevation myocardial infarction.

dialysis, and have shown promise in reducing recurrent ischemic events without increasing bleeding.[14–16,23] In PACIFIC-AMI, asundexian resulted in a dose-dependent inhibition of FXIa activity such that at the 50 mg dose, the mean peak FXIa activity was only 7% of baseline. The trial protocol called for asundexian being added to conventional antiplatelet therapy after MI. The use of dual antiplatelet therapy consisting of aspirin and a P2Y12 inhibitor after MI reduces the long-term incidence of death or recurrent MI.[24,25] Randomization was stratified by the intended use of ticagrelor/prasugrel or clopidogrel and the safety and efficacy of asundexian were similar among patients treated with these agents.

Invasive risk stratification is also an important aspect of the treatment of patients with MI. In the setting of invasive procedures, antithrombotic therapy increases bleeding risk, which in turn is associated with short- and long-term mortality, recurrent MI, stroke, and stent thrombosis.[26–28] PCI with stent placement is the most common form of revascularization after MI and although contemporary drug-eluting stents significantly reduce the risk for restenosis and repeat procedures, there is a risk for stent thrombosis that requires potent antiplatelet therapy. Among patients with an indication for oral anticoagulation, the addition of direct oral anticoagulants or warfarin to P2Y12 inhibitors (without aspirin) reduces both stent thrombosis and bleeding compared with so-called triple therapy consisting of oral anticoagulation, P2Y12 inhibitor, and aspirin. Patients enrolled in PACIFIC-AMI underwent invasive risk stratification as would be expected for a high-risk MI cohort and 99% underwent PCI during index hospitalization. During trial follow-up, the incidence of stent thrombosis was extremely low (<1.0%) in both the asundexian and placebo groups and bleeding was low and not different between asundexian and placebo, suggesting that the addition of asundexian to antiplatelet therapy not only maintains the low stent thrombosis risk seen with contemporary drug-eluting stents[29] but also does not appreciably increase bleeding risk.

Some limitations of PACIFIC-AMI should be noted. First, PACIFIC-AMI was a phase 2 dose-finding trial to determine which dose or doses of asundexian show promise for secondary prevention after acute MI. The trial was not designed for specific hypothesis testing or to provide definitive evidence of efficacy. Second, the trial was not designed to examine the role of asundexian as an acute treatment for MI but rather to evaluate the safety of

asundexian as an adjunct to conventional oral antiplatelet therapy among patients stabilized after an acute MI.

Conclusions

In this phase 2 clinical trial of patients with recent acute MI, 3 doses of asundexian, when used in addition to aspirin plus a P2Y12 inhibitor, were well-tolerated and resulted in dose-dependent, near-complete inhibition of FXIa activity without a significant increase in bleeding and with a low rate of ischemic events. These data support the investigation of asundexian at a dose of 50 mg daily in a larger adequately powered clinical trial in patients after an acute MI to confirm its safety and evaluate its efficacy.

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Supplemental Material

Supplemental Methods

Tables S1–S2

Figures S1–S4

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