KARDIA-1 is a Phase 2 randomized, double-blind (DB), placebo-controlled, dose-ranging study to evaluate the efficacy and safety of zilebesiran in adults with mild-to-moderate hypertension.1

Study Objective1
To evaluate the efficacy and safety of zilebesiran in adults with mild-to-moderate hypertension.

Study Design1,3
• The global, multicenter trial will enroll adults (18 to 75 years) with untreated hypertension or on stable therapy with one or more antihypertensive medications (aHTN) of the following classes: an angiotensin converting enzyme inhibitor (ACEi), angiotensin II-receptor blocker (ARB), renin inhibitor, calcium channel blocker, thiazide diuretic and/or thiazide-like diuretic.
  o Prior to randomization, patients are required to discontinue prior antihypertensive medications (if taking) for a washout period of at least four weeks.
  o Patients should have a mean 24-hour systolic blood pressure (SBP) ≥135 mmHg and ≤160 mmHg by ambulatory blood pressure monitoring (ABPM) at least four weeks after washout of background antihypertensive medication.
  o Key exclusion criteria include:
    — Secondary hypertension or orthostatic hypotension
    — Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN)
    — Elevated potassium >5 mEq/L
    — Estimated glomerular filtration rate (eGFR) of ≤30 mL/min/1.73m²
    — Received an investigational agent within the last 30 days
    — Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus or newly diagnosed Type 2 diabetes mellitus
    — History of any cardiovascular event within six months prior to randomization
    — History of intolerance to subcutaneous injection(s)
• Study participants will be randomized to one of five treatment arms: 150 mg zilebesiran subcutaneously once every six months, 300 mg zilebesiran subcutaneously once every six months, 300 mg zilebesiran subcutaneously once every three months, 600 mg zilebesiran subcutaneously once every six months, or placebo during a 12-month DB period and DB extension period.
  o Patients randomized to receive placebo will be randomized to one of the four initial dose regimens of zilebesiran beginning at month six.
• The planned enrollment for this study is 375 patients and will be conducted at approximately 50 clinical study centers worldwide.

Continued on next page

KARDIA: Zilebesiran Phase 2 Clinical Development Overview

Zilebesiran is an investigational, subcutaneously administered RNA interference (RNAi) therapeutic targeting liver-expressed angiotensinogen (AGT) in development for the treatment of hypertension. As the source of all angiotensin peptides, including the potent vasoconstrictor angiotensin (Ang) II, AGT represents a genetically validated target for hypertension and plays a central role in its pathology.
Study Endpoints

• The primary endpoint is the change from baseline in SBP, assessed by ABPM, after three months of treatment.

• Key secondary and exploratory endpoints will evaluate additional measures of blood pressure reduction over time (including through six and 12 months), general clinical outcomes and safety.

KARDIA-2 is a Phase 2 randomized, DB, placebo-controlled study to evaluate the efficacy and safety of zilebesiran when used in combination with conventional antihypertensive medications.

Study Objective
To evaluate the efficacy and safety of zilebesiran as a concomitant therapy in adults whose blood pressure is not adequately controlled by standard of care antihypertensive medications.

Study Design
• The global, multicenter trial will enroll adults (18 to 75 years) with untreated hypertension or on stable therapy with up to two antihypertensive medications of the following classes: an ACEi, ARB, renin inhibitor, calcium channel blocker, thiazide diuretic and/or thiazide-like diuretic.
  o Patients should have a 24-hour mean SBP >130 mmHg and ≤160 mmHg by ABPM after at least four weeks of run-in on protocol-specified background antihypertensive medication.
  o Key exclusion criteria include:
    — Secondary hypertension or orthostatic hypotension
    — ALT or AST >2 times ULN
    — Total bilirubin >1.5 times ULN (patients with elevated total bilirubin that is secondary to documented Gilbert’s syndrome are eligible if the total bilirubin is <2 times ULN)
    — International normalization ratio (INR) >2.0 (patients on oral anticoagulant [e.g., warfarin] with an INR <3.5 will be allowed)
— Potassium < lower limit of normal range or > 5 mEq/L
— Sodium < lower limit of normal range
— eGFR of ≤ 30 mL/min/1.73m²
— Received an investigational agent within the last 30 days
— Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus or newly diagnosed Type 2 diabetes mellitus
— History of any cardiovascular event within six months prior to randomization
— History of intolerance to subcutaneous injection(s)

• Study participants will be randomized to run-in on one of the three protocol-specified background antihypertensive medications open-label for at least four weeks (olmesartan, amlodipine or indapamide). At the end of the run-in period, those with uncontrolled blood pressure (>130 mm Hg and ≤160 mm Hg) will be randomized 1:1 to receive zilebesiran or placebo for six months during the DB period.
  o After completion of the six-month DB period, patients may be eligible to participate in a separate zilebesiran open-label extension (OLE) study.
• The planned enrollment for this study is approximately 800 patients to be randomized into the run-in period, and eligible patients will be randomized into the DB period. The study will be conducted at approximately 80 clinical study centers worldwide.

Study Endpoints

• The primary endpoint is the change from baseline in 24-hour mean SBP, assessed by ABPM, after three months of treatment.
• Key secondary and exploratory endpoints will evaluate additional measures of blood pressure reduction over time (including through six months), general clinical outcomes and safety.

For more information on KARDIA-1 (NCT04936035) or KARDIA-2 (NCT05103332), please visit www.clinicaltrials.gov or contact media@alnylam.com.
The safety and efficacy of zilebesiran have not been evaluated by the U.S. Food and Drug Administration, European Medicines Agency or any other health authority.

© 2021 Alnylam Pharmaceuticals, Inc.  AGT-USA-00003 V2

3 Data on file.