Zilebesiran: Phase 2 Studies

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

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 was a phase 2 study designed to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients with uncontrolled hypertension and established CV disease or high CV risk, with or without advanced CKD.[4,5]

INDEX

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).[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 for an extension phase of the study.[1,6]

Key study inclusion criteria were[1]:

- Untreated or treated hypertension with a stable regimen of up to 2 antihypertensive medications
- Daytime mean SBP ≥135 mmHg and ≤160 mmHg (evaluated through ABPM) following washout of background antihypertensive medication

Key study exclusion criteria were[1]:

- Secondary hypertension
- Orthostatic hypertension
- Serum potassium >5 mEq/L (5 mmol/L)
- eGFR ≤30 mL/min/1.73m^2
- Type 1 diabetes, poorly controlled type 2 diabetics (HbA_{1C} >9.0%), or laboratory evidence of diabetes during screening (HbA_{1C} ≥7.0%) without known diagnosis

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 included[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, multicenter 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.[3]

The study included an open-label run-in period of at least 4 weeks and a 6-month double-blind treatment period. Following discontinuation of antihypertensive therapies, eligible patients with a screening eGFR <45 mL/min/1.73 m^2 or UACR ≥300 mg/g were preferentially assigned to the olmesartan run-in cohort. The remaining patients were randomized in a 4:7:10 ratio to receive open-label treatment of 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 creatinine clearance ≤60 mL/min at screening enrolled outside of the US, consistent with local labeling). After the run-in period, patients in each cohort with 24-hour mean ambulatory SBP between 130 and 160 mmHg and at least 80% adherence to the protocol-specified background therapy were randomized 1:1 to receive a single subcutaneous injection of either zilebesiran 600 mg or placebo as an add-on treatment during the 6-month double-blind period.[3]

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[3]:

- Secondary hypertension

- Orthostatic hypertension
- Serum potassium >5 mmol/L
- eGFR <30 mL/min/1.73m^2
- Symptomatic heart failure
- Type 1 diabetes, poorly controlled type 2 diabetes, or newly diagnosed diabetes

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 assessed hierarchically in the following order included[3]:
- Between-group difference in 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 was a 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.[4,5]

Study participants were assigned to 1 of 2 cohorts (Cohort A or Cohort B). In Cohort A, participants with an eGFR ≥45 mL/min/1.73 m^2 were randomized (1:1:1) to receive placebo (n=88) or a single subcutaneous injection of zilebesiran 300 (n=91) or 600 mg (n=91). In Cohort B, participants with an eGFR 30 to <45 mL/min/1.73 m^2 were randomized (1:1:1:1) to receive placebo (n=26) or a single subcutaneous injection of zilebesiran 150 (n=25), 300 (n=26), or 600 mg (n=26). A key aim of the KARDIA-3 study was to inform the design of a phase 3 CV outcomes study in this population.[4,5]

Key study inclusion criteria were[4,5]:
- Adult patients with established CV disease or high CV risk (ASCVD score >15%)
- Uncontrolled hypertension (defined as seated automated mean office SBP 140–170 mmHg at screening and 24-hour mean ambulatory SBP 130–170 mmHg before randomization)
- Already prescribed 2 to 4 classes of antihypertensive medications (including a diuretic or CCB)
- Cohort B: eGFR between 30-45 mL/min/1.73m^2

Key study exclusion criteria were[7]:
- 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 was to evaluate the change from baseline in mean seated office SBP at Month 3.[4]

Key secondary endpoints included[4]:

- Change from baseline in mean seated office SBP at Month 6
- Change from baseline in 24-hour mean ambulatory SBP at Months 3 and 6
- Change from baseline in mean daytime and nighttime ambulatory SBP at Month 6

Key exploratory endpoints include[4]:

- Hourly mean daytime and nighttime ambulatory SBP at Month 6

Safety was assessed by the frequency of AEs through Month 6. Cohorts A and B were analyzed separately. Cohort B was not powered to evaluate efficacy and was designed to assess the safety of zilebesiran in patients with an eGFR of 30 to <45 mL/min/1.73 m^2.[5]

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; HbA_{1c} = hemoglobin A1c; mRNA = messenger RNA; Q3M = every 3 months; Q6M = every 6 months; RNAi = RNA interference; SBP = systolic blood pressure; SC = subcutaneous; UACR = urine albumin-to-creatinine ratio.

Updated 10 March 2026

REFERENCES

1. 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
2. Desai AS, Webb DJ, Taubel J, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. *N Engl J Med*. 2023;389(3):228-238. doi:10.1056/NEJMoa2208391
3. Desai AS, Karns AD, Badariene J, et al. Add-on treatment with zilebesiran for inadequately controlled hypertension: the KARDIA-2 randomized clinical trial. *JAMA*. 2025;334(1):46-55. doi:10.1001/jama.2025.6681
4. Pagidipati N, Weber M, Saxena M, et al. KARDIA-3: Zilebesiran as add-on therapy in adults with hypertension who have established cardiovascular disease or are at high cardiovascular risk. Presented at: European Society of Cardiology (ESC) Congress; August 29-September 1, 2025; Madrid, Spain.
5. Pagidipati N, Weber M, Saxena M, et al. KARDIA-3: A randomized trial of zilebesiran versus placebo on top of standard care for patients with hypertension and established cardiovascular disease or high cardiovascular risk with or without chronic kidney disease. Presented at: American Heart Association (AHA) Congress; November 7-10, 2025; New Orleans, LA, USA.
6. Protocol for: 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
7. 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.