# Librexia AF Protocol

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The purpose of the current material is to provide trial rationale of Librexia AF study (NCT05757869) and the clinical/scientific justification of its study design: patient population, endpoints, interventions and dosing considerations.

# Unmet Need

*AF is a Major Risk Factor for Stroke and a Burden for Patients and Healthcare Systems*[1-5]

**There remains an unmet need for patients with AF**

Actual or perceived **bleeding risk** is a key driver for **under prescription**;
~ 40% of eligible patients with AF **do not receive appropriate oral anticoagulation**[4]

2.4X

Patients with AF have a 2.4 fold higher risk of stroke than individuals without AF.[1]

AF-related strokes are, on average, more disabling and more likely to recur than non-AF-related strokes.[2]

AF-related strokes result in longer hospital stays and greater health care burdens than non-AF related strokes.[3]

23%

In the US, as many as 23% of ~ 6 million AF cases are undiagnosed, many are eligible for oral anticoagulant treatment.[5]

AF, atrial fibrillation

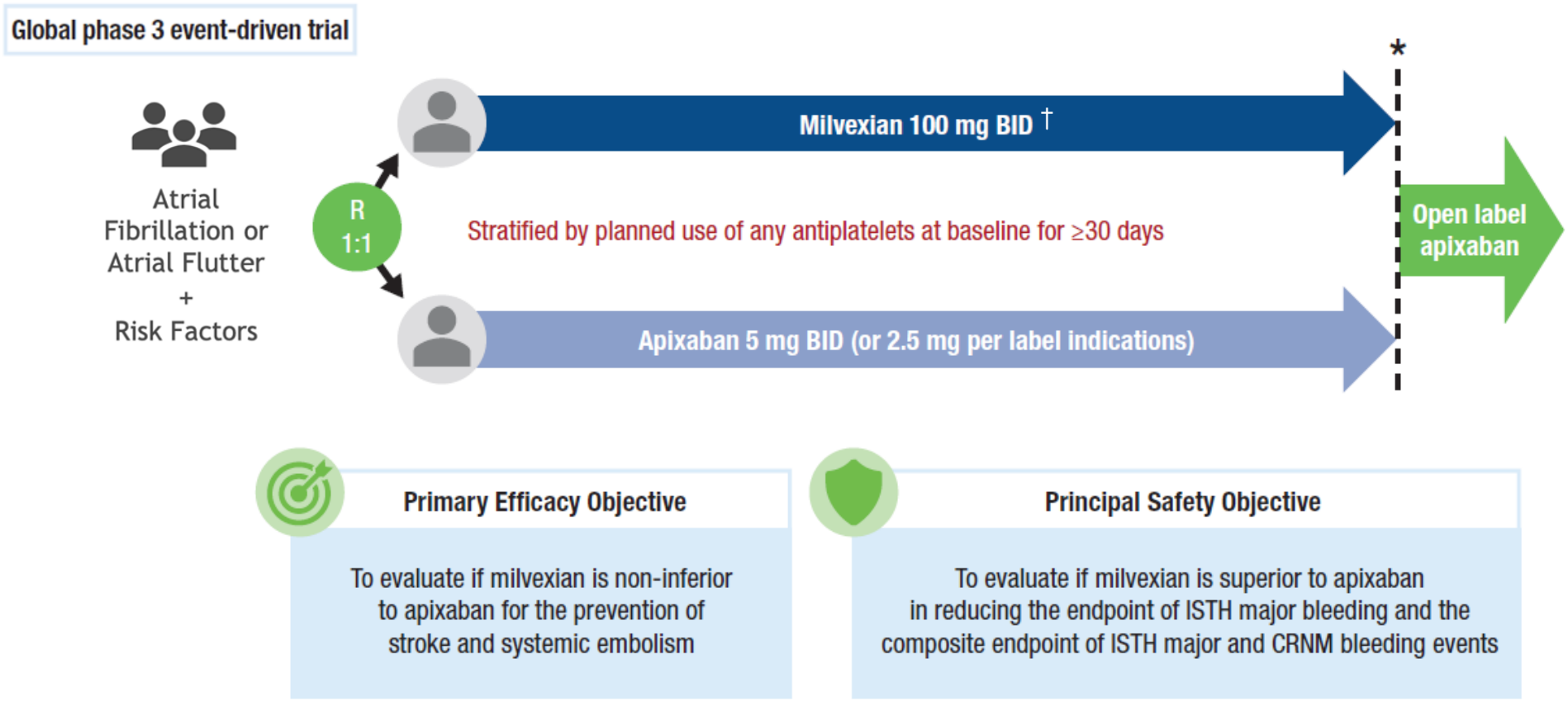
1. Odutayo A, BMJ, 2016. 2. Alkhouli M, J Am Coll Cardiol, 2018. 3. Thygesen SK, Clin Epidemiol, 2009. 4. Petty D, Prescriber, 2014. 5. Turakhia M, Clinical Cardio, 2023.

# Hypothesis

The primary hypothesis is that milvexian† is non-inferior to apixaban in reducing the risk of the composite endpoint of stroke and non-CNS systemic embolism in participants with atrial fibrillation.

*†The safety and efficacy of the investigational compound have not been established*

# Librexia AF Study Design




*Minimum of 13 weeks of treatment with study drug after the last patient is randomized

BID, twice daily; CAD, coronary artery disease; CRNM, clinically relevant non-major; ISTH, International Society of Thrombosis and Hemostasis; MI, myocardial infarction; PAD, peripheral artery disease

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# Milvexian Dosing Considerations

- The choice of milvexian† 100 mg twice daily dose for AF was informed by the totality of early phase data
  - Preclinical pharmacokinetic and pharmacodynamic data
  - Phase 2 AXIOMATIC-TKR results in venous thromboembolic disease (VTE)
    - ✓ Study population: patients undergoing knee arthroplasty (TKR)
    - ✓ Intervention: milvexian (25 mg, 50 mg, 100 mg, or 200 mg twice daily or 25 mg, 50 mg, or 200 mg once daily) or enoxaparin (40 mg once daily)
    - ✓ Primary outcome: composite of asymptomatic DVT, symptomatic VTE or death from any cause
  - Model-based meta-analysis (MBMA)
    - ✓ Incorporated phase 2 AXIOMATIC-TKR data into the network of previous RCTs.
    - ✓ Modeled relative efficacy of different doses of milvexian compared to apixaban 5 mg BID in preventing VTE in patients undergoing TKR or total hip arthroplasty.

- Evaluation of venous thromboembolism disease has been the traditional approach for dosing strategies in AF.

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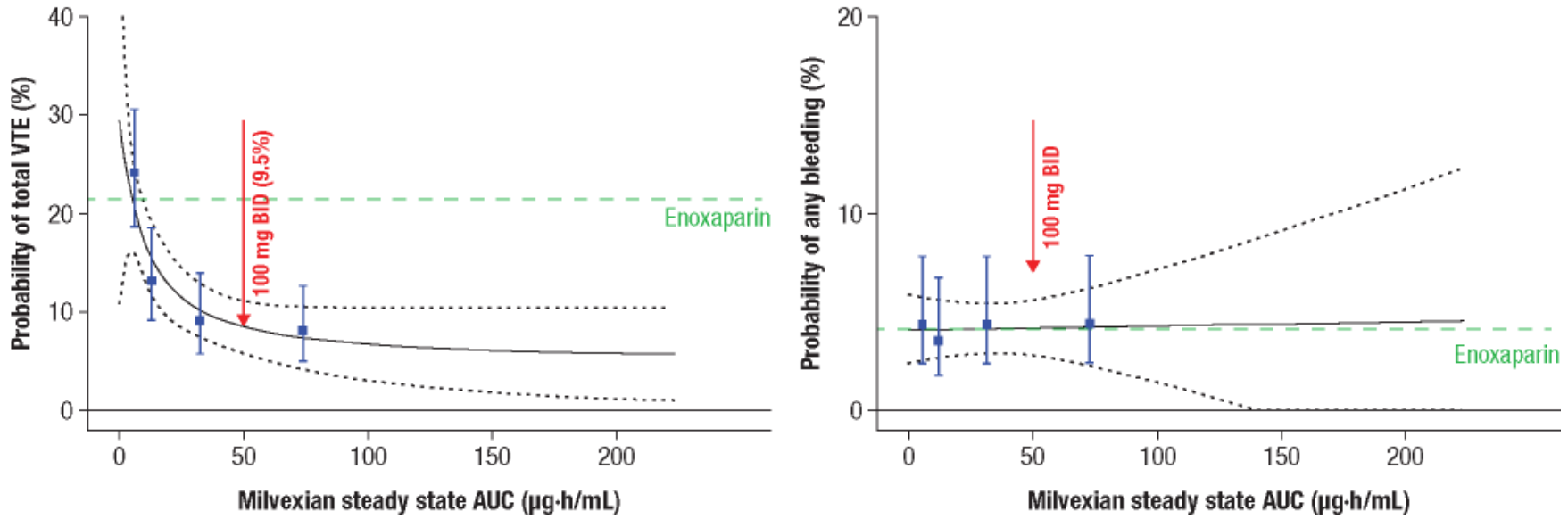
# Milvexian Dosing Rationale: Exposure-Response Relationships

## AXIOMATIC-TKR Phase 2: Exposure-response relationship between VTE or ar steady state exposure




Summary: Dose response relationship for efficacy was observed—total daily doses of ≥100 mg of milvexian provided significant reductions in total VTE events as compared with enoxaparin. Meanwhile, there was no dose-dependent increase in bleeding.

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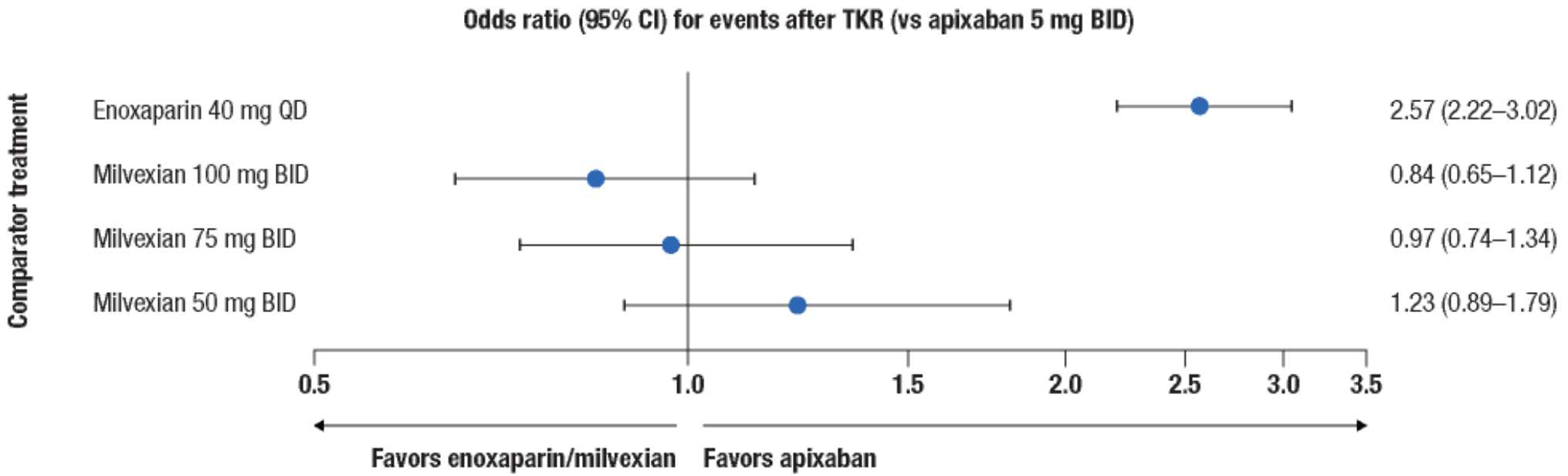
The information on this slide is being shared with you solely to help you better understand the rationale for 100 mg milvexian dose. This slide only describes results from the Ph2 AXIOMATIC-TKR study. No conclusion on the safety or efficacy of the 100 mg milvexian dose being evaluated in the Librexia AF study should be made based upon these data. These results do not constitute confirmatory clinical evidence supporting the efficacy of milvexian in preventing stroke and non-CNS systemic embolism in the AF population. Health authorities consider the results of many studies to understand if an investigational treatment is safe and effective for the use in which it is being studied.

# Milvexian Dosing Rationale: Model-Based Meta-Analysis Results

## VTE outcomes for milvexian versus apixaban 5 mg BID




BID, twice daily; CI, confidence interval; QD, once daily; TKR, total knee replacement; VTE, venous thromboembolism.

The information on this slide is being shared with you solely to help you better understand the rationale for 100 mg milvexian dose. This slide only describes results from a meta-analysis that incorporates phase 2 AXIOMATIC-TKR data into the network of previous RCTs on preventing VTE in patients undergoing TKR or total hip arthroplasty. No conclusion on the safety or efficacy of the 100 mg milvexian dose being evaluated in the Librexia AF study should be made based upon these data. These results do not constitute confirmatory clinical evidence supporting the efficacy of milvexian in preventing stroke and non-CNS systemic embolism in the AF population. Health authorities consider the results of many studies to understand if an investigational treatment is safe and effective for the use in which it is being studied.

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# Primary and Secondary Objectives

- **Primary Efficacy Objective**
  - To evaluate if milvexian is non-inferior to apixaban for the composite of stroke and systemic embolism (SE).

- **Secondary Objectives**
  - To evaluate if milvexian is superior to apixaban in reducing risk of the principal safety endpoint family:
    - ✓ ISTH major bleeding
    - ✓ Composite of ISTH major and CRNM bleeding
  - To evaluate if milvexian is superior to apixaban for:
    - ✓ The composite of CV death (CVD), MI, stroke, and non-CNS SE
    - ✓ CVD
    - ✓ The composite of All Cause Death (ACD), MI, stroke, and non-CNS SE
    - ✓ The composite of CVD, MI, stroke, acute limb ischemia (ALI), and urgent hospitalization for vascular cause of ischemic nature (including thrombotic events: DVT and PE)
      - ALI is defined as any unanticipated revascularization or amputation of ischemic limb.

*The safety and efficacy of the investigational compound have not been established*

# Inclusion Criteria

**Age:** ≥ 18 years of age

**Type of Participant and Disease Characteristics:**

- Medically stable and appropriate for chronic antithrombotic treatment
- Atrial fibrillation (AF) or flutter (Afl), paroxysmal or sustained; not reversible
  - AF or Afl must be documented by ECG evidence (eg, 12-lead ECG, rhythm strip, Holter, or pacemaker interrogation) within 1 year of randomization.
  - If electrical cardioversion or ablation is planned, there is a plan to treat the patient with anticoagulation for the duration of the trial.

+

Must satisfy one or both of the following categories of risk factors (A or B):

**A**

**Any ONE of the following**

Age ≥ 75
OR
Prior stroke

OR

**B**

**Any TWO of the following**

Age 65 to 74
Hypertension
Diabetes
Vascular disease (CAD, MI, PAD)
Congestive Heart Failure

# Exclusion Criteria

- 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
- Current 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 ULN
- Total bilirubin ≥ 1.5 x ULN 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 **next slide**
- 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

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# Prohibited Medications/Therapies

- Current or planned use of isoniazid.
- Aspirin > 100 mg/day > 7 days of consecutive use.
- Concomitant use of omeprazole or esomeprazole with clopidogrel is prohibited.
  - Other use of PPI is allowed and encouraged.
- Additional chronic anticoagulants (e.g., vitamin K antagonists, factor IIa or FXa inhibitors).
- The concomitant use of a combined P-gp and strong CYP3A4 inhibitor (e.g., 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 (e.g., carbamazepine, phenytoin, rifampin) within 7 days of receiving study intervention and during the study is prohibited.

# Recommendations for Study Drug 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

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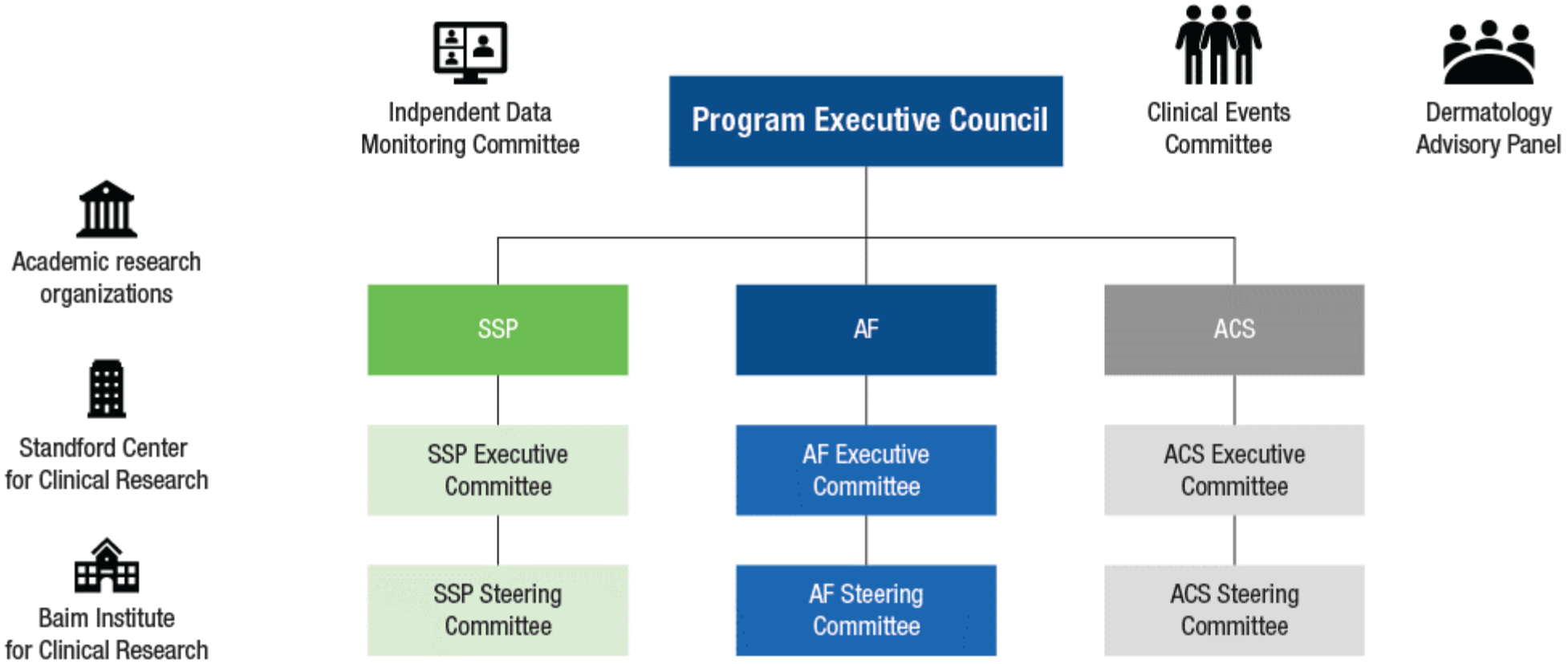
# Statistical Considerations

| Assumptions |
| --- |
| • Event-driven; variable treatment duration, at least minimum of exposure for 13 weeks (3 months)<br>• Non-inferiority margin: 1.37 (67% retention)<br>• HR = 1.00 for milvexian compared to apixaban<br><br>• Total study duration: ~ 4 years<br><br>**Sample Size: Approximately 20,000***<br>**Number of events:**<br>▪ **430 for ST/SE**<br>▪ **530 for ISTH major bleeding** |

* On the basis of estimated blinded event rates and in an effort to accrue the planned number of events, the sponsor in collaboration with the study's academic leadership adjusted the sample size from 15,500 to approximately 20,000 participants.

# Librexia Program Committees

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# Commitment to Diversity and Inclusion

1. Engaged participants are the key to a successful trial

2. Ensured protocol-required assessments were streamlined and accessible (option for virtual visits) to minimize burden on participants

3. 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

4. We are currently building programs to identify participants outside of traditional avenues of clinical trial recruitment

# Librexia AF Study Rationale and Design

Trial Designs

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

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