ORIGINAL ARTICLE

Abelacimab versus Rivaroxaban in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Abelacimab is a fully human monoclonal antibody that binds to the inactive form of factor XI and blocks its activation. The safety of abelacimab as compared with a direct oral anticoagulant in patients with atrial fibrillation is unknown.

METHODS

Patients with atrial fibrillation and a moderate-to-high risk of stroke were randomly assigned, in a 1:1:1 ratio, to receive subcutaneous injection of abelacimab (150 mg or 90 mg once monthly) administered in a blinded fashion or oral rivaroxaban (20 mg once daily) administered in an open-label fashion. The primary end point was major or clinically relevant nonmajor bleeding.

RESULTS

A total of 1287 patients underwent randomization; the median age was 74 years, and 44% were women. At 3 months, the median reduction in free factor XI levels with abelacimab at a dose of 150 mg was 99% (interquartile range, 98 to 99) and with abelacimab at a dose of 90 mg was 97% (interquartile range, 51 to 99). The trial was stopped early on the recommendation of the independent data monitoring committee because of a greater-than-anticipated reduction in bleeding events with abelacimab. The incidence rate of major or clinically relevant nonmajor bleeding was 3.2 events per 100 person-years with 150-mg abelacimab and 2.6 events per 100 person-years with 90-mg abelacimab, as compared with 8.4 events per 100 person-years with rivaroxaban (hazard ratio for 150-mg abelacimab vs. rivaroxaban, 0.38 [95% confidence interval {CI}, 0.24 to 0.60]; hazard ratio for 90-mg abelacimab vs. rivaroxaban, 0.31 [95% CI, 0.19 to 0.51]; P<0.001 for both comparisons). The incidence and severity of adverse events appeared to be similar in the three groups.

CONCLUSIONS

Among patients with atrial fibrillation who were at moderate-to-high risk for stroke, treatment with abelacimab resulted in markedly lower levels of free factor XI and fewer bleeding events than treatment with rivaroxaban. (Funded by Anthos Therapeutics; AZALEA–TIMI 71 ClinicalTrials.gov number, NCT04755283.)

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A Quick Take is available at NEJM.org

Atrial fibrillation is the most common sustained arrhythmia, with an estimated 50 million persons affected worldwide, and is associated with a risk of stroke that is five times greater than that in persons without the condition.[1-3] Consequently, anticoagulation therapy to prevent cardioembolic stroke is a cornerstone of treatment. Guidelines give preference to direct-acting oral anticoagulants (DOACs) over vitamin K antagonists in the treatment of atrial fibrillation because DOACs are at least as effective as vitamin K antagonists in reducing the risk of ischemic stroke and are markedly safer with respect to intracranial hemorrhage.[4-6] Nonetheless, bleeding, especially gastrointestinal bleeding, remains the major complication of treatment with DOACs,[7] a side effect that leads to substantial undertreatment of patients.[8,9] Therefore, a need for safer anticoagulants remains.

Factor XI has emerged as a target for anticoagulants that have the potential to be safer than currently available agents because there is mounting evidence that factor XI is essential for thrombosis but nonessential in most cases for hemostasis.[10,11] Persons with genetically mediated factor XI deficiency have fewer embolic events without an appreciable increase in the occurrence of spontaneous bleeding.[12,13] Therefore, factor XI inhibitors have the potential to uncouple thrombosis from hemostasis.

Abelacimab is a fully human monoclonal antibody that binds to the catalytic domain of factor XI and locks it in the inactive state.[14] Abelacimab has a dual mechanism of action because it also inhibits activated factor XI (XIa). In pharmacokinetic and pharmacodynamic studies, abelacimab administered intravenously resulted in almost complete suppression of factor XI within 1 hour after administration and maintained near maximal inhibition for up to 30 days.[15] In a phase 2 trial involving patients undergoing elective knee arthroplasty, a single 150-mg dose of abelacimab administered intravenously after surgery reduced the incidence of venous thromboembolism by 80% as compared with enoxaparin without increasing the risk of bleeding.[16] Whereas small phase 2 trials across multiple conditions have provided preliminary support of the safety of factor XI pathway inhibitors, their long-term safety as compared with DOACs has not been established.[11]

We evaluated the incidence of bleeding after monthly treatment with 150 mg or 90 mg of abelacimab as compared with the DOAC rivaroxaban among patients with atrial fibrillation and moderate-to-high risk of stroke in A Multicenter, Randomized, Active-Controlled Study to Evaluate the Safety and Tolerability of Two Blinded Doses of Abelacimab Compared with Open-Label Rivaroxaban in Patients with Atrial Fibrillation–Thrombolysis in Myocardial Infarction 71 (AZALEA–TIMI 71).

METHODS

TRIAL OVERSIGHT

AZALEA–TIMI 71 was a multinational, phase 2b, parallel-group, partially blind, randomized, active-controlled trial in which we enrolled patients at 95 centers in seven countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). A steering committee, led by the TIMI Study Group and the trial sponsor, Anthos Therapeutics, was responsible for the design, conduct, and supervision of the trial. The protocol (available at NEJM.org) was approved by the relevant ethics committees at the participating sites. An independent data monitoring committee provided external oversight. The raw database was provided to the TIMI Study Group, and analyses were conducted by the TIMI Study Group independently of the sponsor. The first draft of the manuscript was written by the first author. All the authors participated in subsequent revisions of the manuscript, made the decision to submit the manuscript for publication, and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

TRIAL POPULATION

Patients were eligible if they were at least 55 years of age and had a history of atrial fibrillation or atrial flutter, a plan for anticoagulation treatment, and a CHA_2DS_2-VASc score of 4 or higher or a CHA_2DS_2-VASc score of 3 with either planned concomitant use of antiplatelet medications or an estimated creatinine clearance of 50 ml per minute or less. The CHA_2DS_2-VASc score ranges from 0 to 9, with higher scores indicating a greater risk of stroke. The complete list of inclusion and exclusion criteria is provided in the

Supplementary Appendix. All the patients provided written informed consent.

TRIAL PROCEDURES

Patients underwent screening for up to 4 weeks. Eligible patients were randomly assigned in a 1:1:1 ratio to receive subcutaneous injection of abelacimab at a dose of 150 mg or 90 mg once monthly or oral rivaroxaban at a dose of 20 mg once daily (reduced to 15 mg once daily if the estimated creatinine clearance was 50 ml per minute or less). Details regarding the selection of these doses for the trial are provided in the protocol. The trial was double-blind with respect to the dose levels in the two abelacimab groups, but was open-label with respect to whether a patient was assigned to an abelacimab group or to the rivaroxaban group. Randomization was performed with the use of a central computerized system with stratification according to concomitant use of antiplatelet medication and creatinine clearance (≤50 or >50 ml per minute). Patients were contacted by telephone on day 8 and returned for in-person monthly follow-up visits until trial completion, with safety assessment and laboratory testing every 3 months. At the end of the trial, patients were transitioned to standard-care anticoagulation or to open-label abelacimab (for those who were eligible for an optional open-label extension study).

END POINTS

The primary end point, assessed in a time-to-event analysis, was a composite of major or clinically relevant nonmajor bleeding, as defined according to International Society on Thrombosis and Haemostasis criteria.[17] Secondary end points, assessed in a time-to-event analysis, were major bleeding and any bleeding event (a composite of major, clinically relevant nonmajor, or minor bleeding). Key exploratory end points included gastrointestinal bleeding, ischemic stroke or systemic embolism, and net clinical outcome, which was a composite of ischemic stroke, systemic embolism, major or clinically relevant nonmajor bleeding, or death from any cause. A post hoc end point was death from any cause or any stroke. The levels of free factor XI (i.e., factor XI not bound to abelacimab; see the Supplementary Methods section in the Supplementary Appendix), were measured before and after abelacimab was administered. Safety was assessed with the use of data regarding adverse events and with central laboratory testing. An independent clinical events committee, whose members were unaware of treatment assignment, adjudicated suspected bleeding events, stroke, systemic embolism, and cause of death. Definitions of the end points and the approach to blinding of the adjudication process are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary analysis was the time to the first occurrence of major or clinically relevant nonmajor bleeding in the on-treatment analysis population that was included the final complete data population. Patients were considered to be in the on-treatment population if they were within 60 days after their last dose of trial drug. All analyses were tested at a significance level of 0.05. We calculated that 166 events would provide the trial 80% power to detect a 40% reduction in risk (hazard ratio, 0.60) with abelacimab at each dose level as compared with rivaroxaban. We estimated that approximately 1200 patients followed for a total trial duration of 27 months would provide the necessary number of events. Hazard ratios and 95% confidence intervals were generated with the use of a Cox proportional-hazards model with stratification factors as covariates, and P values for time-to-event analyses were calculated with the use of the log-rank test. The proportional-hazards assumption was assessed and confirmed graphically and numerically with the use of cumulative sums of Martingale-based residuals.[18] In a sensitivity analysis, we used the Fine and Gray regression model to account for competing risks. Secondary and exploratory end points are reported as point estimates and 95% confidence intervals, which were not adjusted for multiplicity and should therefore not be used in place of hypothesis testing. Additional safety evaluations included all the patients who underwent randomization and received at least one dose of a trial drug, and results are reported with chi-square P values without adjustment for multiple testing. No imputation was performed for missing data on clinical outcomes. Ascertainment of the primary end point was complete for 99.7% of the potential patient-years of follow-up.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Rivaroxaban (N=430)	Abelacimab, 150 mg (N=430)	Abelacimab, 90 mg (N=427)
Age			
Median (IQR) — yr	74 (69–79)	74 (69–78)	75 (69–79)
≥80 yr — no. (%)	90 (20.9)	81 (18.8)	87 (20.4)
Female sex — no. (%)	184 (42.8)	193 (44.9)	195 (45.7)
Race — no. (%)†			
White	404 (94.0)	410 (95.3)	404 (94.6)
Asian	24 (5.6)	15 (3.5)	20 (4.7)
Region — no. (%)			
North America	103 (24.0)	106 (24.7)	126 (29.5)
Europe	305 (70.9)	309 (71.9)	282 (66.0)
Asia	22 (5.1)	15 (3.5)	19 (4.4)
Median body-mass index (IQR)‡	30.3 (27.0–34.4)	30.0 (26.7–34.5)	29.5 (26.0–33.6)
Creatinine clearance ≤50 ml/min — no./total no. (%)	88/429 (20.5)	90/430 (20.9)	86/425 (20.2)
Pattern of atrial fibrillation — no./total no. (%)			
First detected or paroxysmal	225/428 (52.6)	220/424 (51.9)	224/426 (52.6)
Persistent or long-standing persistent	97/428 (22.7)	84/424 (19.8)	87/426 (20.4)
Permanent	106/428 (24.8)	120/424 (28.3)	115/426 (27.0)
CHA_2DS_2-VASc score§			
Median (IQR)	5.0 (4.0–6.0)	5.0 (4.0–5.0)	5.0 (4.0–5.0)
≤4 — no. (%)	186 (43.3)	213 (49.5)	191 (44.7)
5 — no. (%)	130 (30.2)	131 (30.5)	135 (31.6)
≥6 — no. (%)	114 (26.5)	86 (20.0)	101 (23.7)
HAS-BLED score¶			
Median (IQR)	3.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)
≥3 — no. (%)	225 (52.3)	213 (49.5)	210 (49.2)
Hypertension — no. (%)	418 (97.2)	417 (97.0)	410 (96.0)
Diabetes — no. (%)	245 (57.0)	231 (53.7)	223 (52.2)
Heart failure — no. (%)	206 (47.9)	182 (42.3)	192 (45.0)
Coronary artery disease — no. (%)	205 (47.7)	199 (46.3)	218 (51.1)
Previous ischemic stroke — no./total no. (%)	75/429 (17.5)	59/430 (13.7)	57/427 (13.3)
Previous transient ischemic attack — no./total no. (%)	32/429 (7.5)	25/429 (5.8)	38/426 (8.9)
History of bleeding — no./total no. (%)			
Any bleeding	36/427 (8.4)	34/425 (8.0)	29/424 (6.8)
Gastrointestinal bleeding	23/428 (5.4)	22/428 (5.1)	16/427 (3.7)
Anticoagulation ≥60 days — no./total no. (%)	404/430 (94.0)	389/430 (90.5)	389/426 (91.3)
Vitamin K antagonist	130/430 (30.2)	130/430 (30.2)	125/426 (29.3)
Direct oral anticoagulant	291/430 (67.7)	271/430 (63.0)	283/426 (66.4)
Parenteral agent	6/430 (1.4)	9/430 (2.1)	3/426 (0.7)
Previous use of >1 anticoagulant	23/430 (5.3)	21/430 (4.9)	22/426 (5.2)

Table 1. (Continued.)

Characteristic	Rivaroxaban (N=430)	Abelacimab, 150 mg (N=430)	Abelacimab, 90 mg (N=427)
Planned concomitant antiplatelet medication — no. (%)	106 (24.7)	105 (24.4)	107 (25.1)
Aspirin — no./total no. (%)	58/106 (54.7)	70/105 (66.7)	72/107(67.3)
P2Y12 inhibitor — no./total no. (%)	42/106 (39.6)	29/105 (27.6)	26/107 (24.3)
Dual antiplatelet therapy — no./total no. (%)	6/106 (5.7)	6/105 (5.7)	9/107 (8.4)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race was reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for one patient in the 150-mg abelacimab group.
§ CHA_2DS_2-VASc scores range from 0 to 9, with higher scores indicating a greater risk of stroke. Congestive heart failure, hypertension, age of 65 to 74 years, diabetes, vascular disease, and female sex are each assigned 1 point; age of 75 years or older, previous stroke, transient ischemic attack, and previous thromboembolism are each assigned 2 points.
¶ Modified HAS-BLED scores range from 0 to 8, with higher scores indicating a greater risk of bleeding. Hypertension, abnormal renal function, abnormal liver function, previous stroke, predisposition to bleeding, labile international normalized ratio (not assessed in this trial, so no points assigned for this variable), age greater than 65 years, concomitant use of aspirin or nonsteroidal antiinflammatory drugs, and excessive alcohol use are each assigned 1 point.

RESULTS

PATIENTS AND FOLLOW-UP

From March through December 2021, a total of 1287 patients underwent randomization, of whom 1280 (99.5%) received at least one dose of trial drug (Fig. S1 in the Supplementary Appendix). The baseline characteristics of the patients appeared to be similar across the treatment groups (Table 1). The representativeness of the trial patients relative to the broader population with atrial fibrillation is described in Table S1. The median age of the patients was 74 years (interquartile range, 69 to 78), and 44% were women. The median CHA_2DS_2-VASc score was 5. At baseline, 92% of the patients had previously received an anticoagulant for at least 60 days, with 66% of those having taken a DOAC.

The independent data monitoring committee recommended early termination of the trial on September 14, 2023, because with both dose levels of abelacimab relative to rivaroxaban the hazard ratio for the primary end point was substantially lower than expected and the benefit-to-risk ratio favored abelacimab. Patients then had their final visits. At the time of recommended termination, the median duration of follow-up was 1.8 years (interquartile range, 1.7 to 1.9). At trial completion, the median duration of follow-up was 2.1 years (interquartile range, 2.0 to 2.3). Early permanent discontinuation of the assigned trial drug occurred in 45 patients (10.5% [5.0% per year]) in the rivaroxaban group, 49 patients (11.4% [5.4% per year]) in the 150-mg abelacimab group, and 58 patients (13.6% [6.6% per year]) in the 90-mg abelacimab group. Consent was withdrawn by 6 patients (1.4% [0.67% per year]) in the rivaroxaban group, 3 patients (0.7% [0.33% per year]) in the 150-mg abelacimab group, and 14 patients (3.3% [1.59% per year]) in the 90-mg abelacimab group.

PHARMACODYNAMIC DATA

Monthly subcutaneous administration of abelacimab led to a sustained reduction in free factor XI levels relative to baseline. At 3 months, the median reduction in the free factor XI level was 97% (interquartile range, 51 to 99) in the 90-mg group and 99% (interquartile range, 98 to 99) in the 150-mg group (Fig. 1).

END POINTS

As of the data-cutoff date, at which time the independent data monitoring committee made the recommendation for early termination of the trial, 87 patients had had a major or clinically relevant nonmajor bleeding event (Table S2). The incidence rate of major or clinically relevant nonmajor bleeding was 2.69 events per 100 person-years with 150-mg abelacimab and 1.87 events per 100 person-years with 90-mg abelacimab, as

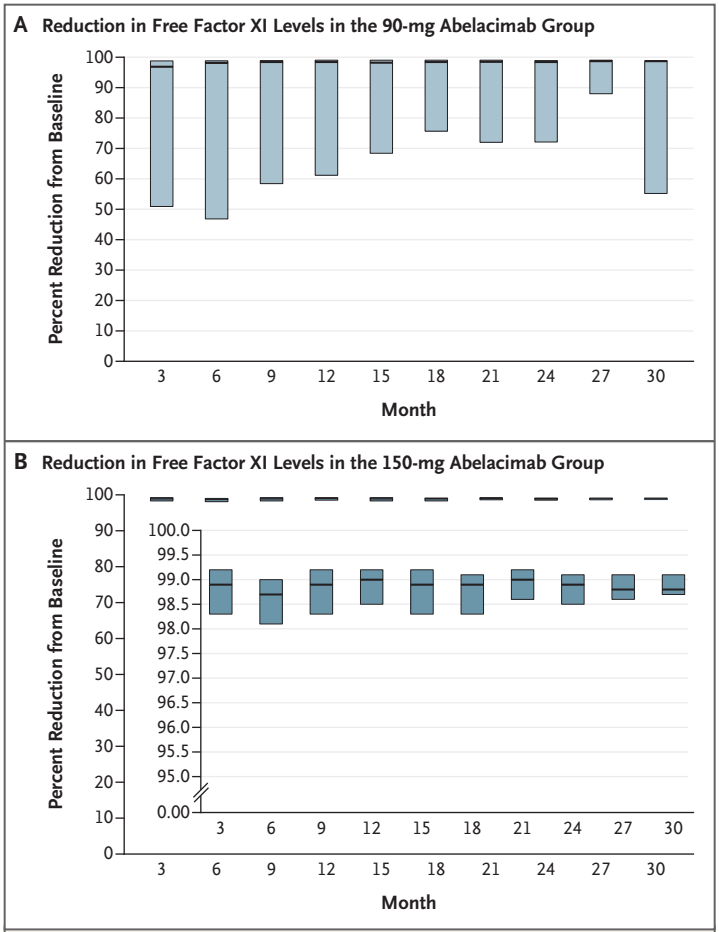


Figure 1. Reduction of Free Factor XI Levels.

Shown is the reduction from baseline in free factor XI levels with abelacimab at a dose of 90 mg (Panel A) and a dose of 150 mg (Panel B); horizontal lines indicate the median, and shaded bars the interquartile range. The inset (Panel B) shows the same data on an expanded y axis. At 3 months, the median reduction in the free factor XI level was 97% (interquartile range, 51 to 99) in the 90-mg group and 99% (interquartile range, 98 to 99) in the 150-mg group.

compared with 8.14 events per 100 person-years with rivaroxaban (hazard ratio for 150-mg abelacimab vs. rivaroxaban, 0.33 [95% confidence interval {CI}, 0.19 to 0.55]; hazard ratio for 90-mg abelacimab vs. rivaroxaban, 0.23 [95% CI, 0.13 to 0.42]; P<0.001 for both comparisons).

In the analysis of the complete data set, a primary end-point event occurred in 113 patients: 26 patients in the 150-mg abelacimab group and 21 patients in the 90-mg abelacimab group as compared with 66 patients in the rivaroxaban group (Table 2). The incidence rate was 3.22 events per 100 person-years with 150-mg abelacimab and 2.64 events per 100 person-years with 90-mg abelacimab, as compared with 8.38 events per 100 person-years with rivaroxaban (hazard ratio for 150-mg abelacimab vs. rivaroxaban, 0.38 [95% CI, 0.24 to 0.60]; hazard ratio for 90-mg abelacimab vs. rivaroxaban, 0.31 [95% CI, 0.19 to 0.51]; P<0.001 for both comparisons) (Fig. 2). A sensitivity analysis with a competing-risks regression model yielded results similar to those reached with the use of the Cox proportional-hazards model.

The incidence rate of major bleeding was 1.22 events per 100 person-years with 150-mg abelacimab and 0.99 events per 100 person-years with 90-mg abelacimab, as compared with 3.73 events per 100 person-years with rivaroxaban (hazard ratio for 150-mg abelacimab vs. rivaroxaban, 0.33 [95% CI, 0.16 to 0.66]; hazard ratio for 90-mg abelacimab vs. rivaroxaban, 0.26 [95% CI, 0.12 to 0.57]). The hazard ratio for the composite of major, clinically relevant nonmajor, or minor bleeding events versus rivaroxaban was 0.68 (95% CI, 0.51 to 0.91) with 150-mg abelacimab and 0.46 with 90-mg abelacimab (95% CI, 0.33 to 0.64). The hazard ratio for major gastrointestinal bleeding with 150-mg abelacimab versus rivaroxaban was 0.11 (95% CI, 0.03 to 0.48) and with 90-mg abelacimab versus rivaroxaban was 0.11 (95% CI, 0.03 to 0.49) (Table 2).

A total of 28 patients had a stroke or systemic embolism (Table 2). The incidence rate of either event was 1.21 per 100 person-years with 150-mg abelacimab and 1.36 per 100 person-years with 90-mg abelacimab, as compared with 0.83 per 100 person-years with rivaroxaban (hazard ratio for 150-mg abelacimab vs. rivaroxaban, 1.47 [95% CI, 0.56 to 3.85]; hazard ratio for 90-mg abelacimab vs. rivaroxaban, 1.65 [95% CI, 0.64 to 4.25]). The incidence rate of ischemic stroke was 1.21 events per 100 person-years with 150-mg abelacimab and 1.24 with 90-mg abelacimab as compared with 0.59 per 100 person-years with rivaroxaban (hazard ratio for 150-mg abelacimab vs. rivaroxaban, 2.06 [95% CI, 0.70 to 6.02]; hazard ratio for 90-mg abelacimab vs. rivaroxaban, 2.10 [95% CI, 0.72 to 6.14]). Hemorrhagic stroke occurred in no patients in the 150-mg abelacimab group, one patient in the 90-mg abelacimab group, and two patients in the rivaroxaban group.

A total of 78 patients died; the incidence rate was 2.65 deaths per 100 person-years with 150-mg

Table 2. End Points.*

End Point	Rivaroxaban (N=428)		Abelacimab, 150 mg (N=427)			Abelacimab, 90 mg (N=425)		
	Patients with Event	Incidence Rate	Patients with Event	Incidence Rate	Hazard Ratio vs. Rivaroxaban (95% CI)	Patients with Event	Incidence Rate	Hazard Ratio vs. Rivaroxaban (95% CI)
	no. (%)	*events/100 person-yr*	*no. (%)*	*events/100 person-yr*		*no. (%)*	*events/100 person-yr*	
Primary end point: major or clinically relevant nonmajor bleeding	66 (15.4)	8.38	26 (6.1)	3.22	0.38 (0.24–0.60)†	21 (4.9)	2.64	0.31 (0.19–0.51)†
Secondary end points								
Major bleeding	31 (7.2)	3.73	10 (2.3)	1.22	0.33 (0.16–0.66)	8 (1.9)	0.99	0.26 (0.12–0.57)
Gastrointestinal bleeding	18 (4.2)	2.14	2 (0.5)	0.24	0.11 (0.03–0.48)	2 (0.5)	0.25	0.11 (0.03–0.49)
Intracranial hemorrhage	4 (0.9)	0.47	2 (0.5)	0.24	0.51 (0.09–2.78)	4 (0.9)	0.49	1.05 (0.26–4.19)
Other major bleeding	9 (2.1)	1.06	6 (1.4)	0.73	0.68 (0.24–1.91)	2 (0.5)	0.25	0.23 (0.05–1.06)
Major, clinically relevant nonmajor, or minor bleeding	112 (26.2)	15.30	78 (18.3)	10.43	0.68 (0.51–0.91)	53 (12.5)	7.04	0.46 (0.33–0.64)
Exploratory end points								
Stroke or systemic embolism	7 (1.6)	0.83	10 (2.3)	1.21	1.47 (0.56–3.85)	11 (2.6)	1.36	1.65 (0.64–4.25)
Ischemic stroke	5 (1.2)	0.59	10 (2.3)	1.21	2.06 (0.70–6.02)	10 (2.4)	1.24	2.10 (0.72–6.14)
Hemorrhagic stroke	2 (0.5)	0.23	0	0	0	1 (0.2)	0.12	0.52 (0.05–5.72)
Systemic embolism	0	0	1 (0.2)	0.12	NA	0	0	NA
Death from any cause	30 (7.0)	3.52	22 (5.2)	2.65	0.77 (0.44–1.34)	26 (6.1)	3.20	0.93 (0.55–1.58)
Net clinical outcome‡	92 (21.5)	11.75	52 (12.2)	6.45	0.55 (0.39–0.77)	54 (12.7)	6.82	0.58 (0.41–0.81)
Death or any stroke	36 (8.4)	4.25	31 (7.3)	3.75	0.90 (0.56–1.46)	36 (8.5)	4.45	1.07 (0.67–1.70)

* The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. NA denotes not applicable.
† P<0.001.
‡ Net clinical outcome is a composite of ischemic stroke, systemic embolism, major or clinically relevant nonmajor bleeding, or death from any cause.

Table 3. Other Safety Events.

Adverse Event	Rivaroxaban (N=428)	Abelacimab, 150 mg (N=427)	P Value*	Abelacimab, 90 mg (N=425)	P Value*
	number (percent)			*number (percent)*	
Any	348 (81.3)	358 (83.8)	0.33	351 (82.6)	0.63
Serious	167 (39.0)	157 (36.8)	0.50	158 (37.2)	0.58
Led to discontinuation of trial drug	29 (6.8)	29 (6.8)	0.99	32 (7.5)	0.67
Injection-site reaction	NA	12 (2.8)	NA	7 (1.6)	NA

* The P value is for the comparison with the rivaroxaban group.

abelacimab and 3.20 deaths per 100 person-years with 90-mg abelacimab, as compared with 3.52 per 100 person-years with rivaroxaban (hazard ratio for 150-mg abelacimab vs. rivaroxaban, 0.77 [95% CI, 0.44 to 1.34]; hazard ratio for 90-mg abelacimab vs. rivaroxaban, 0.93 [95% CI, 0.55 to 1.58]) (Table 2). In the analysis of the net clinical outcome (a composite of ischemic stroke, systemic embolism, major or clinically relevant nonmajor bleeding, or death from any cause), the hazard ratio for an event in the 150-mg abelacimab group as compared with rivaroxaban was 0.55 (95% CI, 0.39 to 0.77) and for an event in the 90-mg abelacimab group as compared with rivaroxaban was 0.58 (95% CI, 0.41 to 0.81).

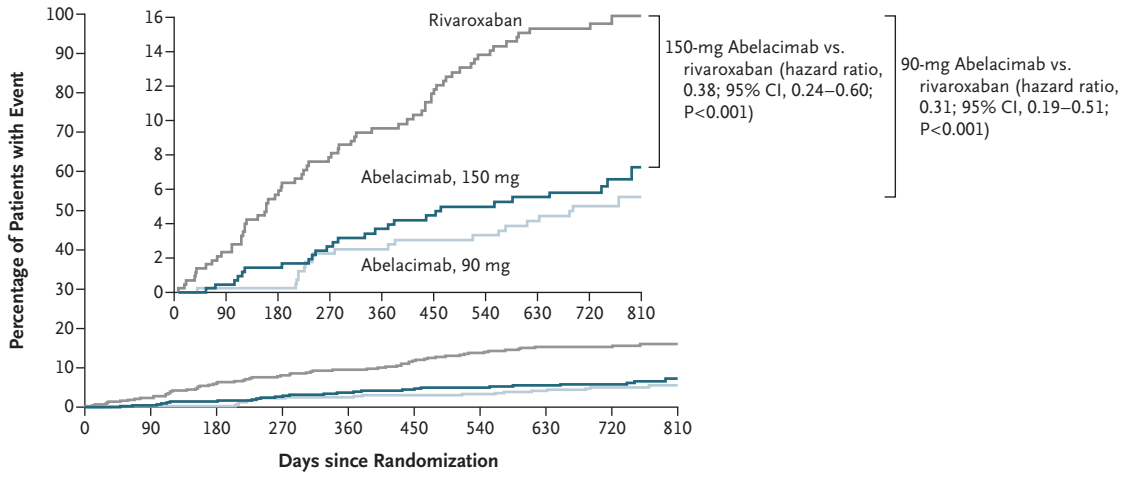
SAFETY

The overall incidence rates of any adverse events, serious adverse events, or adverse events leading to discontinuation of a trial drug are shown in Table 3. Injection-site reactions occurred in 2.8% of the patients who received the 150-mg dose of abelacimab and 1.6% who received the 90-mg dose. Antidrug antibodies did not develop in any patients.

DISCUSSION

Treatment with the fully human monoclonal antibody abelacimab at doses of 150 mg and 90 mg led to marked and sustained reductions in free factor XI levels of 97% or more over the duration of the dosing interval and led to a significantly lower incidence of major or clinically relevant nonmajor bleeding than rivaroxaban (62% lower in the 150-mg abelacimab group and 69% lower in the 90-mg abelacimab group). A composite of major, clinically relevant nonmajor, or minor bleeding occurred in 18.3% of the patients in the 150-mg abelacimab group and in 12.5% of the patients in the 90-mg abelacimab group as compared with 26.2% of those in the rivaroxaban group. Major bleeding occurred in 2.3% of the patients in the 150-mg abelacimab group, in 1.9% of the patients in the 90-mg abelacimab group, and in 7.2% of the patients in the rivaroxaban group. Major gastrointestinal bleeding occurred in 0.5% of the patients in the 150-mg abelacimab group, in 0.5% of the patients in the 90-mg abelacimab group, and in 4.2% of the patients in the rivaroxaban group. There were no differences in the incidence or characteristics of adverse events among the groups.

Although previous small phase 2 trials involving patients with various conditions have supported the safety of factor XI pathway inhibition,[11] our trial used longer-term administration of a factor XI inhibitor (median duration, 2.1 years) than previous trials to establish the favorable bleeding profile of a factor XI inhibitor as compared with a DOAC. In particular, the PACIFIC-AF trial also compared the safety of factor XI pathway inhibition with that observed with a DOAC.[19] In that trial, which included 753 patients with atrial fibrillation, a pooled analysis of two dose levels of asundexian (an oral factor XIa inhibitor administered at a dose of 20 mg or 50 mg once daily) was associated with a lower incidence rate of major or clinically relevant nonmajor bleeding than that observed with apixaban — a finding that was based on a total of 10 events, with no major bleeding events, during the total follow-up of 12 weeks. With a longer follow-up period in our trial, we showed a lower incidence of major and clinically relevant



No. at Risk										
Rivaroxaban	428	415	392	375	365	352	339	328	310	121
Abelacimab, 150 mg	427	419	404	386	375	363	353	343	324	117
Abelacimab, 90 mg	425	413	398	378	372	357	349	338	308	117

Figure 2. Major or Clinically Relevant Nonmajor Bleeding.

Shown is the cumulative incidence of the primary end point event of major or clinically relevant nonmajor bleeding. The inset shows the same data on an expanded y axis.

nonmajor bleeding, as well as a lower incidence of major bleeding and any bleeding event, with abelacimab as compared with rivaroxaban. The incidence of major gastrointestinal bleeding with abelacimab was very low (two events of bleeding in each abelacimab group vs. 18 events in the rivaroxaban group). This finding is of interest for two reasons. First, the gastrointestinal tract is the most common site of bleeding with DOAC treatment, and gastrointestinal bleeding is the one type of bleeding in which DOACs do not have a better risk profile than warfarin. Second, the lower risk of gastrointestinal bleeding with a parenteral anticoagulant raises the possibility that local exposure of the gastrointestinal tract to a direct-acting oral anticoagulant contributes to the risk of bleeding.

Our trial was not designed to provide definitive conclusions regarding the efficacy of abelacimab. The incidence rate of stroke or systemic embolism was low (approximately 1% per year), but numerically, strokes were more frequent in both abelacimab groups than in the rivaroxaban group. This observation was driven by the incidence rates of ischemic stroke. Hemorrhagic stroke, which typically accounts for approximately one sixth of the strokes in patients with atrial fibrillation who are treated with a DOAC, occurred in 2 of 428 patients in the rivaroxaban group and in 1 of 852 patients in the combined abelacimab groups. The incidence rate of the composite outcome event of death from any cause or any stroke was similar among the abelacimab and rivaroxaban groups.

In terms of efficacy data regarding other members of this drug class, the phase 3 OCEANIC-AF trial comparing asundexian 50 mg once daily with apixaban in patients with atrial fibrillation was stopped early because asundexian was less efficacious.[20] This finding has prompted questioning of the utility of inhibiting the factor XI pathway in patients with atrial fibrillation. However, there are important differences between abelacimab and asundexian. First, the mode of action of abelacimab differs from that of asundexian because abelacimab binds to the inactive form of factor XI and prevents the generation of the activated form (factor XIa), whereas asundexian only inhibits factor XIa activity. Second, whereas abelacimab achieves 99% reduction in free factor XI levels at the 150-mg dose being evaluated in phase 3 trials, asundexian at a dose of 50 mg, the dose tested in OCEANIC-AF, appears to be less potent.[19,21] Third, and most important, the

proof of concept that abelacimab reduces the risk of thrombosis was provided in the ANT-005 trial, which assessed abelacimab as compared with enoxaparin for thromboprophylaxis after elective knee arthroplasty.[16] In contrast, no such proof-of-concept trial was performed with asundexian. Ultimately, however, the results of ongoing phase 3 trials are necessary to establish the benefit-to-risk ratio of abelacimab.

Our trial has strengths and weaknesses. The strengths include the relatively long duration of follow-up and the dose-response relationship in the reduction in bleeding with the two doses of abelacimab relative to daily doses of rivaroxaban. Although the open-label randomization to abelacimab or rivaroxaban is a limitation, bias was minimized by blinding with regard to the two abelacimab doses and by the central adjudication of outcome events by a committee whose members were unaware of trial-group assignments. The relatively small sample size precludes assessment of the clinical efficacy of abelacimab, and larger trials are needed. In addition, most patients we enrolled were White, so generalizability to other races is limited. We are also unable to define the relative incidence of bleeding associated with abelacimab to that associated with DOACs other than rivaroxaban.

In patients with atrial fibrillation who are at moderate-to-high risk for stroke, administration of abelacimab at a dose of 90 mg or 150 mg resulted in a sustained marked reduction in factor XI levels and significantly fewer bleeding events than treatment with rivaroxaban. The efficacy of abelacimab as compared with placebo for preventing ischemic stroke and systemic embolization in high-risk patients with atrial fibrillation in whom currently available anticoagulation therapies have been deemed to be unsuitable is currently being evaluated in the ongoing phase 3 LILAC–TIMI 76 trial (ClinicalTrials.gov number, NCT05712200).

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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