# Zilebesiran: KARDIA-3 Study

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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.

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## 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.[1,2] Zilebesiran utilizes GalNAc conjugation, which enables subcutaneous dosing for liver-specific silencing of AGT mRNA.[3]
- KARDIA-3 is a phase 2 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 in patients with eGFR ≥45 mL/min/1.73m$^2$ (Cohort A) and patients with an eGFR between 30-45 mL/min/1.73m$^2$ (Cohort B).[1]
  - In Cohort A, the least squares mean from baseline in office SBP at Month 3 was -5.0 (95% CI -9.9, -0.2; P=0.04) mmHg in the zilebesiran 300 mg arm and -3.3 (95% CI -8.2, -1.6; P=0.18) mmHg in the zilebesiran 600 mg arm compared with the placebo arm. These results were not statistically significant after controlling for multiplicity.[1]
  - In Cohort B, the least squares mean change from baseline in office SBP at Month 3 was -5.4 (95% CI -14.9, 4.1) mmHg in the zilebesiran 150 mg arm, -2.4 (95% CI -11.7, 6.8) mmHg in the zilebesiran 300 mg arm, and -1.1 (95% CI -10.5, 8.2) mmHg in the zilebesiran 600 mg arm compared with the placebo arm.[4]
  - Subgroup analyses of patients on diuretic treatment in Cohort A were conducted and showed greater reductions from baseline in office SBP at Month 3.[1]
  - The majority of AEs were mild or moderate in severity. Rates of hyperkalemia, kidney dysfunction, and hypotension and associated adverse events were low in Cohort A and in Cohort B, consistent with findings from previous zilebesiran studies.[1,4]


## INDEX



## STUDY DESIGN

The KARDIA-3 (NCT06272487) study is 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 or without CKD. A key aim of the KARDIA-3 study was to inform the design of a phase 3 CV outcomes study in this population.[1,2,5]

The KARDIA-3 study included two cohorts (Cohort A or Cohort B). Cohort A included patients with an eGFR ≥45 mL/min/1.73m$^2$ and Cohort B included patients with an eGFR between 30-45 mL/min/1.73m$^2$.[1]

In Cohort A, 270 participants were randomized (1:1:1) to receive placebo (n=88) or a single subcutaneous injection of zilebesiran 300 mg (n=91) or 600 mg (n=91). In Cohort B, 105 participants were randomized (1:1:1:1) to receive placebo (n=26) or a single subcutaneous injection of zilebesiran 150 mg (n=26), 300 mg (n=27), or 600 mg (n=26). Antihypertensive intensification was permitted during Months 3–6 in both cohorts.[1,4]

The primary endpoint of the study is to evaluate the change from baseline in mean office SBP at Month 3. Key secondary endpoints include the change from baseline in mean office SBP at Month 6, the change from baseline to Months 3 and 6 in 24-hour mean ambulatory SBP, and the change from baseline in mean daytime and nighttime ambulatory SBP at Month 6. A key exploratory endpoint is the hourly mean daytime/nighttime ambulatory SBP at Month 6. A mixed model for repeated measurements was used for the primary analysis.[1] Cohorts A and B were analyzed separately. Cohort B was not powered to evaluate efficacy; results are descriptive only.[4]

Safety was assessed by the frequency of AEs throughout the 6-month double-blind period in both Cohort A and Cohort B.[1,4]

Key study inclusion criteria are[1,4]:

- Adult patients with established CV disease or high CV risk (10-year ASCVD score >15%)
- Uncontrolled hypertension
  - Mean office SBP 140–170 mmHg at screening
  - 24-hour mean ambulatory SBP 130–170 mmHg within 7 days prior to randomization
- Already prescribed 2–4 antihypertensive medications (including a diuretic or CCB)
- Cohort B: eGFR between 30-45 mL/min/1.73m$^2$

Key study exclusion criteria are[5]:

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

## PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

### Cohort A

Demographics and baseline characteristics of patients in Cohort A are shown in **Tables 1**-**3**.[1]

**Table 1. Cohort A: Patient Demographics and Baseline Characteristics.**[1]

| Baseline Characteristics | Placebo (N=88) | Zilebesiran (N=182) | |
|---|---|---|---|
| | | 300 mg (n=91) | 600 mg (n=91) |
| Age, years, mean (SD) | 66.3 (9.0) | 67.2 (8.7) | 65.6 (8.2) |
| Age ≥65 years, n (%) | 55 (62.5) | 52 (57.1) | 55 (60.4) |

| Baseline Characteristics | Placebo (N=88) | Zilebesiran (N=182) | |
|---|---|---|---|
| | | 300 mg (n=91) | 600 mg (n=91) |
| Female sex, n (%) | 33 (37.5) | 45 (49.5) | 43 (47.3) |
| Black, n (%) | 20 (22.7) | 19 (20.9) | 23 (25.3) |
| Hispanic or Latino, n (%) | 49 (55.7) | 51 (56.0) | 50 (54.9) |
| Previous CV event or CVD history, n (%) | 19 (21.6) | 27 (29.7) | 15 (16.5) |
| ASCVD score in patients without prior CV event, mean (SD) | 29.6 (12.8) | 29.5 (13.1) | 29.4 (11.7) |
| Diabetes mellitus, n (%) | 47 (53.4) | 42 (46.2) | 50 (54.9) |
| eGFR ≥60 mL/min/1.73m$^2$, n (%) | 79 (89.8) | 82 (90.1) | 82 (90.1) |

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; SD = standard deviation.

**Table 2. Cohort A: Baseline Blood Pressure.**[1]

| Baseline Characteristics | Placebo | Zilebesiran (N=182) | |
|---|---|---|---|
| | | 300 mg | 600 mg |
| Office BP, mmHg | N=88 | n=91 | n=91 |
| Systolic BP, mean (SD) | 144.1 (12.4) | 143.4 (13.1) | 143.4 (13.4) |
| Diastolic BP, mean (SD) | 79.6 (10.3) | 80.2 (11.5) | 80.3 (10.8) |
| 24-Hour Mean Ambulatory BP, mmHg | N=88 | n=91 | n=89 |
| Systolic BP, mean (SD) | 142.9 (9.0) | 141.6 (8.3) | 142.9 (7.7) |
| Diastolic BP, mean (SD) | 79.1 (8.6) | 78.8 (8.5) | 78.0 (8.9) |

Abbreviations: BP = blood pressure; SD = standard deviation.

**Table 3. Cohort A: Baseline Antihypertensive Medications.**[1]

| Baseline Characteristics | Placebo (N=88) | Zilebesiran (N=182) | |
|---|---|---|---|
| | | 300 mg (n=91) | 600 mg (n=91) |
| Baseline medication, n (%) | | | |
| ACEi or ARB | 78 (88.6) | 83 (91.2) | 84 (92.3) |
| Thiazide, thiazide-like, or loop diuretic | 55 (62.5) | 62 (68.1) | 61 (67.0) |
| CCB | 58 (65.9) | 52 (57.1) | 46 (50.5) |
| Number of oral antihypertensives, n (%) | | | |
| 2 | 47 (53.4) | 40 (44.0) | 57 (62.6) |
| 3 | 32 (36.4) | 37 (40.7) | 27 (29.7) |
| ≥4 | 9 (10.2) | 14 (15.4) | 7 (7.7) |

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker.

### Cohort B

Demographics and baseline characteristics for patients in Cohort B are provided in **Table 4**.[4]

**Table 4. Cohort B: Patient Demographics and Baseline Characteristics.**[4]

| Baseline Characteristics | Placebo (N=26) | Zilebesiran | | |
|---|---|---|---|---|
| | | 150 mg (N=25) | 300 mg (N=26) | 600 mg (N=26) |
| Mean age, years (SD) | 70.7 (7.9) | 71.6 (10.7) | 71.3 (8.0) | 67.8 (9.1) |
| Female sex, n (%) | 9 (34.6) | 16 (64.0) | 11 (42.3) | 9 (34.6) |
| Black, n (%) | 4 (15.4) | 7 (28.0) | 6 (23.1) | 8 (30.8) |
| Hispanic or Latino, n (%) | 14 (53.8) | 9 (36.0) | 9 (34.6) | 10 (38.5 |
| Previous CV event or CV disease history, n (%) | 4 (15.4) | 5 (20.0) | 3 (11.5) | 4 (15.4) |
| Median eGFR, mL/min/1.73 $m^2$ (IQR) | 39.7 (32.9-43.9) | 41.4 (36.2-43.1) | 36.9 (31.8-44.5) | 38.9 (33.2-44.1) |
| Median urine albumin to creatinine ratio, mg/g (IQR) | 68.0 (27.0-332.0) | 87.0 (31.0-485.0) | 39.0 (8.0-178.0) | 162.5 (34.0-445.0) |
| Mean office systolic BP, mmHg (SD) | 146.2 (12.5) | 150.3 (12.5) | 143.3 (13.8) | 147.5 (17.6) |
| Receiving ACEi or ARB, n (%) | 23 (85.2) | 23 (95.8) | 19 (73.1) | 22 (84.6) |
| Receiving diuretic (thiazide, thiazide-like, or loop diuretic), n (%) | 16 (59.3) | 18 (75.0) | 16 (61.5) | 17 (65.4) |
| Receiving ≥3 antihypertensives, n (%) | 17 (63.0) | 19 (79.2) | 15 (57.7) | 22 (84.6) |

Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CV = cardiovascular, eGFR = estimated glomerular filtration rate; IQR = interquartile range; SD = standard deviation.

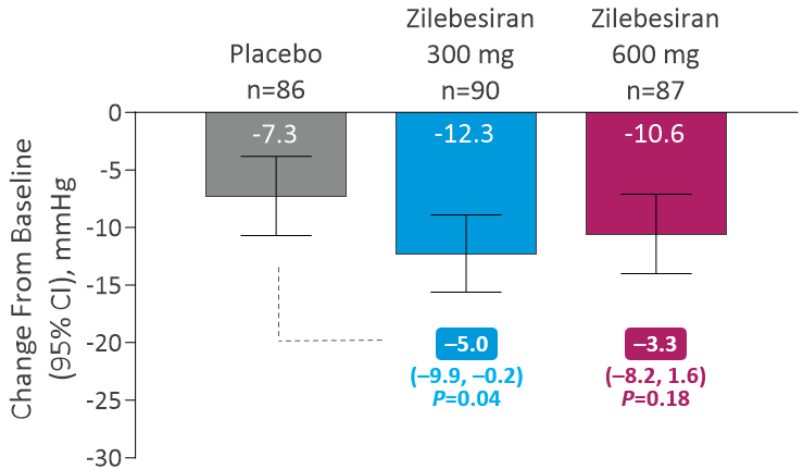
## EFFICACY RESULTS

### Cohort A

Primary Endpoint

In Cohort A, the mean change from baseline in office SBP at Month 3 was -7.3 mmHg in the placebo arm, -12.3 mmHg in the zilebesiran 300 mg arm, resulting in a least squares means of -5.0 (95% CI -9.9, -0.2; P=0.04) mmHg compared with placebo, and -10.6 mmHg in the zilebesiran 600 mg arm, resulting in a least squares mean of -3.3 (95% CI -8.2, 1.6; P=0.18) mmHg compared with placebo (**Figure 1**).[1]

**Figure 1. Cohort A: Placebo-Adjusted Change from Baseline in Office SBP at Month 3.**[1]



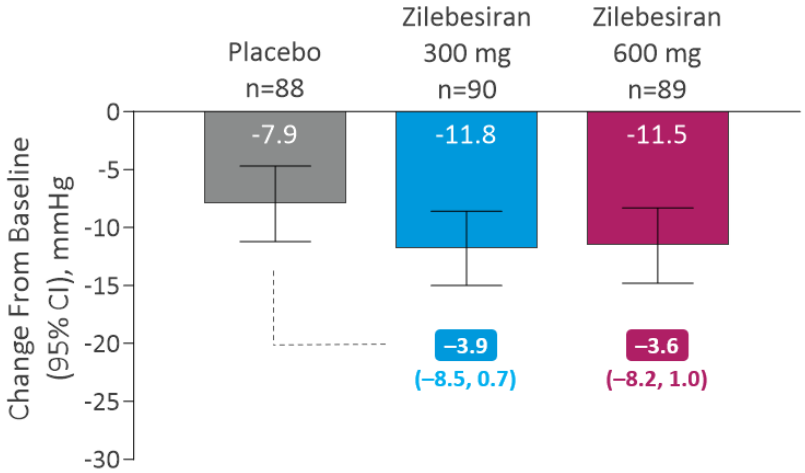

Abbreviations: CI = confidence interval; SBP = systolic blood pressure.
Changes from baseline are estimated by least squares means (95% CI). Statistical significance under Hochberg multiplicity control: If *P* value of one dose exceeds 0.05 (2-sided), threshold for remaining dose is *P*≤0.025. Statistical significance in office SBP was not reached at Month 3.
From Pagidipati et al.[1]

## Cohort A Key Secondary Endpoints

### *Change from Baseline in Office SBP at Month 6*

In Cohort A, the mean change from baseline in office SBP at Month 6 was -7.9 mmHg in the placebo arm, -11.8 mmHg in the zilebesiran 300 mg arm, resulting in a least squares means (95% CI) of -3.9 (-8.5, 0.7) mmHg compared with placebo, and -11.5 mmHg in the zilebesiran 600 mg arm, resulting in a least squares mean (95% CI) of -3.6 (-8.2, 1.0) mmHg compared with placebo (**Figure 2**).[1]

**Figure 2. Cohort A: Placebo-Adjusted Change from Baseline in Office SBP at Month 6.**[1]




Abbreviations: CI = confidence interval; SBP = systolic blood pressure.
Changes from baseline are estimated by least squares means (95% CI).
From Pagidipati et al.[1]

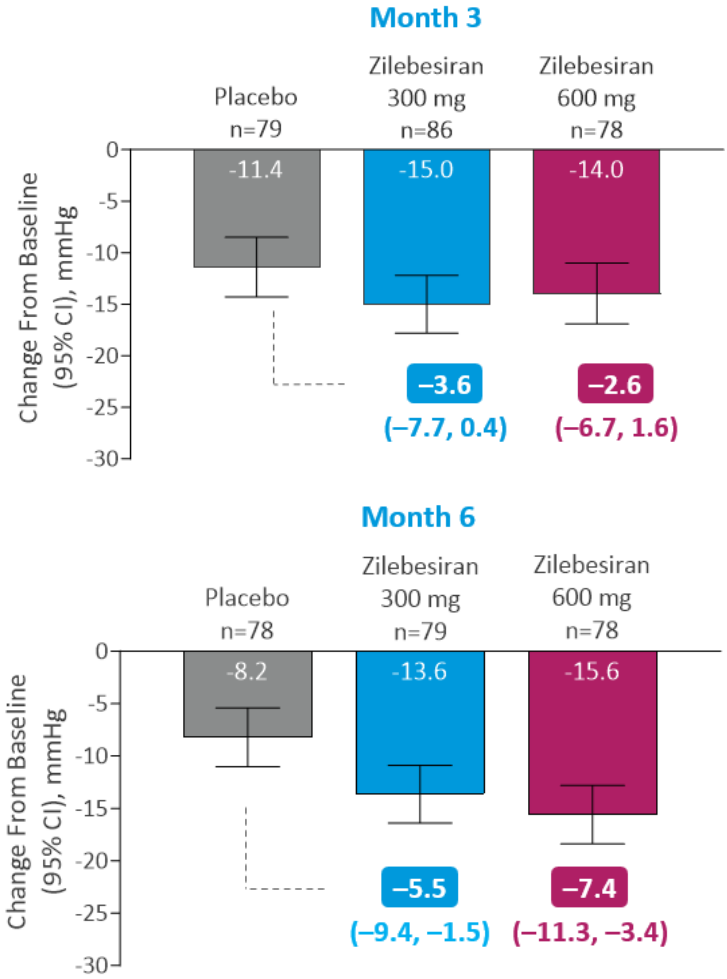
### *Change from Baseline in 24-Hour Mean Ambulatory SBP at Months 3 and 6*

In Cohort A, the mean change from baseline in 24-hour mean ambulatory SBP at Month 3 was -11.4 mmHg in the placebo arm, -15.0 mmHg in the zilebesiran 300 mg arm, resulting in a least

squares mean (95% CI) of -3.6 (-7.7, 0.4) mmHg compared with placebo, and -14.0 mmHg in the zilebesiran 600 mg arm, resulting in a least squares mean (95% CI) of -2.6 (-6.7, 1.6) mmHg compared with placebo (**Figure 3**).[1]

In Cohort A, the mean change from baseline in 24-hour mean ambulatory SBP at Month 6 was -8.2 mmHg in the placebo arm, -13.6 mmHg in the zilebesiran 300 mg arm, resulting in a least squares mean (95% CI) of -5.5 (-9.4, -1.5) mmHg compared with placebo, and -15.6 mmHg in the zilebesiran 600 mg arm, resulting in a least squares mean (95% CI) of -7.4 (-11.3, -3.4) mmHg compared with placebo (**Figure 3**).[1]

**Figure 3. Cohort A: Placebo-Adjusted Change from Baseline in 24-Hour Mean Ambulatory SBP at Months 3 and 6.**[1]



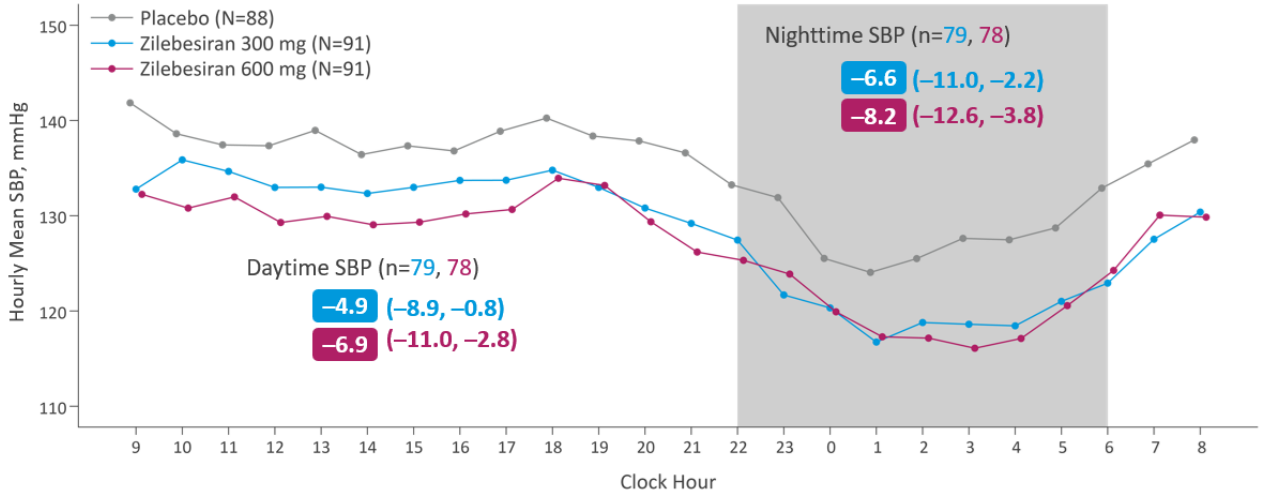

Abbreviations: CI = confidence interval; SBP = systolic blood pressure.
Changes from baseline are estimated by least squares means (95% CI).
From Pagidipati et al.[1]

Additional Secondary and Exploratory Endpoints

In Cohort A, the ambulatory SBP measured across a 24-hour period over 6 months with the hourly mean daytime/nighttime ambulatory SBP at Month 6 is provided in **Figure 4**. The change (95% CI) from baseline in mean daytime ambulatory SBP was -4.9 (-8.9, -0.8) mmHg in the zilebesiran 300 mg arm and -6.9 (-11.0, -2.8) mmHg in the zilebesiran 600 mg arm, and the change (95% CI) from baseline in

mean nighttime ambulatory SBP was -6.6 (-11.0, -2.2) mmHg in the zilebesiran 300 mg arm and -8.2 (-12.6, -3.8) mmHg in the zilebesiran 600 mg arm (**Figure 4**).[1]

**Figure 4. Cohort A: Hourly Mean (Exploratory Endpoint) and Placebo-Adjusted Change from Baseline (Secondary Endpoint) in Mean Daytime/Nighttime Ambulatory SBP at Month 6.**[1]



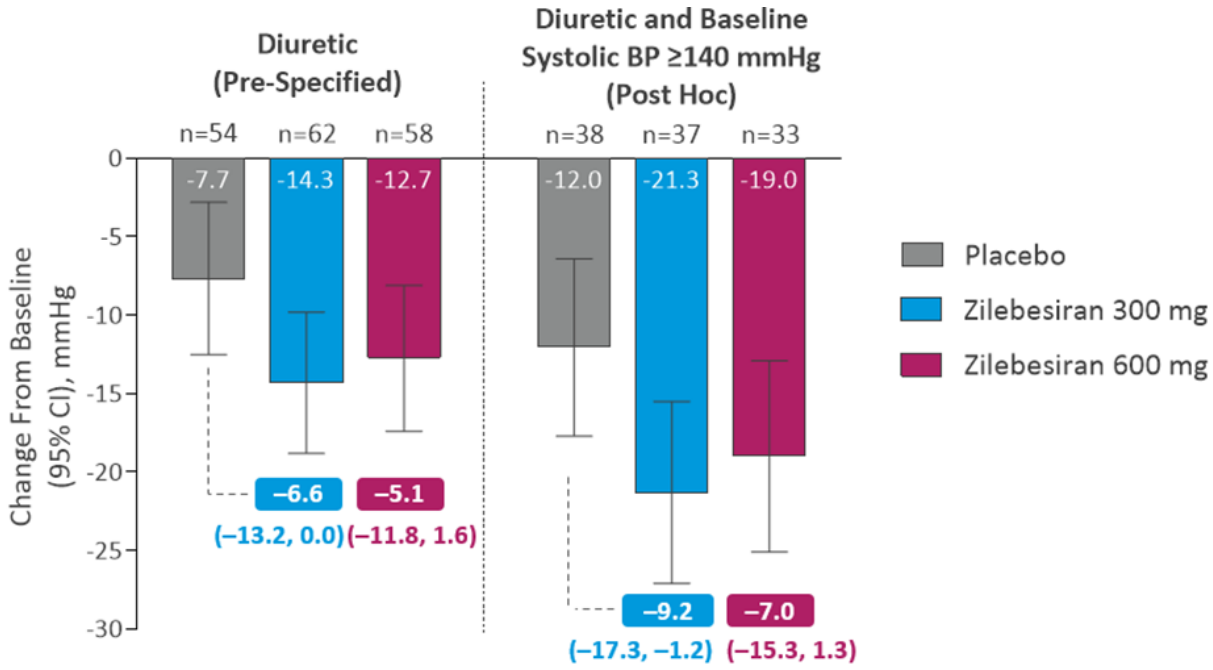

Abbreviations: SBP = systolic blood pressure.
From Pagidipati et al.[1]

Subgroup Analyses: Diuretic Treatment ± Baseline SBP ≥140 mmHg

In a prespecified subgroup analysis of patients on diuretic treatment in Cohort A, the mean change from baseline in office SBP at Month 3 was -7.7 mmHg in the placebo arm, -14.3 mmHg in the zilebesiran 300 mg arm, resulting in a least squares mean (95% CI) of -6.6 (-13.2, 0.0) mmHg compared with placebo, and -5.1 mmHg in the zilebesiran 600 mg arm, resulting in a least squares mean (95% CI) of -5.1 (-11.8, 1.6) mmHg compared with placebo (**Figure 5**).[1]

In a post-hoc subgroup analysis of patients on diuretic treatment and with a baseline SBP ≥140 mmHg in Cohort A, the mean change from baseline in office SBP at Month 3 was -12.0 mmHg in the placebo arm, -21.3 mmHg in the zilebesiran 300 mg arm, resulting in a least squares mean (95% CI) of -9.2 (-17.3, -1.2) mmHg compared with placebo, and -19.0 mmHg in the zilebesiran 600 mg arm, resulting in a least squares mean (95% CI) of -7.0 (-15.3, 1.3) mmHg compared with placebo (**Figure 5**). The least squares mean (95% CI) in office SBP was sustained to Month 6: -8.3 (-16.4, -0.2) mmHg in the zilebesiran 300 mg arm and -6.2 (-14.4, 2.0) mmHg in the zilebesiran 600 mg arm compared with placebo.[1]

**Figure 5. Cohort A: Placebo-Adjusted Change from Baseline in Office SBP at Month 3.**[1]



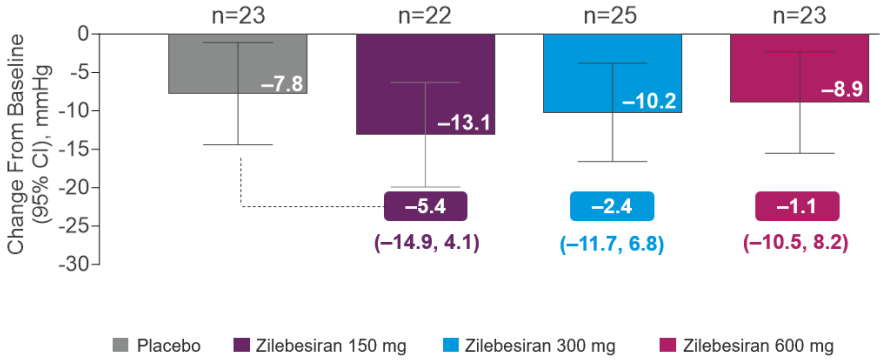

Abbreviations: CI = confidence interval; SBP = systolic blood pressure.
Changes from baseline are estimated by least squares means (95% CI).
From Pagidipati et al.[1]

**Cohort B**

Primary Endpoint

In Cohort B, the mean change from baseline in office SBP at Month 3 was -7.8 mmHg in the placebo arm, -13.1 mmHg in the zilebesiran 150 mg arm resulting in a least squares mean (95% CI) of -5.4 (-14.9, 4.1) mmHg compared with placebo, -10.2 mmHg in the zilebesiran 300 mg arm resulting in a least squares mean (95% CI) of -2.4 (-11.7, 6.8) mmHg compared with placebo, and -8.9 in the zilebesiran 600 mg arm resulting in a least squares mean (95% CI) of -1.1 (-10.5, 8.2) mmHg compared with placebo (**Figure 6**).[4]

**Figure 6. Cohort B: Placebo-Adjusted Change from Baseline in Office SBP at Month 3.**[4]




Abbreviations: CI = confidence interval; SBP = systolic blood pressure.
From Pagidipati et al.[4]

## SAFETY RESULTS

### Cohort A

The majority of AEs through Month 6 were mild or moderate in severity. The rates of hyperkalemia, kidney dysfunction, and hypotension were low and consistent with findings from previous zilebesiran studies. Most instances of hyperkalemia or kidney dysfunction were not confirmed by subsequent measurement (**Table 5**).[1]

**Table 5. Cohort A: Adverse Events Through Month 6.**[1]

| n (%) | Placebo (N=88) | Zilebesiran (N=182) | |
|---|---|---|---|
| | | 300 mg (n=91) | 600 mg (n=91) |
| At least 1 AE | 38 (43.2) | 47 (51.6) | 46 (50.5) |
| At least 1 serious AE | 4 (4.5) | 1 (1.1) | 6 (6.6) |
| Suspected unexpected serious adverse reaction | 0 | 0 | 1 (1.1) |
| Death | 0 | 0 | 0 |
| Hypotension/orthostatic hypotension AE | 3 (3.4) | 3 (3.3) | 4 (4.4) |
| Potassium >5.5 mmol/L | 4 (4.5) | 4 (4.4) | 8 (8.8) |
| Confirmed by subsequent measurement | 1 (1.1) | 3 (3.3) | 1 (1.1) |
| Potassium >6.0 mmol/L | 0 | 0 | 0 |
| eGFR ≥30% decrease from baseline ($mL/min/1.73m^2$) | 1 (1.1) | 5 (5.5) | 8 (8.8) |
| Confirmed by subsequent measurement | 1 (1.1) | 2 (2.2) | 2 (2.2) |

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

### Cohort B

Zilebesiran had an acceptable safety profile, with most AEs being mild to moderate and transient. One serious AE (hospitalization for cholecystitis and laparoscopic cholecystectomy) reported in a patient who received zilebesiran 150 mg was considered related by the Investigator, which was later resolved and the patient fully recovered. One death by cardiac arrest on Day 85 was reported in a patient who received zilebesiran 150 mg, which was not considered treatment-related by the Investigator. Additional details are provided in (**Table 6**).[4]

Most hyperkalemia events were transient and occurred by Month 2. No hyperkalemia events required hospitalization or dialysis. Most reductions in eGFR were transient and none required hospitalization or dialysis. The 2 events of dizziness and syncope were transient and not serious.[4]

**Table 6. Cohort B: Adverse Events Through Month 6.**[4]

| n (%) | Placebo (N=27) | Zilebesiran | | | |
|---|---|---|---|---|---|
| | | 150 mg (N=24) | 300 mg (N=26) | 600 mg (N=26) | Pooled (N=76) |
| At least 1 AE | 15 (55.6) | 16 (66.7) | 13 (50.0) | 13 (50.0) | 42 (55.3) |
| At least 1 serious AE | 1 (3.7) | 3 (12.5) | 1 (3.8) | 1 (3.8) | 5 (6.6) |
| At least 1 serious related AE | 0 | 1 (4.2) | 0 | 0 | 1 (1.3) |
| Death | 0 | 1 (4.2) | 0 | 0 | 1 (1.3) |
| Potassium >5.5 mmol/L, n (%) | 3 (11.1) | 3 (12.5) | 3 (11.5) | 4 (15.4) | 10 (13.2) |
| Confirmed by subsequent measurement | 0 | 2 (8.3) | 0 | 1 (3.8) | 3 (3.9) |
| Potassium >6 mmol/L, n (%) | 1 (3.7) | 1 (4.2) | 0 | 1 (3.8) | 2 (2.6) |
| Confirmed by subsequent measurement | 0 | 0 | 0 | 0 | 0 |
| eGFR ≥30% decrease from baseline | 3 (11.1) | 3 (12.5) | 1 (3.8) | 3 (11.5) | 7 (9.2) |
| Confirmed by subsequent measurement | 0 | 0 | 1 (3.8) | 1 (3.8) | 2 (2.6) |
| At least 1 hypotension AE | 0 | 0 | 0 | 0 | 0 |
| At least 1 AE potentially related to hypotension | 1 (3.7) | 0 | 1 (3.8) | 0 | 1 (1.3) |
| Dizziness | 1 (3.7) | 0 | 0 | 0 | 0 |
| Syncope | 0 | 0 | 1 (3.8) | 0 | 1 (1.3) |

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

## ABBREVIATIONS

ACEi = angiotensin-converting enzyme inhibitor; AE = adverse event; AGT = angiotensinogen; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CCB = calcium channel blocker; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GalNAc = N-acetyl galactosamine; mRNA = messenger RNA; RNAi = RNA interference; SBP = systolic blood pressure; SD = standard deviation.

*Updated 7 January 2026*

## REFERENCES


1. 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.
2. 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 January 24, 2025.
3. 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
4. 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.
5. 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.