

Zilebesiran: Phase 2 KARDIA Pooled Safety

The following information is provided in response to your unsolicited inquiry. It is intended 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 Federal 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](https://www.alnylam.com/US/medical-affairs).

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 to reduce CV risk in adult patients with hypertension.¹ Zilebesiran utilizes GalNAc conjugation, which enables subcutaneous dosing for liver-specific silencing of AGT mRNA.²
- The phase 2 KARDIA-1, KARDIA-2, and KARDIA-3 studies were conducted to assess safety, efficacy, and optimal dosing of zilebesiran monotherapy or as add-on therapy in adults with hypertension with low or high CV risk.³⁻⁶
- In a pooled analysis of adverse events in the phase 2 KARDIA studies⁷:
 - Zilebesiran was associated with low rates of hypotension, hyperkalemia, and eGFR decline; most AEs were mild to moderate in severity, resolved without intervention, and laboratory abnormalities were typically transient.
 - Patients receiving zilebesiran concomitantly with RAASi had similar rates of hyperkalemia and eGFR decline as those in the overall phase 2 population.

INDEX

[Phase 2 KARDIA Studies](#) – [Phase 2 Pooled Safety Analysis](#) – [Abbreviations](#) – [References](#)

PHASE 2 KARDIA STUDIES

KARDIA-1

The KARDIA-1 study was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study evaluating the efficacy and safety of zilebesiran as monotherapy in adults with mild-to-moderate hypertension. Three hundred and ninety-four study participants were randomized 1:1:1:1 to receive subcutaneous administration of either zilebesiran (150 mg q6m, 300 mg q6m, 300 mg q3m, or 600 mg q6m) or placebo. The primary endpoint was the change from baseline in 24-hour mean ambulatory SBP at 3 months.³

KARDIA-2

The KARDIA-2 study was a phase 2, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of zilebesiran as an add-on therapy in adults with hypertension that was not adequately controlled by a standard-of-care (SOC) antihypertensive medication (e.g.

indapamide, amlodipine, or olmesartan). Six hundred and sixty-three patients were randomized 1:1 in each of the three SOC arms to receive a single subcutaneous injection of either zilebesiran 600 mg or placebo as an add-on treatment. The primary endpoint was the difference in the change from baseline in 24-hour mean ambulatory SBP at 3 months.⁴

KARDIA-3

The KARDIA-3 study was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study evaluating the efficacy, safety, and optimal dosing of zilebesiran as an add-on therapy in patients with uncontrolled hypertension and cardiovascular disease or high CV risk, with eGFR ≥ 45 mL/min/1.73 m² (Cohort A) or with eGFR 30-44 mL/min/1.73 m² (Cohort B). There were 375 patients in both cohorts. In Cohort A, patients were randomized (1:1:1) to receive a single subcutaneous injection of zilebesiran 300 mg or 600 mg or placebo. In Cohort B, patients were randomized (1:1:1:1) to receive a single subcutaneous injection of zilebesiran 150 mg, 300 mg, or 600 mg or placebo. Cohort B was not powered to evaluate efficacy and results are descriptive only. The primary endpoint of the study was the difference from baseline in mean office SBP at 3 months. A key aim of the KARDIA-3 study was to inform the design of a phase 3 CV outcomes study in this population.^{5,6}

PHASE 2 KARDIA POOLED SAFETY ANALYSIS

A pooled analysis of adverse events from the KARDIA studies was conducted to provide a comprehensive safety summary of the phase 2 zilebesiran clinical studies. AEs in patients from KARDIA-1 and KARDIA-2 (hypertension with low-CV risk), and AEs from Cohorts A & B of KARDIA-3 (hypertension with high-CV risk) were analyzed separately up to 6 months. A subgroup analysis was conducted to assess the safety of combining zilebesiran with background RAASi in patients from KARDIA-2 and KARDIA-3. Baseline demographics and patient characteristics are provided in **Table 1**.⁷

Table 1. Baseline Demographics and Characteristics.⁷

Parameter	KARDIA-1 and 2		KARDIA-3 (Cohorts A & B)	
	Placebo N=404	Zilebesiran N=631	Placebo N=115	Zilebesiran N=258
Age, years, mean (SD)	58.2 (10.5)	57.6 (10.4)	67.3 (8.9)	67.5 (8.9)
Age ≥ 65 years, n (%)	130 (32.2)	187 (29.6)	76 (66.1)	165 (64.0)
Female, n (%)	176 (43.6)	273 (43.3)	42 (36.5)	124 (48.1)
Black, n (%)	111 (27.5)	169 (26.8)	24 (20.9)	63 (24.4)
Hispanic or Latino, n (%)	111 (27.5)	188 (29.8)	63 (54.8)	129 (50.0)
Diabetes mellitus, n (%)	82 (20.3)	133 (21.1)	67 (58.3)	134 (51.9)
Baseline eGFR, mL/min/1.73 m ² , median (IQR)	79.1 (22.2)	80.1 (20.6)	80.9 (40.9)	71.3 (44.6)
Baseline eGFR < 60 mL/min/1.73 m ² , n (%)	43 (10.6)	61 (9.7)	35 (30.4)	93 (36.0)
Serum potassium, mmol/L, median (IQR)	4.25 (0.50)	4.30 (0.50)	4.30 (0.60)	4.30 (0.60)
Office systolic BP, mmHg, mean (SD)	144.7 (12.6) ^a	142.8 (11.6) ^b	144.6 (12.3)	144.5 (13.8)
24-hour mean ambulatory systolic BP, mmHg, mean (SD)	143.0 (8.2)	142.7 (8.3)	143.7 (9.6)	142.1 (8.4) ^c

^aPatients with available data n=401.

^bPatients with available data n=630.

^cPatients with available data n=256.

Treatment-Emergent Adverse Events

Most AEs were mild or moderate in severity, transient, and resolved without intervention. There were 2 deaths during the double-blind period: cardiopulmonary arrest on day 5 after zilebesiran in KARDIA-1, and cardiac arrest on day 85 after zilebesiran in KARDIA-3. Deaths were not considered treatment-related by the Investigator (**Table 2**).⁷

Table 2. Proportion of Patients (%) With TEAEs.⁷

Parameter	KARDIA-1 and 2		KARDIA-3 (Cohorts A & B)	
	Placebo N=404	Zilebesiran N=631	Placebo N=115	Zilebesiran N=258
At least 1 AE	46.3	57.2	46.1	52.3
AE leading to study drug discontinuation ^a	2.0	2.1	-	-
Any SAE related to study drug	0.2	0.2	0	0.8
Death	0	0.2	0	0.4

Abbreviations: AE = adverse event; OLE = open-label extension; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

^aAEs were only reportable for patients in KARDIA-1 and KARDIA-2, where an OLE was planned.

Hypotension

The majority of hypotension AEs and potentially related AEs were mild or moderate in severity, transient, and resolved without intervention. Zilebesiran-treated patients requiring interventions mainly received increased fluid or sodium intake or adjustments of background antihypertensive medications (**Table 3**).⁷

Table 3. Proportion of Patients (%) With Hypotension and Related AEs.⁷

Parameter	KARDIA-1 and 2		KARDIA-3 (Cohorts A & B)	
	Placebo N=404	Zilebesiran N=631	Placebo N=115	Zilebesiran N=258
At least 1 hypotension AE	2.0	3.8	2.6	2.7
Dizziness	2.2	4.4	0.9	1.2
Syncope	0	0.3	0	0.8

Abbreviations: AE = adverse event.

Hyperkalemia

All hyperkalemia events were mild or moderate in severity and nonserious; the majority resolved without intervention. Seven patients received potassium binders (placebo n=2, zilebesiran n=5), 5 of whom had baseline eGFR <60 mL/min/1.73 m² (**Table 4**).⁷

Table 4. Proportion of Patients (%) With Hyperkalemia.⁷

Parameter	KARDIA-1 and 2		KARDIA-3 (Cohorts A & B)	
	Placebo N=404	Zilebesiran N=631	Placebo N=115	Zilebesiran N=258
Potassium > 5.5 mmol/L	1.0	5.7	6.1	8.5
Confirmed by subsequent measurement ^a	0	1.1	0.9	2.7
Potassium > 6.0 mmol/L	0.2	1.3	0.9	0.8
Confirmed by subsequent measurement ^a	0	0	0	0

^aAssessment remained in defined range on the next available measurement.

Renal AEs

The majority of renal AEs were mild or moderate in severity, nonserious, and resolved without intervention (**Table 5**).⁷

Table 5. Proportion of Patients (%) With Renal AEs.⁷

Parameter	KARDIA-1 and 2		KARDIA-3 (Cohorts A & B)	
	Placebo N=404	Zilebesiran N=631	Placebo N=115	Zilebesiran N=258
eGFR decline $\geq 30\%$ and eGFR < 60 mL/min/1.73 m ²	2.0	4.6	3.5	7.8
Confirmed by subsequent measurement ^a	0.7	0.6	0.9	2.3

Abbreviations: AE = adverse event; eGFR = estimated glomerular filtration rate.

^aAssessment remained in defined range on the next available measurement.

ISRs and Hepatic AEs

ISRs were TEAEs, mostly transient, mild or moderate in severity, and nonserious with no associated systemic AEs. There were two patients that had ISRs that led to study drug discontinuation. No patients met biochemical Hy's law criteria. Most hepatic AEs were mild or moderate and resolved while receiving study drug. No hepatic AEs were serious or accompanied by bilirubin increase (**Table 6**).⁷

Table 6. Proportion of Patients (%) With ISRs and Hepatic AEs.⁷

Parameter	KARDIA-1 and 2		KARDIA-3 (Cohorts A & B)	
	Placebo N=404	Zilebesiran N=631	Placebo N=115	Zilebesiran N=258
ISRs	0.2	4.6	0	1.6
ALT or AST $> 3x$ ULN	1.2	2.4	0	0.8

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ISR = injection site reaction.

Concomitant Use With RAASi

A subgroup analysis was conducted to assess the safety of combining zilebesiran with background RAASi in patients from KARDIA-2 and KARDIA-3. Patients in the placebo and zilebesiran groups received olmesartan in KARDIA-2 and standard of care RAASi (baseline ACEi or ARB) in KARDIA-3. Rates of hyperkalemia and eGFR decline were similar to those in the overall phase 2 population (**Table 7**).⁷

Table 7. Proportion of Patients (%) With Hyperkalemia and Renal AEs.⁷

Parameter	KARDIA-2 and 3 (Cohorts A & B)	
	Placebo (with RAASi) N=246	Zilebesiran 150, 300, or 600 mg q6m (with RAASi) N=379
Potassium > 5.5 mmol/L	3.7	7.7
Confirmed by subsequent measurement ^a	0	2.4
Potassium > 6.0 mmol/L	0.8	1.1
Confirmed by subsequent measurement ^a	0	0
eGFR decline $\geq 30\%$ and eGFR < 60 mL/min/1.73 m ²	3.3	7.7
Confirmed by subsequent measurement ^a	0.8	2.2

Abbreviations: AE = adverse event; eGFR = estimated glomerular filtration rate; RAASi = renin-angiotensin-aldosterone system inhibitors.

^aAssessment remained in defined range on the next available measurement.

ABBREVIATIONS

ACEi = angiotensin-converting enzyme inhibitor; AE = adverse event; AGT = angiotensinogen; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; GalNAc = N acetyl galactosamine; ISR = injection site reaction; mRNA = messenger RNA; q3m = every 3 months; q6m = every 6 months; RAASi = renin-angiotensin-aldosterone system inhibitors; RNAi = RNA interference; SBP = systolic blood pressure; TEAE = treatment-emergent adverse event.

Updated 3 April 2026

REFERENCES

1. Alnylam Pharmaceuticals. Zilebesiran in patients with hypertension not adequately controlled and with either established cardiovascular disease or high risk for cardiovascular disease (ZENITH). Available from: <https://clinicaltrials.gov/study/NCT07181109>. Accessed April 3, 2026.
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. 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
4. 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. doi:10.1001/jama.2025.6681
5. 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.
6. 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.
7. Desai AS, Saxena M, Granger CB, et al. Pooled safety analysis of zilebesiran, an investigational long-acting RNA interference therapeutic, from phase 2 studies in patients with hypertension. Presented at: American College of Cardiology (ACC) Scientific Sessions; March 28-30, 2026; New Orleans, LA, USA.