

|| KARDIA: Zilebesiran Phase 2 Clinical Development Overview

Zilebesiran is an investigational, subcutaneously administered RNA interference (RNAi) therapeutic targeting hepatic synthesis of angiotensinogen (AGT) in development for the treatment of hypertension. As the source of all angiotensin peptides, AGT represents a genetically validated target for hypertension and plays a central role in its pathology.

KARDIA

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

Study Objective^{1,2}

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

Study Design^{1,2}

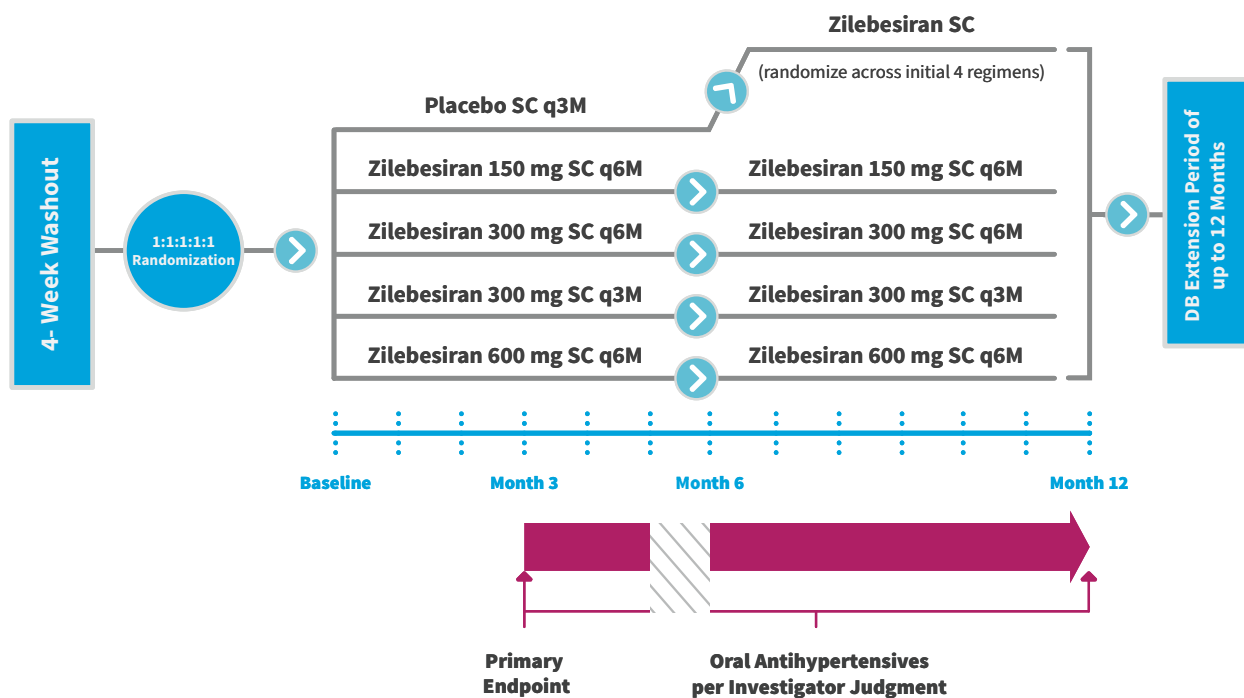
- The global, multicenter trial enrolled adults (18 to 75 years) with untreated hypertension or on stable therapy with up to two antihypertensive medications.
 - Prior to randomization, patients were required to discontinue prior antihypertensive medications (if taking) for a washout period of at least two to four weeks.
 - Patients had a daytime mean systolic blood pressure (SBP) ≥ 135 mmHg and ≤ 160 mmHg by ambulatory blood pressure monitoring (ABPM) after washout of background antihypertensive medication.
- Study participants were 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.
 - Patients randomized to receive placebo are randomized to one of the four initial dose regimens of zilebesiran beginning at Month 6.
 - At Month 12, patients entered a DB extension period.
- The study enrolled 394 patients representing a diverse patient population and is being conducted at 78 clinical study sites worldwide.



HYPERTENSION

is a leading cause of cardiovascular disease, including heart attack, stroke and chronic kidney disease, and carries a substantial risk of morbidity and mortality worldwide.³

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Study Endpoints²

- The primary endpoint is the change from baseline in 24-hour mean SBP, assessed by ABPM, after three months of treatment.
- Secondary endpoints include additional measures of blood pressure reduction (e.g., change from baseline at Month 3 and Month 6 in office SBP, change from baseline at Month 6 in 24-hour mean SBP assessed by ABPM) and change in daytime average and night-time average blood pressure.

KARDIA₂

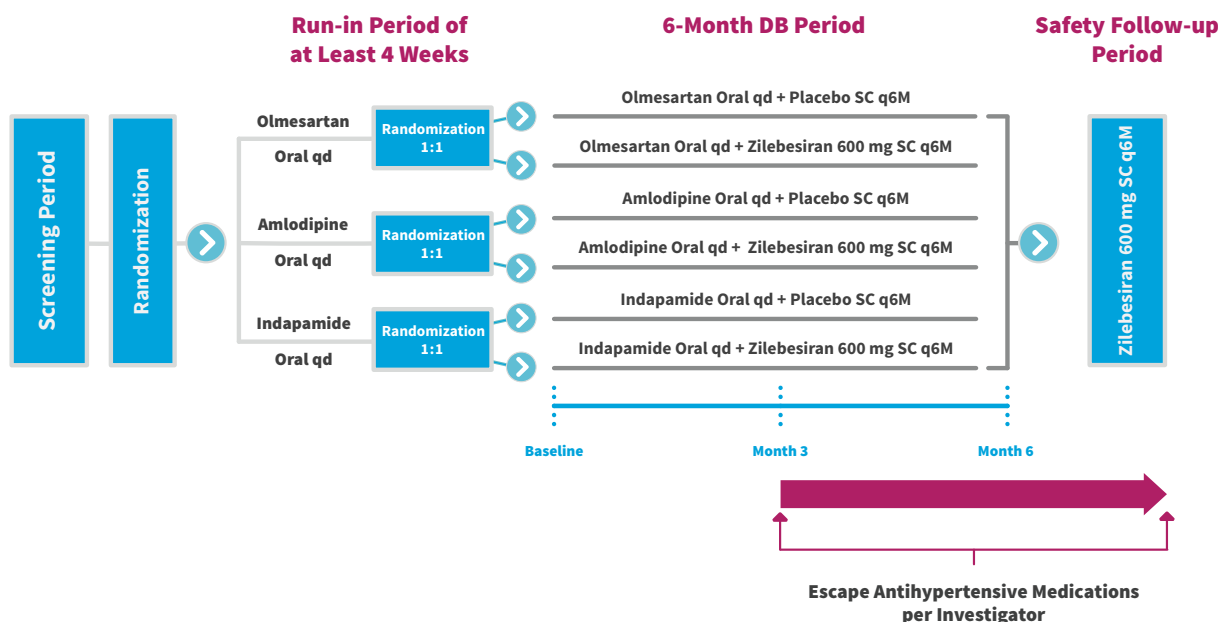
KARDIA-2 is a Phase 2 randomized, DB, placebo-controlled study to evaluate the efficacy and safety of zilebesiran when used in combination with one of three standard classes of antihypertensive medications in adults with mild-to-moderate hypertension.⁴

Study Objective⁴

To evaluate the efficacy and safety of zilebesiran in combination with one of three standard classes of antihypertensive medications in adults whose blood pressure is not adequately controlled on standard of care antihypertensive therapies.

Study Design^{4,5}

- The global, multicenter trial enrolled adults (18 to 75 years) with untreated hypertension or on stable therapy with up to two antihypertensive medications.
 - 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.
- Study participants were 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 mmHg and ≤160 mmHg) were randomized 1:1 to receive a single dose of 600 mg zilebesiran or placebo for six months during the DB period.
 - After completion of the six-month DB period, patients entered a safety follow-up period.
- The study enrolled patients randomized into the run-in period, and 672 eligible patients were randomized into the DB period. The study is being conducted at 102 clinical study sites worldwide.



Study Endpoints⁴

- The primary endpoint is the change from baseline in 24-hour mean SBP, assessed by ABPM, after three months of treatment.
- Secondary endpoints include additional measures of blood pressure reduction up to six months (e.g., change from baseline at Month 3 and Month 6 in office SBP, change from baseline at Month 6 in 24-hour mean SBP), time-adjusted change in blood pressure, and change in daytime average and night-time average blood pressure.

KARDIA₃

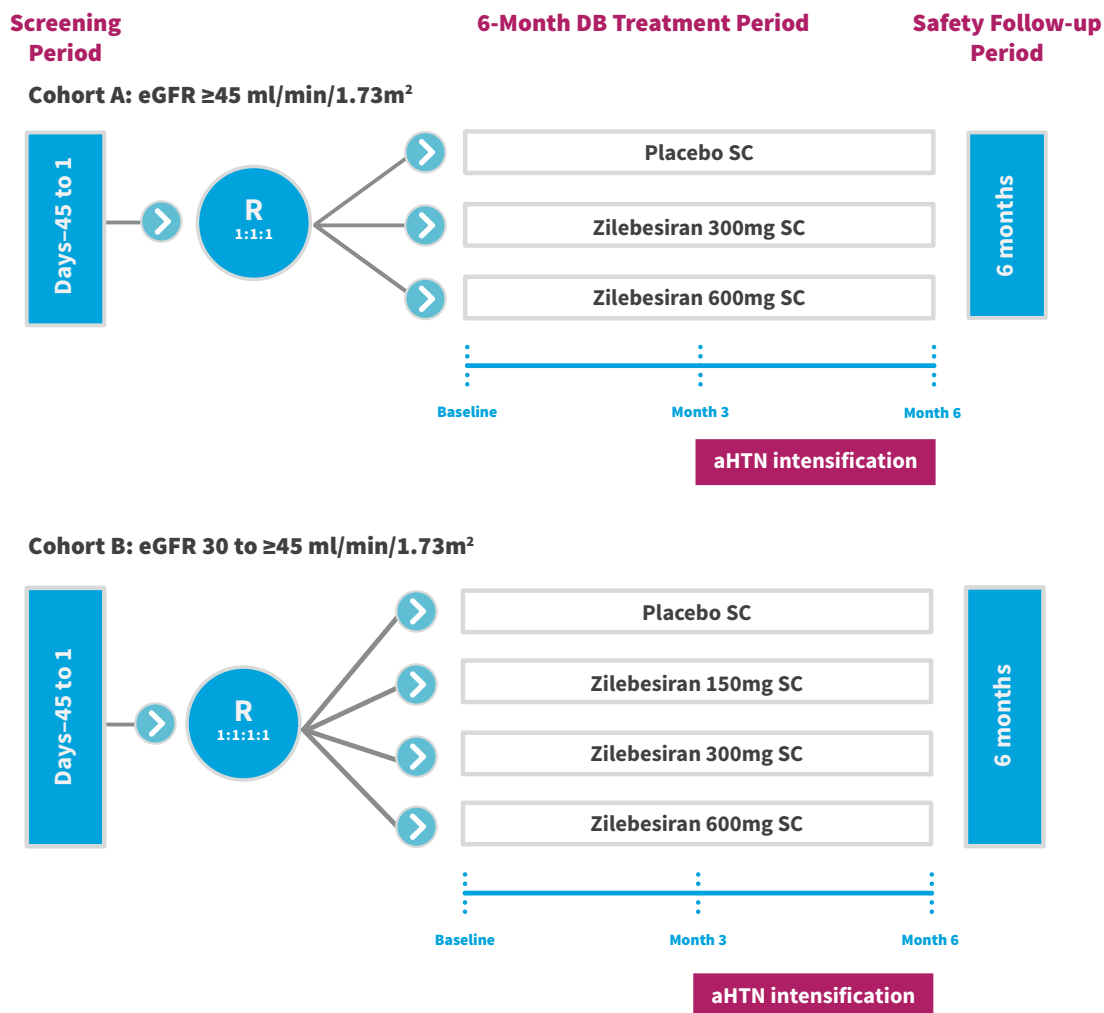
KARDIA-3 is a Phase 2 randomized, DB, placebo-controlled, two-cohort study to evaluate the efficacy and safety of zilebesiran in combination with two to four antihypertensive medications in adult patients with uncontrolled hypertension at high CV risk.⁶

Study Objective⁶

To evaluate the efficacy and safety of zilebesiran as an add-on therapy with two to four antihypertensive medications in adults with high CV risk whose blood pressure is not adequately controlled by standard of care antihypertensive therapies.

Study Design^{5,6}

- The global, multicenter trial will enroll adults (18 years and older) with a history of CV disease, high CV risk, or eGFR ≥ 30 to < 60 mL/min/1.73m², who are on stable therapy with two to four classes of antihypertensive medications.
 - Patients must have a mean seated office SBP ≥ 140 mmHg and ≤ 170 mmHg and 24-hour mean SBP ≥ 130 mmHg and ≤ 170 mmHg by ABPM.
 - All patients must be on stable doses of two to four background antihypertensive medications for at least 30 days prior to screening and plan to remain on stable doses of these medications during screening and through the 6-month DB treatment period.
- Patients with eGFR ≥ 45 mL/min/1.73m² will be enrolled in Cohort A, and patients with eGFR 30 to < 45 mL/min/1.73m² will be enrolled in Cohort B to gain additional safety and efficacy data in patients with advanced chronic kidney disease.
 - In Cohort A, patients will be randomized to receive 300 mg or 600 mg zilebesiran or placebo.
 - In Cohort B, patients will be randomized to receive 150 mg, 300 mg or 600 mg zilebesiran, or placebo.
- The planned enrollment for this study is approximately 390 patients, with approximately 270 in Cohort A and 120 in Cohort B.



Study Endpoints⁶

- The primary endpoint is the change from baseline in mean seated office SBP after three months of treatment.
- Secondary endpoints include additional measures of blood pressure reduction up to six months (e.g., change from baseline at Month 6 in mean seated office SBP, change from baseline at Month 3 and Month 6 in 24-hour mean SBP assessed by ABPM) and change in daytime average and night-time average blood pressure.

For more information on KARDIA-1 (NCT04936035), KARDIA-2 (NCT05103332) or KARDIA-3 (NCT06272487), 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. Zilebesiran is being co-developed and co-commercialized by Alnylam and Roche.

¹ Bakris GL, et al. *JAMA*. 2024;331(9):740-749.

² Alnylam Pharmaceuticals. A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients With Mild-To-Moderate Hypertension (KARDIA-1). Available from: <https://clinicaltrials.gov/ct2/show/NCT04936035>. Accessed March 2024.

³ Mills, K. et al. *Nat Rev Nephrol*. 2020;16:223-237.

⁴ Alnylam Pharmaceuticals. Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2). Available from: <https://clinicaltrials.gov/ct2/show/NCT05103332>. Accessed March 2024.

⁵ Data on file.

⁶ Alnylam Pharmaceuticals. Zilebesiran as Add-on Therapy in Patients With High Cardiovascular Risk and Hypertension Not Adequately Controlled by Standard of Care Antihypertensive Medications (KARDIA-3) (KARDIA-3). Available from: <https://clinicaltrials.gov/ct2/show/NCT06272487>. Accessed March 2024.