Zilebesiran: KARDIA-3 Study

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The safety and efficacy of zilebesiran are currently being investigated in clinical studies and has not been evaluated by the FDA or any health authority.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- Zilebesiran is an investigational subcutaneously administered RNAi therapeutic that targets the synthesis of hepatic AGT, leading to a reduction in blood pressure, and is currently being studied for the treatment of hypertension in adults.[1] Zilebesiran utilizes GalNAc conjugation, which enables subcutaneous dosing for liver-specific silencing of AGT mRNA.[2]
- The phase 2 study, KARDIA-3, is an ongoing study to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients with established CV disease or high CV risk, and hypertension.[1]

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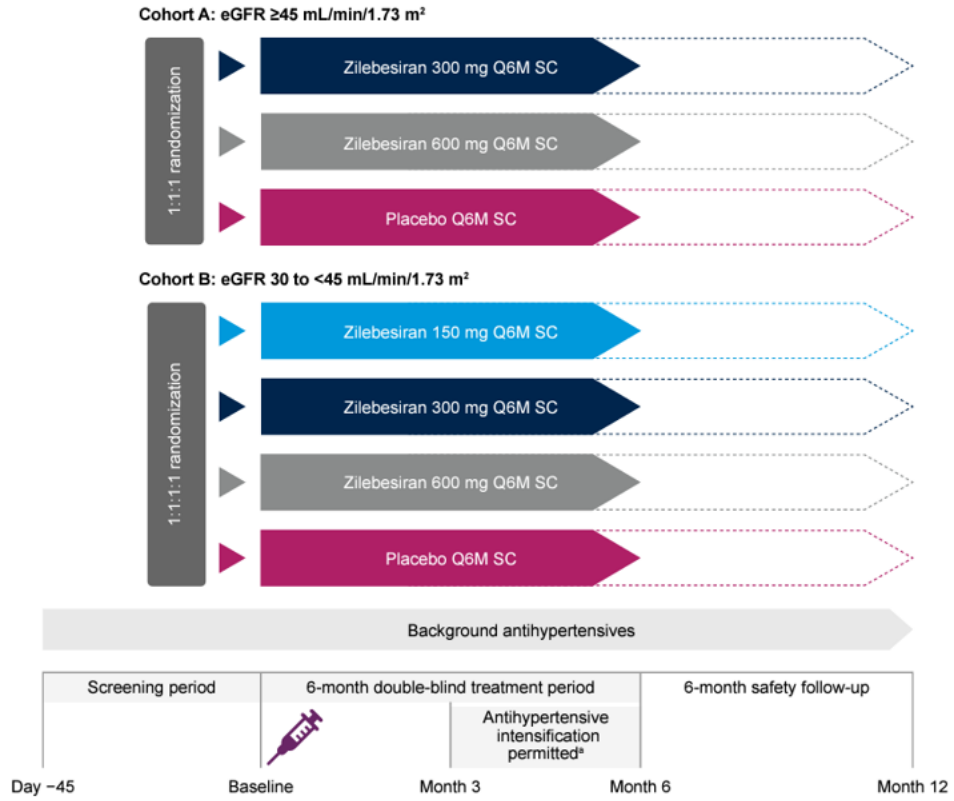
STUDY DESIGN

The KARDIA-3 (NCT06272487) study is an ongoing, phase 2, randomized, double-blind, placebo-controlled, dose-ranging multicenter study to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients with established CV disease or high CV risk with or without CKD, and with hypertension that is not adequately controlled with 2 to 4 standard-of-care antihypertensives.[1]

Study participants will be assigned to 1 of 2 cohorts (Cohort A or Cohort B). In Cohort A, approximately 270 participants with an eGFR ≥45 mL/min/1.73 m^2 will be randomized (1:1:1) to receive placebo or a single subcutaneous injection of zilebesiran 300 or 600 mg (~90 participants per arm). In Cohort B, up to 120 participants with an eGFR 30 to <45 mL/min/1.73 m^2 will be randomized (1:1:1:1) to receive placebo or a single subcutaneous injection of zilebesiran 150, 300, or 600 mg (≤30 participants per arm) (**Figure 1**). Cohort B is included in this study to gain additional safety and efficacy data in patients with advanced CKD.[1]

Figure 1. KARDIA-3 Study Design.[1]



[a]Antihypertensives may be intensified (defined as an increase in the dose or start of any antihypertensive) in line with investigator judgment for elevated blood pressure.
Abbreviations: eGFR = estimated glomerular filtration rate; Q6M = every 6 months; SC = subcutaneous.
From: Havasi et al.[1]

The primary endpoint of the study is to evaluate the change from baseline in mean seated office SBP at Month 3.[1]

Key secondary endpoints include[1]:

- Change from baseline in mean seated office SBP at Month 6
- Change from baseline in mean seated office DBP at Month 3 and Month 6
- Change from baseline in 24-hour, daytime, and nighttime mean ambulatory SBP and DBP at Month 3 and Month 6
- Proportion of patients with mean seated office SBP <140 mmHg and/or reduction ≥10 mmHg without intensification of antihypertensive regimen at Month 6
- Proportion of patients with 24-hour mean ambulatory SBP <130 mmHg and/or reduction ≥10 mmHg without intensification of antihypertensive regimen at Month 6
- Change from baseline in serum AGT levels through Month 6

Key exploratory endpoints include[1]:

- Change from baseline in cardiac biomarkers (hscTnT, hsCRP, NT-proBNP) through Month 6
- Change from baseline in renal biomarkers (UACR) through Month 6

Safety will be assessed by the frequency of AEs throughout the 6-month double blind period and in the 6-month safety follow-up period.[1]

Key study inclusion criteria are[1]:

- Adult patients with established CV disease or high CV risk (ASCVD score >15%) with or without advanced CKD (Stage 3B)
- Seated automated mean office SBP 140–170 mmHg at screening
- 24-hour mean ambulatory SBP 130–170 mmHg before randomization
- Must be on stable therapy with 2 to 4 classes of antihypertensive medications

Key study exclusion criteria are[1]:

- Secondary hypertension
- Orthostatic hypertension
- Proteinuria >3 g/day or UACR >2 g/g
- Serum potassium >4.8 mEq/L

The trial is listed as recruiting as of November 26, 2024.[3]

ABBREVIATIONS

AE = adverse event; AGT = angiotensinogen; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; GalNAc = N-acetyl galactosamine; hsCRP = high-sensitivity C-reactive protein; hscTnT = high-sensitivity cardiac troponin T; mRNA = messenger RNA; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; Q6M = every 6 months; RNAi = RNA interference; SBP = systolic blood pressure; SC = subcutaneous; UACR = urine albumin-to-creatinine ratio.

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REFERENCES

1. Havasi A, Pagidipati N, Bakris GL, et al. KARDIA-3 study design: Zilebesiran as add-on therapy in patients with high cardiovascular risk and hypertension inadequately controlled by standard of care antihypertensives. Presented at: European Meeting on Hypertension and Cardiovascular Protection (ESH); May 31-June 3, 2024; Berlin, Germany.
2. Bakris GL, Saxena M, Gupta A, et al. RNA interference with zilebesiran for mild to moderate hypertension: The KARDIA-1 randomized clinical trial. *JAMA*. 2024;331(9):740-749. doi:10.1001/jama.2024.0728
3. 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). Available from: https://www.clinicaltrials.gov/study/NCT06272487. Accessed November 22, 2024.