Zilebesiran: Phase 2 Studies

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The safety and efficacy of zilebesiran are currently being investigated in clinical studies and have not been evaluated by the US Food and Drug Administration 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]
- KARDIA-1 was a phase 2 study designed to evaluate the efficacy and safety of zilebesiran as a monotherapy in patients with mild-to-moderate hypertension.[1]
- KARDIA-2 was a phase 2 study designed to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients with hypertension not adequately controlled by a standard-of-care antihypertensive medication.[3]
- KARDIA-3 is an ongoing study to evaluate the efficacy and safety of zilebesiran as an add-on therapy in combination with standard of care treatment for hypertension in patients with established CV disease or high-risk CV risk, and uncontrolled hypertension.[4]

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KARDIA-1

The KARDIA-1 study (NCT04936035) was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging multicenter study to evaluate the efficacy and safety of zilebesiran as monotherapy in patients aged 18 to 75 years with mild-to-moderate hypertension (N=394). Patients included in the study had a daytime mean SBP ≥135 mmHg and ≤160 mmHg (evaluated through ABPM) without antihypertensive medication.[1]

Study participants were randomized 1:1:1:1 to receive subcutaneous injections of placebo Q3M or zilebesiran 150 mg Q6M, 300 mg Q6M, 300 mg Q3M, or 600 mg Q6M for the first 6 months of the 12-month double-blind treatment period. Patients randomized to placebo were re-randomized at Month 6 to 1 of the 4 initial dosing regimens until the end of the 12-month double-blind treatment period. Patients randomized to zilebesiran remained on their originally assigned treatment regimen throughout the study.[1,5]

Key study exclusion criteria were[1]:

- Secondary hypertension
- Orthostatic hypertension
- Serum potassium >5 mEq/L
- eGFR ≤30 mL/min/1.73m^2

The primary endpoint of the study was to evaluate the change from baseline in 24-hour mean ambulatory SBP at Month 3.[1]

Key secondary endpoints include:[1]

- Change from baseline in 24-hour mean ambulatory SBP at Month 6
- Change from baseline in mean sitting office SBP at Month 3
- Change from baseline in mean sitting office SBP at Month 6
- Proportion of patients with 24-hour mean ambulatory SBP <130 mmHg and/or reduction of ≥20 mmHg without additional antihypertensive medications at Month 6

KARDIA-2

The KARDIA-2 study (NCT05103332) was a phase 2, randomized, double-blind, placebo-controlled, multi-center study designed to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients aged 18 to 75 years with hypertension that was not adequately controlled by a standard-of-care antihypertensive medication. Participants received a single subcutaneous injection of either zilebesiran 600 mg or placebo as an add-on treatment to the following antihypertensive agents: indapamide (diuretic) 2.5 mg daily, amlodipine (CCB) 5 mg daily, or olmesartan (ARB) 40 mg daily (20 mg daily for patients with a CrCl ≤60 mL/min at screening enrolled outside of the US, consistent with local labeling) for the 6 month double-blind period. In the OLE, participants who were randomized to placebo received zilebesiran once every 6 months; participants who were randomized to zilebesiran remained on their originally assigned treatment regimen.[3,6]

Key study inclusion criteria were[3]:

- An office SBP at screening ≥155 mmHg and ≤180 mmHg for patients with untreated hypertension
- An office SBP at screening ≥145 mmHg and ≤180 mmHg for patients on antihypertensive medications
- 24-hour mean SBP >130 mmHg and ≤160 mmHg by ABPM after at least 4 weeks of run-in on protocol-specified background antihypertensive medication

Key study exclusion criteria were[6]:

- Secondary hypertension
- Orthostatic hypertension
- Serum potassium >5 mEq/L
- eGFR <30 mL/min/1.73m^2

The primary endpoint of the study was to evaluate the change from baseline in 24-hour mean ambulatory SBP at Month 3.[3]

Key secondary endpoints include[3,6]:

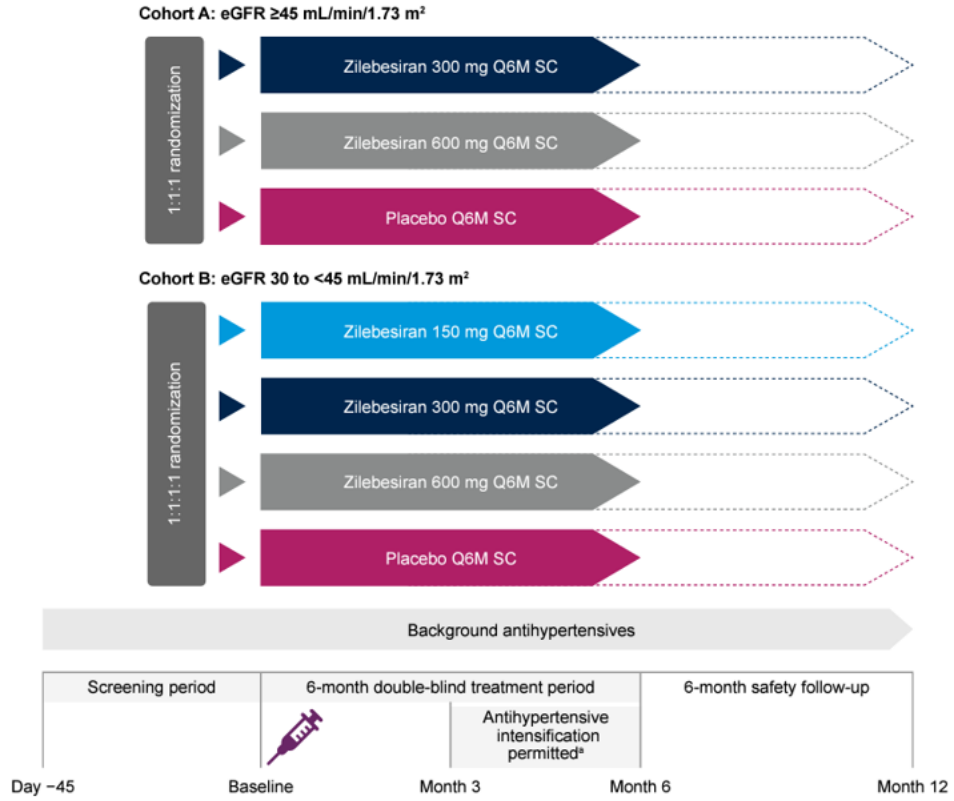
- Change from baseline in serum AGT through Month 6
- Change from baseline in office SBP at Month 3
- Time-adjusted change from baseline in 24-hour mean ambulatory SBP at Month 6
- Time-adjusted change from baseline in office SBP at Month 6
- Proportion of patients with 24-hour mean ambulatory SBP <130 mmHg and/or a reduction from baseline ≥20 mmHg without rescue antihypertensive medication at Month 6

KARDIA-3

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. 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.[4]

Figure 1. KARDIA-3 Study Design.[4]



[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.[4]

Key study inclusion criteria are[4]:

- 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[4]:

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

The primary endpoint of the study is to evaluate the change from baseline in mean seated office SBP at Month 3.[4]

Key secondary endpoints include[4]:

- 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[4]:

- 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.[4]

The trial is listed as recruiting as of January 22, 2025.[7]

ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring; AE = adverse event; AGT = angiotensinogen; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CCB = calcium channel blocker; 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; OLE = open-label extension; Q6M = every 6 months; RNAi = RNA interference; SBP = systolic blood pressure; SC = subcutaneous; UACR = urine albumin-to-creatinine ratio.

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