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Milvexian vs apixaban for stroke prevention in atrial fibrillation: The LIBREXIA atrial fibrillation trial rationale and design

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Background Direct oral anticoagulants are the standard of care for stroke prevention in eligible patients with atrial fibrillation and atrial flutter; however, bleeding remains a significant concern, limiting their use. Milvexian is an oral Factor XIa inhibitor that may offer similar anticoagulant efficacy with less bleeding risk.

Methods LIBREXIA AF (NCT05757869) is a global phase III, randomized, double-blind, parallel-group, event-driven trial to compare milvexian with apixaban in participants with atrial fibrillation or atrial flutter. Participants are randomly assigned to milvexian 100 mg or apixaban (5 mg or 2.5 mg per label indication) twice daily. The primary efficacy objective is to evaluate if milvexian is noninferior to apixaban for the prevention of stroke and systemic embolism. The principal safety objective is to evaluate if milvexian is superior to apixaban in reducing the endpoint of International Society of Thrombosis and Hemostasis (ISTH) major bleeding events and the composite endpoint of ISTH major and clinically relevant nonmajor (CRNM) bleeding events. In total, 15,500 participants from approximately 1,000 sites in over 30 countries are planned to be enrolled. They will be followed until both 430 primary efficacy outcome events and 530 principal safety events are observed, which is estimated to take approximately 4 years.

Conclusion The LIBREXIA AF study will determine the efficacy and safety of the oral Factor XIa inhibitor milvexian compared with apixaban in participants with either atrial fibrillation or atrial flutter.

Trial registration ClinicalTrials.gov NCT05757869 (Am Heart J 2024;277:145–158.)

Atrial fibrillation (AF) affects over 50 million people globally and poses a significant clinical and societal burden.[1-4] Patients with AF have a 1.5 to 2 fold higher risk of death and 2.4 fold higher risk of stroke than individuals without AF.[5-7] AF-related strokes are more disabling and result in longer hospital stays than non-AF-related strokes.[8,9] This increased risk of adverse outcomes in patients with AF, coupled with the increasing incidence and prevalence of AF due to the aging population and

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improved survival of patients with underlying comorbidities, underscores the importance of optimizing management strategies to mitigate AF-related risks effectively and safely.[1]

The evolution of AF anticoagulation therapy with the development of direct oral anticoagulants (DOACs) was a pivotal shift from vitamin K antagonists (VKAs) for stroke prevention.[1,10] Compared with VKAs, such as warfarin, DOACs have been shown to be more effective in preventing stroke and safer with respect to serious bleeding, particularly intracranial hemorrhage.[10-13] Furthermore, DOACs do not require routine coagulation monitoring or dietary restrictions. However, it is estimated that 35% to 40% of eligible patients with AF do not receive appropriate oral anticoagulation.[14,15] Concern for bleeding impacts the proportion of patients with AF who are either not given anticoagulant therapy or inappropriately receive a low dose DOAC regimen.[16-18] Therefore, there remains an unmet need for an anticoagulant that can offer effective prevention of stroke and systemic embolism (SE) in patients with AF with a lower burden of bleeding than current therapies.

Factor XI has emerged as a target for new anticoagulants that have the potential to be safer than those in current use. Factor XI is essential for pathologic thrombosis but mostly dispensable for physiologic hemostasis. Individuals with hereditary factor XI deficiency or with low factor XI levels are at lower risk for ischemic strokes and venous thromboembolisms (VTE) than subjects with normal factor XI levels yet rarely experience spontaneous bleeding.[19-21] In contrast, individuals with elevated factor XI levels are at increased risk of thrombosis.[22] The interest in factor XI as a target for new anticoagulants is evidenced by phase II trials of parenteral and oral factor XI/XIa inhibitors.[23-32] Indeed prolonged factor XI inhibition with monthly subcutaneous abelacimab, a monoclonal antibody to factor XI, was associated with less bleeding than daily oral rivaroxaban in patients with AF.[28]

Milvexian is a small molecule that binds reversibly to the active site of factor XIa with high affinity and specificity, blocking its activity.[33] Milvexian is orally bioavailable and exhibits dose-proportional plasma concentrations after single doses and once daily administration of 20 to 200 mg, a half-life (11 to 18 hours after repeated dosing) suitable for once daily or twice daily administration, and relatively low variability in pharmacokinetic parameters.[34] Less than 20% of a milvexian dose given as an oral spray dried dispersion, a formulation similar to the one used in the phase III program, is excreted unchanged by the kidneys.[34] In addition, milvexian is metabolized by cytochrome P450 (CYP) 3A4.[35] Single ascending doses up to 500 mg and multiple ascending doses up to 200 mg twice daily were well tolerated in healthy participants.[34] Milvexian prolongs the activated partial thromboplastin (aPTT) time in a dose-dependent manner and has no effect on the prothrombin time.[23,34] Generally, timing for prolongation of aPTT coincides with the plasma milvexian concentration-time profile.[23,34,36] The efficacy and safety of milvexian were evaluated in two phase II randomized controlled trials, AXIOMATIC-TKR and AXIOMATIC-SSP, which are described in further detail below.[23,24]

We describe the rationale and design for a large, international, phase III study evaluating milvexian compared with apixaban for the prevention of thromboembolic events in patients with AF. The primary hypothesis is that milvexian is noninferior to apixaban in reducing the risk of the composite endpoint of stroke and SE. The principal safety hypotheses are that milvexian is superior to apixaban in reducing the principal safety endpoint of International Society on Thrombosis and Hemostasis (ISTH) major bleeding events and the composite of ISTH major and clinically relevant nonmajor (CRNM) bleeding events.

Study design

LIBREXIA AF (NCT05757869) is a randomized, double-blind, double-dummy, parallel-group, multicenter, event-driven, active-controlled study (**Graphical Abstract**). Patients will be stratified by baseline planned use of any antiplatelet medication for at least 30 days. The study includes a screening and randomization period, a double-blinded treatment period, and a 30 day follow up period starting at the global targeted endpoint date, which is defined as the date when the projected target number of primary efficacy endpoint events has been achieved. At the end of treatment visit, participants will be provided with a 30-day supply of apixaban to encourage open-label apixaban use at the appropriate dose until safe transition to clinically indicated long-term anticoagulant therapy.

Objectives

Scientific

The primary efficacy objective of LIBREXIA AF is to evaluate if milvexian is noninferior to apixaban for the prevention of stroke (ischemic, hemorrhagic, or undetermined) and SE. Hence, the primary efficacy endpoint is time to the first occurrence of the composite endpoint of stroke and SE. The principal safety objective is to evaluate if milvexian is superior to apixaban in reducing the risk of ISTH major and CRNM bleeding. The principal safety endpoints are time to first occurrence of ISTH major bleeding, and time to first occurrence of the composite of ISTH major and CRNM bleeding.

Secondary efficacy endpoints include 1) time to first occurrence of the composite endpoint of CV death, myocardial infarction (MI), stroke, and SE, 2) time to cardiovascular (CV) death, 3) time to the first occurrence of the composite endpoint of all-cause death, MI, stroke and

SE, and 4) time to the first occurrence of composite endpoint of CV death, MI, stroke, acute limb ischemia, and urgent hospitalization for a vascular disorder of a thrombotic or ischemic nature (including deep vein thrombosis and pulmonary embolism). Additionally, the primary endpoint of composite stroke and SE will be tested for superiority of milvexian compared with apixaban if criteria for noninferiority are first met. The order and weight of efficacy events will be finalized in the statistical analysis plan before database lock.

Additional exploratory analyses include the evaluation of patient-reported outcomes, medical resource utilization, and pharmacokinetics and pharmacodynamics of milvexian, including measurements of the activated partial thromboplastin time (aPTT), D-dimer, and proteomic analysis.

Operational

The trial leadership followed three key principles during the design of the study. First, we engaged patients as partners in developing the protocol and informed consent form so that patient perspectives and insights would be incorporated. This process involved patient interviews at multiple stages of the design process to ensure the trial requests were manageable and to promote patient retention. For example, some assessments focused on ensuring number of visits, frequency of visits, types of visits including telemedicine visits, and tests were manageable for a diverse patient population with AF. Second, we considered each of the protocol-required assessments and evaluations to ensure they were integrated in the typical clinical follow-up of patients with AF to minimize the burden on participants, study investigators, and health system resources. Third, we actively promoted diversity in sex, race, ethnicity, geography, and expertise across all aspects of the study, including the trial leadership, site investigators, and planned participants. We have devised strategies to optimize diversity and enhance retention, including efforts to identify patients outside of traditional avenues of clinical trial recruitment and prescreen patients for possible enrollment. These efforts are being implemented throughout the trial.

Patient population

Approximately 15,500 participants with permanent or paroxysmal AF from a planned 1,070 sites in 39 countries are being enrolled and followed until the prespecified number of adjudicated endpoint events is observed. The inclusion and exclusion criteria are shown in Table 1. Inclusion criteria follow the general principles of the CHA_2DS_2-VASc score while also taking into account contemporary evidence that female sex is a risk modifier rather than a risk factor.[37] Importantly, this trial was designed to include patients who were often excluded from previous anticoagulation studies in order to provide clinicians with evidence-based data for the care of these populations. For example, patients with a history of ischemic and hemorrhagic stroke, recent MI, recent PCI, and patients requiring single or dual antiplatelet therapy are eligible for this trial unless they are excluded based on the criteria shown in Table 1. AF must be documented electrically (eg, 12-lead electrocardiogram, rhythm strip, Holter Monitor, pacemaker interrogation) within 1 year before randomization. If electrical cardioversion or ablation is planned, to be eligible for enrollment, the investigator must plan to treat the participant with anticoagulation for the duration of the trial.

Intervention and follow-up

Participants will be randomly assigned in a 1:1 ratio to receive either milvexian 100 mg twice daily or apixaban 5 mg twice daily (2.5 mg twice daily for participants with at least 2 of the following characteristics: 1) age $\geq$80 years, 2) body weight $\leq$60 kg, or 3) serum creatinine $\geq$1.5 mg/dL).[1] Apixaban was chosen as the active comparator because of its established efficacy and because it is considered as one of the standards of care for reductions of the risk of stroke and systemic embolism in patients with AF.[1,38]

After randomization, all patients will be followed for the duration of the trial. Visits up to Week 52 will occur every 13 weeks (3 months) and will be onsite. Visits after Week 52 will occur every 13 weeks and alternate between being onsite and remote. The last participant randomized will have a minimum of 13 weeks of treatment with study intervention. The total study duration from the first patient enrolled to the last patient visit is estimated to be approximately four years. The average participation length will be approximately two years.

Dosing considerations

The choice of the milvexian 100mg twice daily dose was informed by preclinical pharmacokinetic and pharmacodynamic data, the phase II AXIOMATIC-TKR results in venous thromboembolic disease, and a model-based meta-analysis (MBMA) comparing milvexian to the active comparator apixaban.[23,39,40] Evaluation of venous thromboembolic disease has been the traditional approach to assessing antithrombotic efficacy and dosing strategies in AF, and our dosing selection process mirrors this approach taken for prior anticoagulants, including apixaban.[41]

AXIOMATIC-TKR randomized 1,242 participants undergoing elective total knee replacement to one of several milvexian regimens blinded to dose, spanning from 25 mg once a day to 200 mg twice a day or open-label enoxaparin 40 mg subcutaneously daily. Overall,

Table 1. Principal inclusion and exclusion criteria for the LIBREXIA AF study

Inclusion	Exclusion
• Age ≥ 18 years of age • Medically stable and appropriate for chronic antithrombotic treatment • Atrial fibrillation or flutter paroxysmal or sustained; not due to a reversible cause • Atrial fibrillation or atrial flutter must be documented by ECG within 1 year of randomization. • If taking vitamin K antagonists, INR must be ≤ 2.0 at the time of randomization • If female, must not be of childbearing potential • **Plus, the participant should meet one or both of the following categories of risk:** a. Category 1. **One or more of the following:** i. ≥ 75 years of age at screening ii. History of any type of stroke, including symptomatic stroke (ischemic, hemorrhagic, lacunar, or undetermined) or silent brain infarcts, or cerebral microbleeds (as long as does not meet exclusion criteria) b. Category 2. **Two or more of the following:** i. Age 65–74 ii. Hypertension: defined as use of antihypertensive medications ≤6 months before the screening visit or persistent systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg iii. Diabetes mellitus: defined as a history of diabetes mellitus and current use of antidiabetic medications iv. Atherosclerotic vascular disease: Defined as peripheral artery disease or coronary artery disease. PAD is defined as one or both of the following: a) a documented history of a resting ankle-brachial index (ABI) of <0.85 b) prior major vascular (non-traumatic) amputation (ankle or above), peripheral bypass, or peripheral percutaneous or surgical intervention for limb ischemia. CAD is defined as one of the following: a) a recent or past MI, excluding periprocedural or definite Type 2 MI b) history of coronary revascularization, either percutaneous (PCI) or surgical (CABG) v. Symptomatic Heart Failure: defined as either 1) history of hospitalization with heart failure as primary cause, regardless of ejection fraction, or 2) ejection fraction < 40% with most recent assessment ≤ 1 year before randomization regardless of history of heart failure hospitalization	• History of ischemic stroke if ≤7 days of randomization • History of CNS bleeding if ≤90 days of randomization • Prior disabling stroke with current modified Rankin Scale ≥3 • Hemodynamically significant valve disease that will potentially require surgical valve replacement • Atrial myxoma or left ventricular thrombus • Active endocarditis • Hospitalized for acute heart failure at the time of randomization • Active liver disease • Requires dialysis at the time of randomization • Significant drug allergy • Allergies, hypersensitivity, or intolerance to milvexian (or apixaban) • Unable to swallow medications • Any condition (other than AF) that requires chronic anticoagulation • Any condition that contraindicates anticoagulant therapy • Isoniazid use or potential use • Platelet count <50,000 mm^3 • ALT >3 x the upper limit of normal • Total bilirubin ≥1.5 x the upper limit of normal unless an alternative causative factor such as Gilbert's syndrome is identified • Hemoglobin <8.0 g/dL • eGFR <25 mL/min/1.73 m^2 at screening • Life expectancy of <12 months • Participants who are incarcerated • Known current substance abuse that could impact study compliance • Employee of the investigator or study site • Planned use of any disallowed therapies as noted in Appendix A • Received an investigational intervention or used an invasive investigational medical device ≤4 weeks before the planned first dose of study intervention or is currently enrolled in an investigational interventional study • Prior participation in a clinical study including a Factor XIa inhibitor • Any exclusions per apixaban local labeling information, such as for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome

dose response relationship for efficacy was observed wherein total daily doses of ≥100 mg of milvexian provided significant reductions in total VTE events as compared with enoxaparin (Figure 1). On the other hand, there was no dose-dependent increase in bleeding. Adverse events, including major or CRNM bleeding rates, were infrequent and similar between treatment groups and dosing regimens. Furthermore, twice daily dosing minimized peak to trough fluctuations in aPTT. MBMA methodology was used to contextualize these data and perform external comparator assessment with apixaban which had been previously studied in TKR patients (Figure 2). The executive committee selected a dose of 100 mg twice daily to maximize potential efficacy while minimizing adverse events, and in particular adverse bleeding events.

The 100 mg twice daily dose of milvexian was similarly shown to be safe in the phase II AXIOMATIC-SSP trial of milvexian (studied in doses ranging from 25 mg daily to 200 mg twice daily) vs placebo in participants with non-cardioembolic ischemic stroke/ transient ischemic attack receiving background antiplatelet therapy.[24] While the

Figure 1. AXIOMATIC-TKR phase 2: exposure-response relationship between VTE or any bleeding and milvexian steady state exposure. Black lines represent the E_{max} logistic model predicted median values (solid) and 95% of the prediction interval (dotted). Blue squares (bars) represent the endpoint rate (95% CI) in each milvexian AUC quartile. *AUC*, area under the curve; *BID*, twice daily; *VTE*, venous thromboembolism.
AUC, area under the curve; BID, twice daily; VTE, venous thromboembolism.

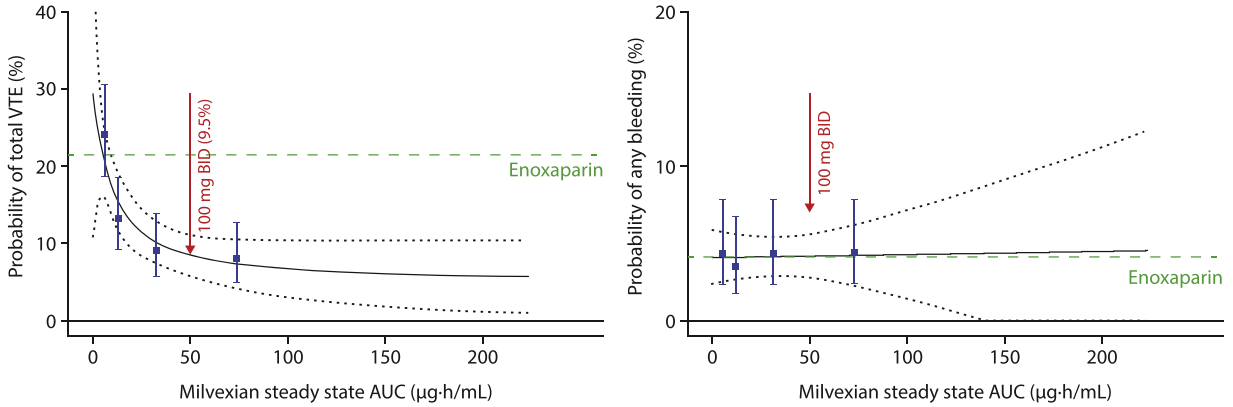
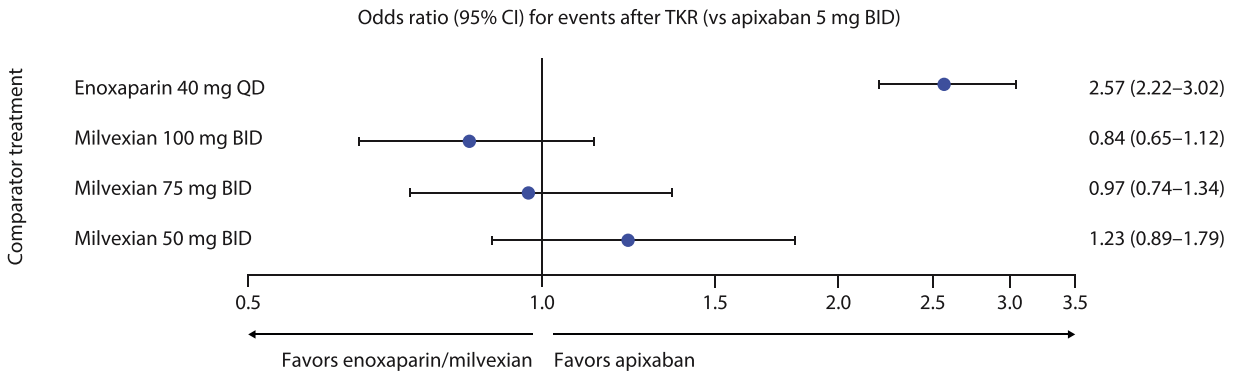


Figure 2. Model-based meta-analysis (MBMA) results: VTE outcomes for milvexian vs apixaban 5 mg BID. MBMA based on 45 clinical studies and 56,392 participants in total knee or total hip replacement surgery was conducted to estimate the dose-response on the relative treatment effect (odds ratio) for milvexian vs apixaban 5 mg BID. The median VTE odds ratio showed a dose-dependent response favoring milvexian over apixaban for doses ≥75 mg BID.
BID, twice daily; CI, confidence interval; QD, once daily; TKR, total knee replacement; VTE, venous thromboembolism.



study did not meet the primary efficacy endpoint of reduction in composite symptomatic ischemic stroke and covert brain infarction (identified by MRI) at 90 days, there was no dose response observed for major bleeding. The overall adverse events and serious adverse events profile for milvexian 100 mg twice daily were similar to placebo.

The OCEANIC AF phase III trial (NCT05643573), which evaluated a different small molecule factor XIa inhibitor, asundexian, was stopped early for inferior efficacy on the recommendation of the study's Data Monitoring Committee.[42] No other details are available as of the time of this publication. The phase II development programs were different for milvexian and asundexian. Milvexian was studied in two phase II programs in total knee replacement and secondary stroke prevention.[23,24] Asundexian was studied in three phase II trials, including secondary stroke prevention, acute coronary syndromes, and atrial fibrillation,[25-27] but did not include evaluation for thromboprophylaxis after knee arthroplasty. The selected dose of milvexian in LIBREXIA AF (100 mg twice daily) is 4-fold higher than the dose of asundexian studied in OCEANIC AF (50 mg daily), and milvexian had a higher potency in the FXIa enzyme inhibition assay in vitro compared to that reported for asundexian.[43,44] Accordingly, the aPTT ratio for milvexian 100 mg twice daily is higher than that for asundexian 50 mg daily.[23,45] Additionally, LIBREXIA AF uses a twice-a-day dosing strategy which min-

imizes peak to trough fluctuations, instead of the once-a-day dosing used in OCEANIC AF.

Concurrent interventions

An operational goal of LIBREXIA AF is to efficiently integrate the clinical trial activities with clinical care flow and encourage adherence to local standards and clinical care guidelines. Concomitant antiplatelet therapy consistent with current guidelines is permitted, eg, patients with antiplatelet therapy after recent percutaneous coronary intervention may still be enrolled. These patients are at increased risk for both bleeding and ischemic events. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used concomitantly on a temporary basis but should be avoided for chronic use (>4 consecutive weeks). The use of aspirin is permitted unless it exceeds >100mg/day for >7 days. The remaining concurrent and prohibited medications are detailed in Appendix A. When necessary, investigators should temporarily interrupt the study drug in a manner that matches recommendations for apixaban. Recommendations for the management of study drug for urgent or elective surgeries or procedures are provided in Table 2.

Efficacy and safety evaluations

The primary efficacy endpoint is the composite of stroke and SE and follows the intention-to-treat (ITT) principle. The ITT approach will be used rather than a per-protocol population to maintain consistency with prior studies used to determine event rates, estimate treatment effects, and determine sample size.[12,13,38] Stroke is defined as an acute episode of neurological dysfunction caused by focal brain, spinal cord, or retinal vascular injury because of hemorrhage or infarction. SE is defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms, such

Table 2. Recommendations for study intervention interruption for urgent or elective surgery or procedures

	Higher bleeding risk surgery or procedure	Lower bleeding risk surgery or procedure
	Urgent surgery or procedure	
Preprocedure	**Urgent surgery or procedure may proceed without delay.** Prophylactic tranexamic acid may be considered to reduce bleeding	
	Elective surgery or procedure	
Preprocedure	Stop or hold study intervention ≥2 days (48 hours) before surgery or procedure	Stop or hold study intervention ≥1 day (24 hours) before surgery or procedure
	Urgent or elective surgery or procedure	
Postprocedure	Study intervention should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established	

Thromboprophylaxis, if required, preprocedure and postprocedure may be administered according to standard of care and local guidelines. Study intervention should not be administered concomitantly with oral or parenteral anticoagulation

Note:

- No requirement for unblinding prior to surgery or procedure
- Lapses in therapy should be avoided and if anticoagulation must be temporarily discontinued for any reason, therapy should be restarted as soon as possible
- Administer procedure-required anticoagulation as per local and standard of care guidelines, regardless of the timing of the last dose of study intervention
- Management of aspirin and/or P2Y12 inhibitor treatment should be according to standard of care and local guidelines
- Tranexamic acid has been recently shown to reduce bleeding for noncardiac surgery and during coronary artery bypass graft (CABG) may be helpful in limiting perioperative bleeding.[55,56] Prophylactic tranexamic acid may be considered when surgery or procedure involve a vascular bed with high fibrinolytic activity (eg, oral buccal cavity or genitourinary tract)
- The presence of milvexian may increase the activated clotting time (ACT) to a higher level than expected for standard anticoagulation dosing; however, the clinical significance of the prolonged ACT is unknown
- Reversal of heparin with protamine during CABG or other procedures should follow standard guidelines
- Some very low bleeding risk surgeries or procedures may not require study intervention interruption (eg, skin, biopsy, pacemaker implantation) per local guidelines and investigator discretion

as trauma, atherosclerosis, or instrumentation. For the principal safety endpoints, participants will be analyzed according to actual intervention received. ISTH major bleeding in the nonsurgical and surgical setting definitions match previously described definitions by Schulman et al.[46,47] CRNM bleeding constitutes acute or subacute clinically overt bleeding that does not satisfy the criteria for major bleeding and that leads to physician-guided medical or surgical treatment for bleeding, hospitalization for bleeding, or a change in antithrombotic therapy. The safety outcomes will be analyzed using the safety population defined as all randomized patients who received at least one dose of drug, assigned to the treatment received. All primary and secondary endpoints are provided in Appendix B and will be adjudicated by an independent, blinded adjudication committee.

Statistical methods and considerations

The executive committee chose a noninferiority design for the primary efficacy endpoint of stroke and SE in LIBREXIA AF due to the proven efficacy of apixaban and its incorporation as the standard of care. Statistical noninferiority in this setting would imply that the efficacy of milvexian is superior to or similar to that of apixaban, whereby the noninferiority margin reflects the minimum acceptable retention of apixaban benefit over placebo that would need to be preserved with milvexian. Once noninferiority is established, the decision of which therapy to use can be guided by other metrics, including bleeding risk and tolerability.

An essential aspect of developing an adequate sample size for this trial is arriving at the appropriate noninferiority margin from historical studies while aligning for constancy of the primary endpoint (stroke and SE) and study population. Apixaban was never compared with placebo in AF because warfarin was the previous evidence-based standard of care. Therefore, we estimated an imputed apixaban vs placebo effect using the indirect comparison method for the composite of stroke and SE. The number of events in each treatment arm and the total number of participants was estimated using published study data for the most similarly matched definitions for stroke and SE.[48-53] From this extraction, we calculated a pooled odds ratio for warfarin vs placebo of 0.32 (95% CI 0.23-0.45) for stroke and SE. Using data on stroke and SE efficacy events and the number of participants from each arm in ARISTOTLE, we calculated an odds ratio of 0.79 (95% CI 0.66-0.95) for apixaban compared with warfarin.[38] Combining these estimates using the indirect method resulted in a pooled odds ratio for the imputed apixaban vs placebo effect of 0.25 (95% CI 0.17-0.38).

Using the fixed margin approach,[54] a noninferior margin was calculated by selecting a preserved fraction of the apixaban vs placebo effect of 50%, which yields a noninferiority margin of 1.62 for stroke and SE. Due to potential sources of heterogeneity in the indirect estimates, constancy limitations, and historical precedent from Factor Xa inhibitor trials, the executive committee proposed a more conservative noninferiority margin of 1.37 for stroke and non-CNS SE. This margin would preserve approximately 67% of the estimated apixaban vs placebo effect.

To achieve 90% power to test for noninferiority using a margin of 1.37, and assuming 1-sided significance level of 0.025, apixaban treatment group annualized event rate of 1.33% for the primary efficacy composite outcome, hazard ratio of 1.0 for milvexian compared with apixaban, and nonuniform enrollment over the course of the trial, 430 events of the composite of stroke and SE will be needed requiring a sample size of approximately 15,500 participants (7,750 per arm). We also expect to have power to detect a significant difference in ISTH major bleeding. Blinded data will be used to estimate overall event rates at various times. On the basis of estimated blinded event rates and in an effort to accrue the planned number of events, the sample size may be adjusted.

The primary and secondary endpoints will be tested using a prespecified testing procedure in order to control the family-wise type I error rate from multiple testing. If the primary efficacy hypothesis (noninferiority) is met for the primary endpoint of stroke and non-CNS systemic embolization, then the secondary endpoints listed in Appendix B will be tested using a graphical testing procedure.

Administrative organization

LIBREXIA AF is part of the LIBREXIA Program (Figure 3), which also includes the LIBREXIA Stroke (NCT05702034) and LIBREXIA ACS trials (NCT05754957). The LIBREXIA Program is a phase III program evaluating milvexian in three major cardiovascular conditions and will enroll over 45,000 patients. The Program is overseen by a Program Executive Council (Appendix C). The Program has a common Independent Data Monitoring Committee (IDMC) and Adjudication Committee (Appendix D).

The LIBREXIA AF study is overseen by an academic Executive Committee. The committee provided oversight for the design of the protocol, supervises trial execution, and is accountable for analysis of results and publication (Appendix E). A Steering Committee of National Leaders from each country (Appendix F) provides global support for regulatory filing, recruitment and retention, analyses, and dissemination of the results.

The LIBREXIA program is being co-developed and co-funded under a collaboration agreement between Bristol Myers Squibb Company and Janssen Research & Development, LLC. Two academic research organizations, the Stanford Center for Clinical Research and the BAIM Clinical Research Institute, are partnering to provide program

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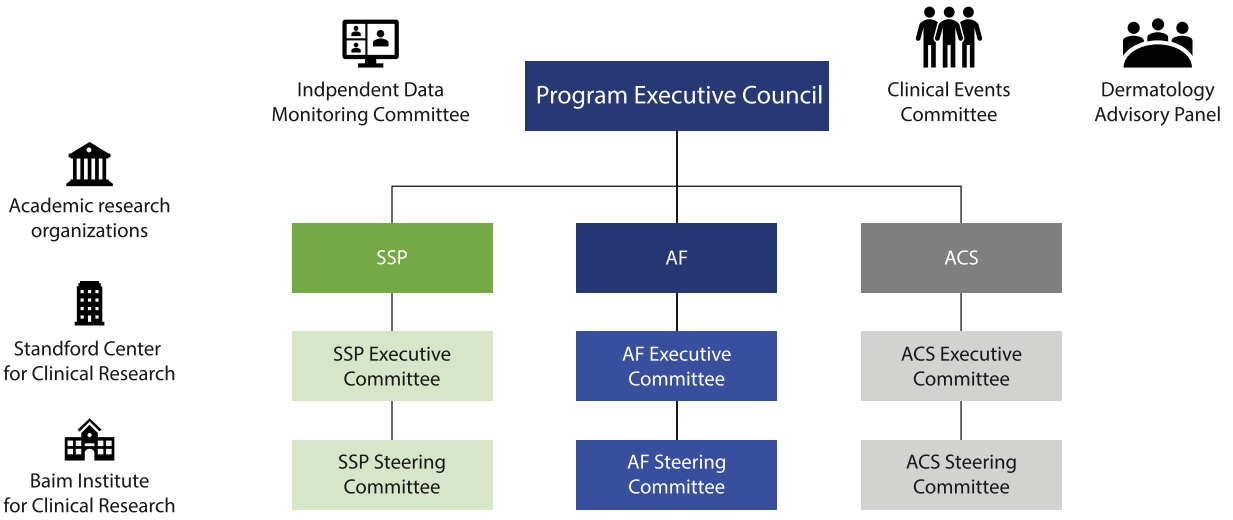
Figure 3. LIBREXIA program partners and structure. Description of the structure of the LIBREXIA program. *ACS*, acute coronary syndrome; *AF*, atrial fibrillation; *SSP*, secondary stroke prevention.



management, event adjudication, and focused efforts to enhance the racial and ethnic diversity of participants. IDMC statistics will be performed by an independent academic group at BAIM, and there will be independent statistical analyses of primary trial results by academic groups.

Conclusions

LIBREXIA AF is a global phase III, randomized, double-blind trial evaluating the noninferiority of milvexian, an oral factor XIa inhibitor, vs apixaban in participants with AF. It is one of the first head-to-head trials of a new anticoagulant vs apixaban in participants with AF. The trial has an enrollment target of 15,500 participants and is estimated to last 4 years. At completion, LIBREXIA AF will inform the efficacy and safety of milvexian compared with apixaban for the prevention of stroke in participants with AF.

Disclosures

SSJ reports consulting fees from Bristol Myers Squibb, ARTIS Ventures, and Broadview Ventures outside of the submitted work. **KWM**'s financial disclosures can be reviewed at http://med.stanford.edu/profiles/kenneth-mahaffey. **KSP** is a member of The Thrombosis Research Institute which has received institutional research grant support from Anthos Therapeutics and Bayer Pharmaceuticals. She has received honoraria from Element Science and Artivion, Inc. **WS** has received honoraria (>10K USD) from Daiichi Sankyo, Nippon Boehringer Ingelheim, and Pfizer Japan, and research grants (>50K USD) from Daiichi Sankyo and Nippon Boehringer Ingelheim. **CTR** reports Research Grants through Institution from: Athos, AstraZeneca, Daiichi Sankyo, Janssen and Novartis. Honoraria for scientific ad boards and consulting from: Anthos, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Janssen and Pfizer. He is a member of The TIMI Study Group which has received institutional research grant support through Brigham and Women's Hospital from: Abbott, Abiomed, Inc, Amgen, Anthos Therapeutics, ARCA Biopharma, Inc, AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Ionis Pharmaceuticals, Inc, Janssen Research & Development, LLC, MedImmune, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc, Roche, Saghmos Therapeutics, Inc, Siemens Healthcare Diagnostics, Inc, Softcell Medical Limited, The Medicines Company, Verve Therapeutics, Inc, Zora Biosciences. **PRK** reports consultancy from Anthos, J&J, BMS and Bayer. **GS** has received research grants from Amarin, AstraZeneca, and Sanofi; has participated in clinical trials, consulting, or speaking for Amarin, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Idorsia, Janssen, Novartis, Novo Nordisk, PhaseBio, Pfizer, and Sanofi; is a Senior Associate Editor at Circulation; and serves as the CMO for Bioquantis. **RM** reports institutional research payments from: Abbott, Affluent Medical, Alleviant Medical, Amgen, AstraZeneca, BAIM, Beth Israel Deaconess Medical Center, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CERC, Chiesi, Concept Medical, Daiichi Sankyo, Duke, Faraday, Idorsia, Janssen, MedAlliance, Medscape, Mediasphere, Medtelligence, Medtronic, Novartis, OrbusNeich, Pi-Cardia, Protembis, RM Global Bioaccess Fund Management, Sanofi; consultant to Affluent Medical, Boehringer Ingelheim, Chiesi USA, Cordis, Esperion Science/Innovative Bio-

pharma, Gaffney Events, Educational Trust, Global Clinical Trial Partners, Ltd., IQVIA, Medscape/WebMD Global, NovoNordisk, PeerView Institute for Medical Education, TERUMO Europe N.V., Radcliffe and honoararia from AMA and ACC. **SCJ** has received research support from Jansen, BMS, and AstraZeneca. **GJH** reports personal honoraria outside the submitted work from the American Heart Association (Associate Editor, *Circulation*), Bristol Myers Squibb (Steering Committee, AXIOMATIC-SSP trial of milvexian [factor XIa inhibitor] for secondary stroke prevention) and Janssen (Co-chair, Executive Committee, Librexia Stroke trial of milvexian for secondary stroke prevention). **RAH** has received research grants/contracts from NHLBI (ISCHEMIA), Duke/PCORI (ADAPTABLE), Janssen (Factor Xia inhibitor), CSL (HDL), Baim Institute, UColorado, Harvard (BWH), and Merck; has served as a consultant/advisor for NHLBI (COVID/CONNECTS), Atropos Health, Bitterroot Bio, Bristol Myers Squibb, Bridge Bio, Chiesi, CSL Behring, Edwards Lifesciences Corp, Element Science, Foresight, Merck, and WebMD; and serves on the Board of Directors for AHA and Cytokinetics. **CSPL** is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has Received research support from Novo Nordisk and Roche Diagnostics; has Served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, CPC Clinical Research, Eli Lilly, Hanmi, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd., Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as Co-founder and nonexecutive director of Us2.ai. The remaining authors report no relevant disclosures or competing interests.

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Appendix A. Other concomitant therapies

Isoniazid is not permitted. If clopidogrel is prescribed, concomitant use of omeprazole or esomeprazole is prohibited in accordance with the clopidogrel label. Clopidogrel is metabolized to its active metabolite in part by CYP2C19; concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. However, other use of proton pump inhibitors is allowed. Additional chronic anticoagulants such as VKA, factor IIa, or Factor Xa inhibitors are not allowed, and study intervention must be interrupted or discontinued in participants who require open-label anticoagulant treatment for conditions other than AFib. The concomitant use of a combined P-glycoprotein (P-gp) and strong CYP3A4 inhibitor (eg, atazanavir, clarithromycin, itraconazole, ketoconazole, ritonavir, saquinavir) within 7 days of receiving study intervention and during the study is prohibited.

The concomitant use of a combined P-gp and strong CYP3A4/5 inducer (eg, carbamazepine, phenytoin, rifampin) within 7 days of receiving study intervention and during the study is prohibited.

Appendix B. Primary and secondary objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate if milvexian is noninferior to apixaban for the composite of stroke and non-CNS systemic embolism.	Time to the first occurrence of composite endpoint of stroke and non-CNS systemic embolism.
Secondary*	
To evaluate if milvexian is superior to apixaban in reducing the risk of the principal safety endpoint family: • ISTH major bleeding. • Composite of ISTH major and CRNM bleeding.	• Time to the first occurrence of ISTH major bleeding. • Time to the first occurrence of the composite of ISTH major and CRNM bleeding.
To evaluate if milvexian is superior to apixaban for the composite of stroke and non-CNS systemic embolism.	Time to the first occurrence of composite endpoint of stroke and non-CNS systemic embolism.
To evaluate if milvexian is superior to apixaban as assessed by CV death.	Time to CV death.
To evaluate if milvexian is superior to apixaban as assessed by the composite of all-cause death, MI, stroke, and non-CNS systemic embolism.	Time to the first occurrence of the composite endpoint of all-cause death, MI, stroke, and non-CNS systemic embolism.
To evaluate if milvexian is superior to apixaban as assessed by the composite of CV death, MI, stroke, acute limb ischemia (ALI [any unanticipated revascularization or amputation of ischemic limb]), and urgent hospitalization for vascular cause of ischemic nature (including thrombotic events: deep vein thrombosis and pulmonary embolism).	Time to the first occurrence of the composite endpoint of CV death, MI, stroke, acute limb ischemia (ALI [any unanticipated revascularization or amputation of ischemic limb]), and urgent hospitalization for the vascular cause of ischemic nature (including deep vein thrombosis and pulmonary embolism).

*Additionally, the primary endpoints of stroke and systemic embolism will be tested to evaluate if milvexian is superior to apixaban. The order and weight of efficacy events will be finalized in the statistical analysis plan before database lock.

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