# Zilebesiran in Combination With a Diuretic in Patients With Uncontrolled Hypertension: a Subgroup Analysis From the Phase 2 KARDIA-3 Trial

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Zilebesiran is being co-developed by Alnylam and Roche.

# Introduction and Zilebesiran Overview

- Uncontrolled HTN is the greatest contributor to CV morbidity and mortality worldwide
  - Among BP measures, nighttime BP is one of the strongest predictors of CV risk
- Poor adherence to daily oral therapies is an important contributor to BP goals not being met
- Zilebesiran is an investigational RNA interference therapeutic that reduces hepatic production of angiotensinogen, the most upstream precursor in the RAAS pathway
- Zilebesiran has the potential to provide continuous control of BP with twice-yearly subcutaneous dosing

## KARDIA$_3$ A Phase 2 Trial in Patients With Uncontrolled HTN on 2–4 Antihypertensives and High CV Risk or Established CVD

**Cohort A full population (N=270)**

eGFR ≥45 mL/min/1.73 m$^2$

COHORT A (1:1:1)

- Zilebesiran 300 mg SC (N=91)
- Zilebesiran 600 mg SC (N=91)
- Placebo SC (N=88)

**Prespecified analysis (N=174)**

Patients receiving a diuretic at baseline

***Post hoc* analysis (N=108)**

Patients receiving a diuretic at baseline, with baseline office systolic BP ≥140 mmHg

**COHORT B**

eGFR 30–44 mL/min/1.73 m$^2$

M3 ⟷ M6

Intensification of background antihypertensives permitted

**Objective**

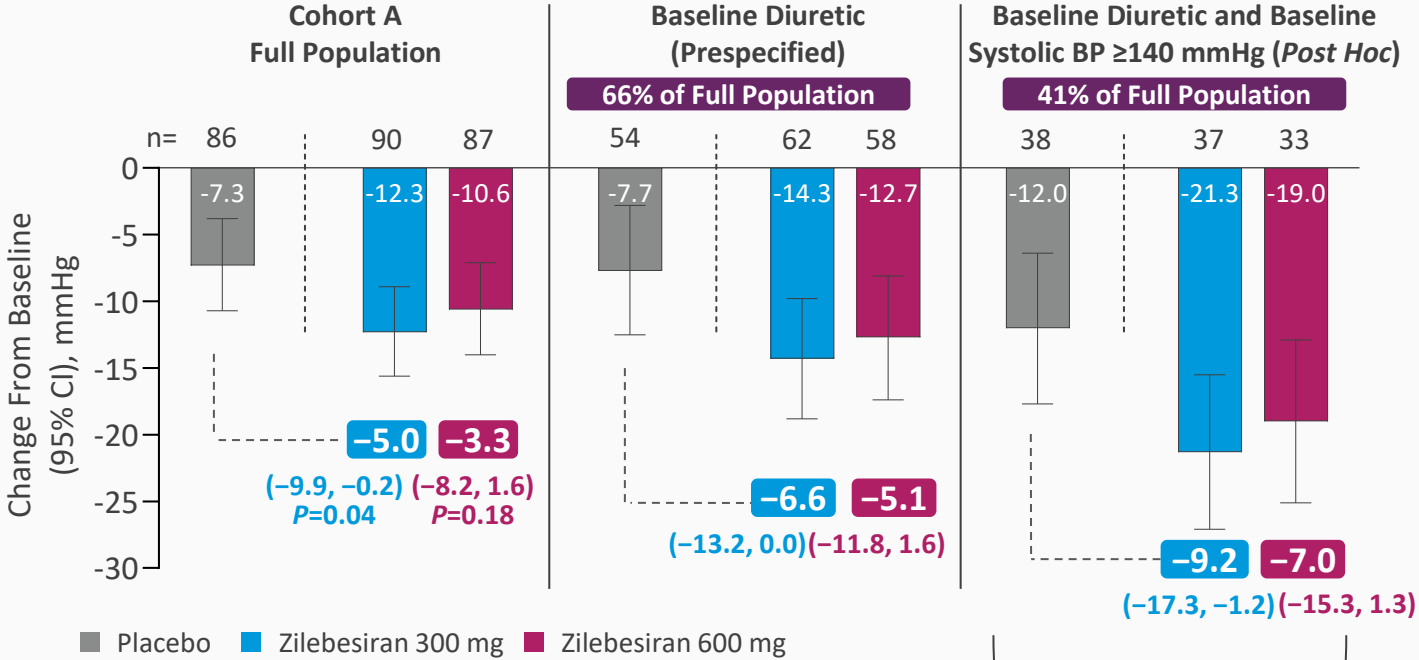
To assess the BP-lowering effects of zilebesiran in patients with uncontrolled HTN receiving a diuretic at baseline

KARDIA 3

# Baseline Characteristics

| Demographic/Characteristic | Cohort A Full Population | | *Post Hoc*: Baseline Diuretic and Baseline Office Systolic BP ≥140 mmHg | |
|---|---|---|---|---|
| | Placebo (N=88) | Zilebesiran 300 + 600 mg Pooled (N=182) | Placebo (N=39) | Zilebesiran 300 + 600 mg Pooled (N=71) |
| Age, years, mean (SD) | 66.3 (9.0) | 66.4 (8.4) | 66.2 (9.3) | 66.0 (8.5) |
| Female, % | 37.5 | 48.4 | 38.5 | 53.5 |
| Black, % | 22.7 | 23.1 | 17.9 | 15.5 |
| Hispanic or Latino, % | 55.7 | 55.5 | 69.2 | 71.8 |
| Previous CV event or CVD history, % | 21.6 | 23.1 | 12.8 | 18.3 |
| Type 2 diabetes, % | 53.4 | 50.5 | 48.7 | 49.3 |
| eGFR, mL/min/1.73 $m^2$, median (IQR) | 88.4 (26.6) | 82.0 (26.2) | 92.8 (24.3) | 86.4 (20.0) |
| UACR, mg/g, median (IQR) | 10.0 (14.0) | 10.3 (16.0) | 8.0 (14.0) | 10.0 (13.0) |
| BMI, kg/$m^2$, median (IQR) | 29.6 (5.4) | 31.1 (7.0) | 30.1 (6.3) | 31.9 (7.6) |
| Office systolic BP, mmHg, median (IQR) | 144.0 (15.0) | 142.0 (16.0) | 147.0 (13.0) | 149.0 (14.0) |
| 24-hour ambulatory systolic BP, mmHg, median (IQR) | 142.0 (12.5) | 141.5 (12.5) | 145.0 (14.0) | 144.0 (14.0) |
| Receiving ACEi or ARB, % | 88.6 | 91.8 | 84.6 | 88.7 |

# Office Systolic BP Reductions at Month 3

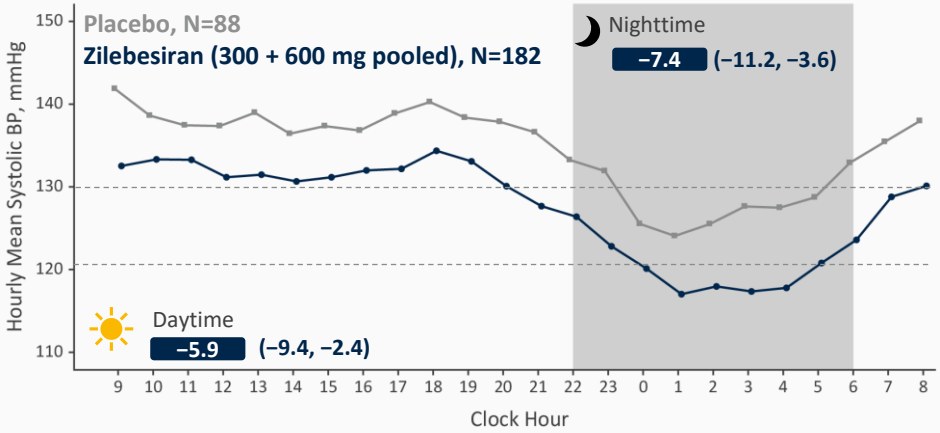



Statistical significance under Hochberg multiplicity control: If the *P* value of one dose exceeds 0.05 (two-sided), the threshold for the remaining dose is $P \leq 0.025$

Changes sustained to Month 6:
**−8.3 (−16.4, −0.2) mmHg**
**−6.2 (−14.4, 2.0) mmHg**

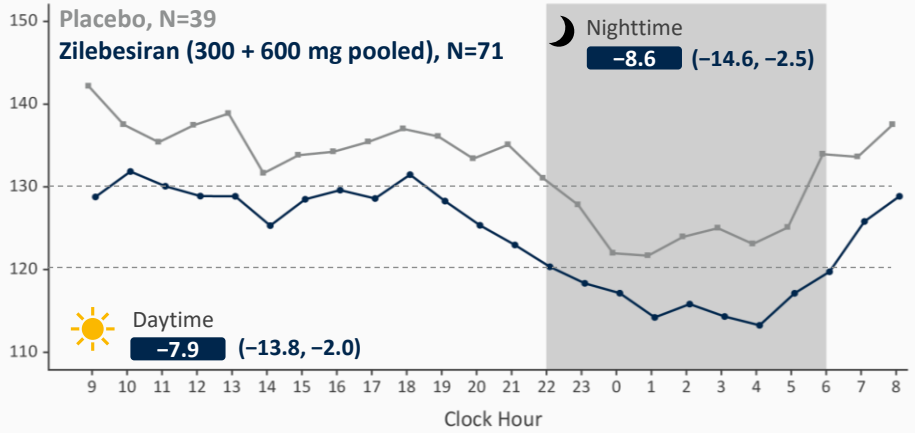
# Placebo-Adjusted Change From Baseline in Daytime, Nighttime, and 24-hour Ambulatory Systolic BP at Month 6

## Cohort A Full Population




## Baseline Diuretic and Baseline Office Systolic BP ≥140 mmHg

*Post Hoc*




**Placebo-adjusted change from baseline** (95% CI)

- Placebo-adjusted change from baseline in 24-hour systolic BP at Month 6 was **−6.4 (−9.8, −3.0)** in the full population, and **−8.1 (−13.9, −2.4)** in patients receiving a baseline diuretic and with baseline systolic BP ≥140 mmHg

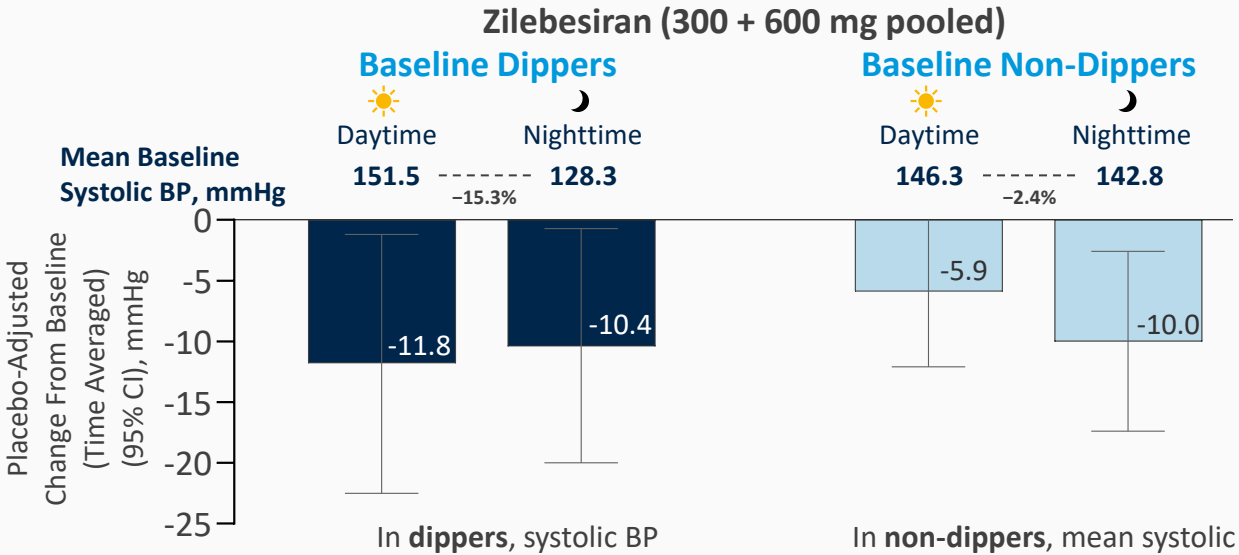
# Placebo-Adjusted Change From Baseline in 24-Hour Mean Ambulatory Systolic BP To Month 6 by Baseline Dipping Status (Time Averaged)

## *Post Hoc:* Baseline Diuretic and Baseline Office Systolic BP ≥140 mmHg

### Baseline Dipper Status

| N (%) | Dippers | Non-dippers |
|---|---|---|
| Placebo | 16 (41.0) | 23 (59.0) |
| Zilebesiran (300 + 600 mg pooled) | 17 (23.9) | 53 (74.6) |

Non-dipper was defined as <10% reduction in mean nighttime versus mean daytime systolic BP at baseline




In **dippers**, systolic BP reductions with zilebesiran were generally consistent across the 24-hour interval

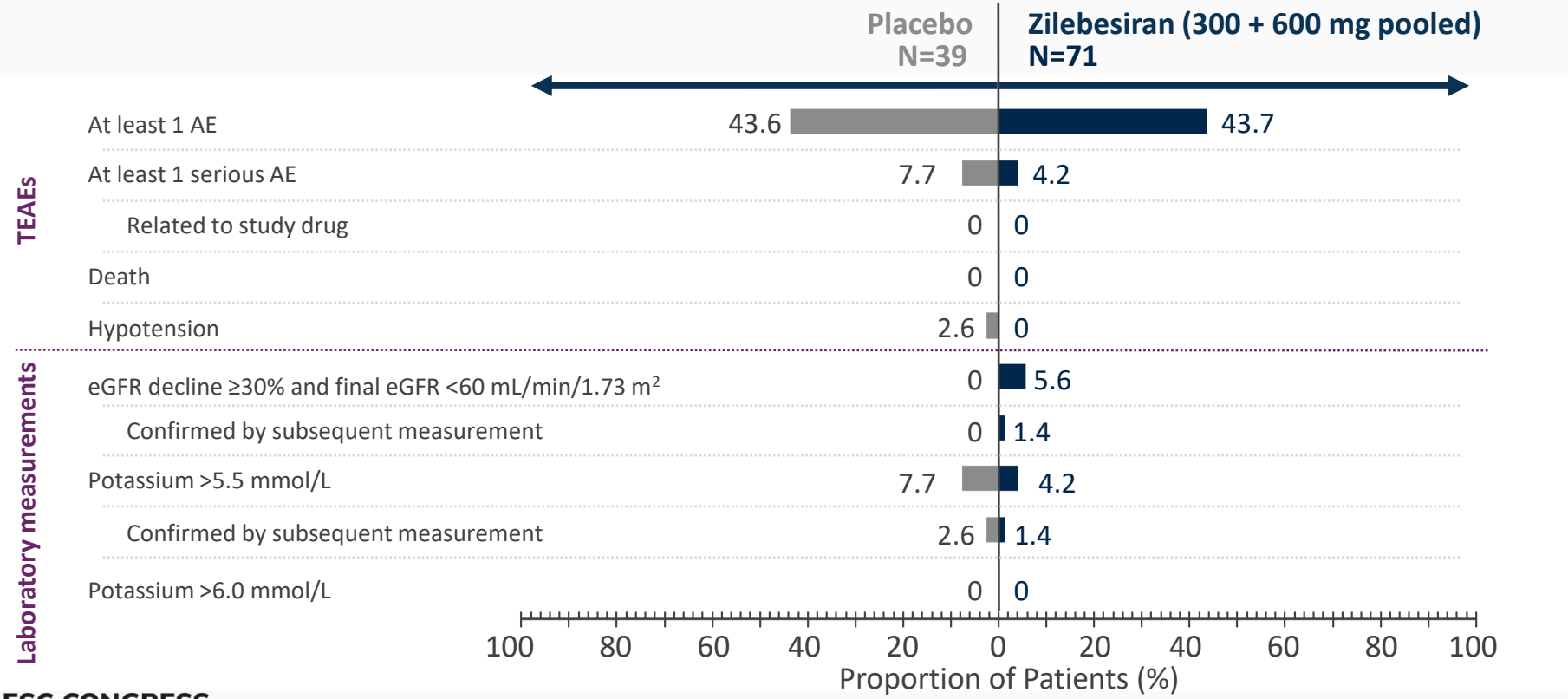
In **non-dippers**, mean systolic BP reductions of 10.0 mmHg were observed during the nighttime period



------ Indicates % change between daytime and nighttime BP

# Safety to Month 6

## *Post Hoc:* Baseline Diuretic and Baseline Office Systolic BP ≥140 mmHg



# KARDIA-3 Subgroup Analysis Conclusions

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- In KARDIA-3 Cohort A (eGFR ≥45 mL/min/1.73 $m^2$), single doses of zilebesiran led to reductions in office systolic BP at Month 3 compared with placebo; although statistical significance was not reached
- In this *post hoc* analysis of patients receiving a diuretic with office systolic BP ≥140 mmHg at baseline/randomization, greater BP lowering was seen with zilebesiran than in the overall population
  - This suggests complementary effects on BP reduction when combining zilebesiran with a diuretic-containing standard of care regimen
  - Zilebesiran treatment was associated with reductions in BP across the diurnal cycle including at nighttime, one of the strongest predictors of CV risk
- The safety profile of zilebesiran in this *post hoc* subgroup was consistent with that seen across the zilebesiran Phase 2 program, with low rates of hypotension, hyperkalemia, and eGFR decline
- This analysis informed the design of ZENITH (NCT07181109), an ongoing CV outcomes trial of zilebesiran in patients with HTN receiving at least two antihypertensives, including a diuretic, systolic BP ≥140 mmHg at randomization, and CVD or high CV risk