Scientific Sessions

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

Neha Pagidipati[1], Michael Weber[2], Manish Saxena[3,4], Bryan Williams[5], Shaun G Goodman[6,7], Zhihua Xiang[8], Shruti Daga[9], Monica Bengus[10], Dion Zappe[8], Ishir Bhan[8], Christopher B Granger[1]

[1]Duke Clinical Research Institute, Durham, NC, USA; [2]SUNY Downstate College of Medicine, SUNY Downstate Health Sciences University, New York, NY, USA; [3]Barts Health NHS Trust, London, UK; [4]Queen Mary University of London, London, UK; [5]Institute of Cardiovascular Science, University College London, London, UK; [6]St. Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada; [7]Canadian VIGOUR Centre, University of Alberta, Edmonton, AB, Canada; [8]Alnylam Pharmaceuticals, Cambridge, MA, USA; [9]Roche Products Ltd, Welwyn Garden City, UK; [10]F. Hoffmann-La Roche, Basel, Switzerland

American Heart Association.

Zilebesiran is being co-developed and will be co-commercialized by Alnylam and Roche.

#AHA25

NEHA PAGIDIPATI

Duke Clinical Research Institute, Durham, NC, USA

Research support from Alnylam, Amgen, Bayer, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, Merck

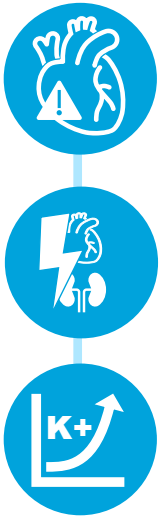
Consultation/Advisory Panels for Alnylam, Amgen, Bayer, Boehringer Ingelheim, Corcept, Corsera, Eli Lilly, Esperion, AstraZeneca, Merck, Metsera, New Amsterdam, Novartis, and Novo Nordisk.

DSMB for trials sponsored by Janssen and Novartis.

UNLABELED/UNAPPROVED USES DISCLOSURE:

Zilebesiran is an investigational product in development for treatment of patients with hypertension.

THE PROBLEM: UNCONTROLLED HYPERTENSION



Uncontrolled hypertension (HTN) is the greatest modifiable risk factor for cardiovascular (CV) morbidity and mortality worldwide

The risks of CV events and end organ damage are further elevated for those with chronic kidney disease (CKD)

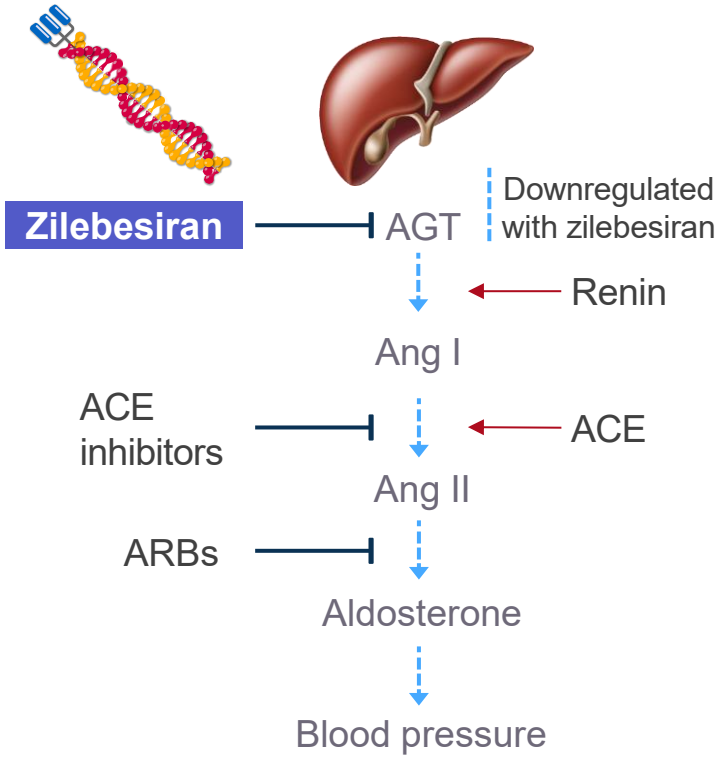
Patients with CKD are also at a high risk of adverse events (AEs) from treatment, including hyperkalemia

An effective therapy with an acceptable safety profile that provides continuous control of BP may help to reduce the burden of uncontrolled HTN and CV disease, including for patients with CKD

ZILEBESIRAN

Zilebesiran Suppresses the RAAS Pathway

- An investigational RNA (RNAi) interference therapeutic
- Specifically designed to reduce hepatic production of angiotensinogen (AGT), the most upstream precursor in the RAAS pathway
- Has the potential to provide continuous control of BP with subcutaneous (SC) dosing every 6 months



KARDIA-3 STUDY OBJECTIVE

To determine the efficacy, safety, and optimal dosing of zilebesiran among individuals with uncontrolled HTN and high CV risk, with or without CKD, in order to inform the design of a CV outcomes study in this population

Cohort A: Presented at ESC 2025
To assess efficacy and safety in patients with eGFR ≥45 mL/min/1.73 m^2

Cohort B:
To assess safety in patients with eGFR 30–44 mL/min/1.73 m^2

KEY DETAILS

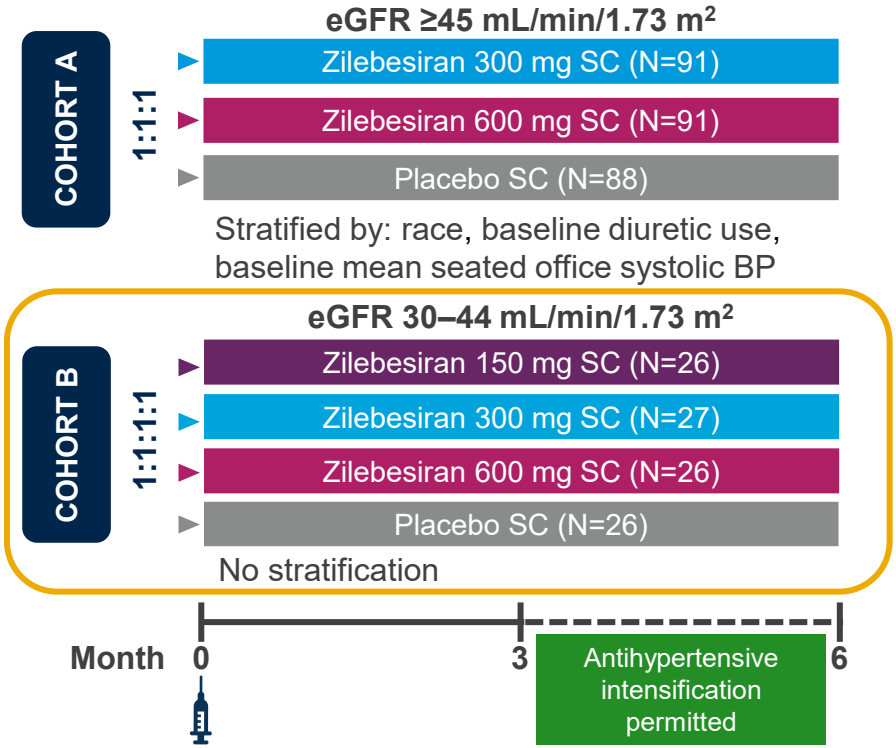
Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial

Across 5 countries:
US, Australia, Canada, UK, Switzerland

Key inclusion criteria

- Established CV disease or high risk for CV disease (>15% 10-year ASCVD)
- Uncontrolled HTN (mean office systolic BP 140–170 mmHg at screening and 24-hour mean ambulatory systolic BP 130–170 mmHg in the 7 days before randomization)
- Already prescribed 2–4 antihypertensive drugs (including a diuretic or calcium channel blocker)
- Serum potassium ≤4.8 mEq/L
- **Cohort B:** eGFR 30–44 mL/min/1.73 m^2

STUDY DESIGN



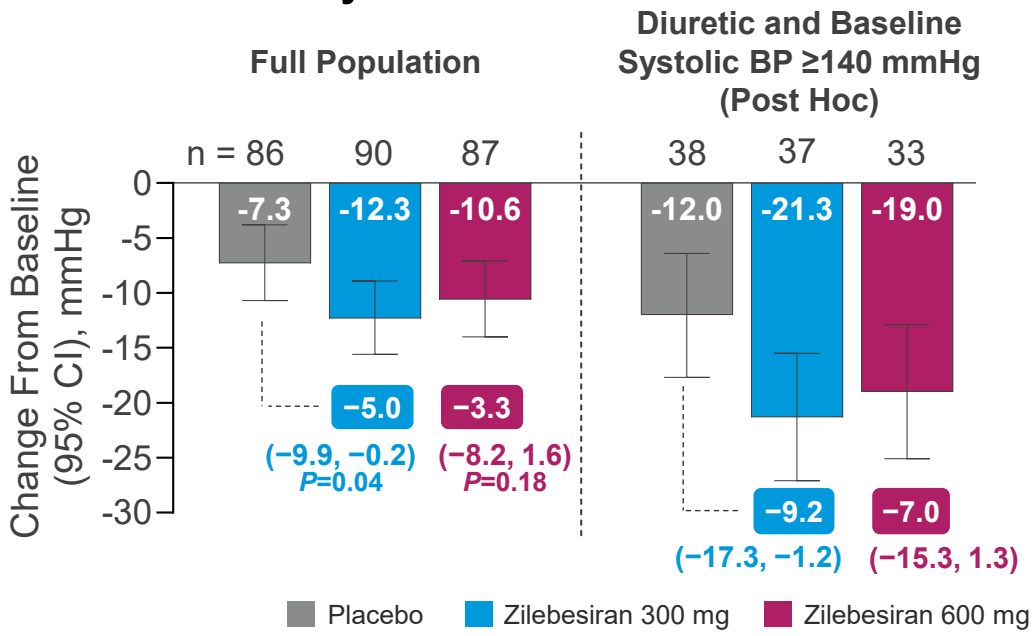
Cohort B Key Outcomes

- Frequency of AEs through Month 6
- Change from baseline to Month 3 in mean office systolic BP

Change from baseline estimated by least-squares mean (95% CI).
Cohorts A and B were analyzed separately; ***Cohort B was not powered to evaluate efficacy****; results are descriptive only.*

SUMMARY OF EFFICACY AND SAFETY
COHORT A (eGFR ≥45 mL/min/1.73 m²)

Month 3 Office Systolic BP



Primary results were not statistically significant after accounting for multiplicity (if both doses did not have P<0.05, then any single dose must have had P<0.025 to be considered statistically significant).

Safety to Month 6

- Acceptable safety, with most AEs mild or moderate
- Low rates of hyperkalemia, kidney dysfunction, and hypotension
- Most instances of hyperkalemia or kidney dysfunction were not confirmed by subsequent measurement

Cohort A data were presented at ESC 2025: Pagidipati N *et al.* European Society of Cardiology Congress, August 29–September 1, 2025, Madrid, Spain.

KARDIA-3
COHORT B RESULTS

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DEMOGRAPHICS AND DISEASE CHARACTERISTICS
COHORT B (eGFR 30–44 mL/min/1.73 m²)

	Placebo	Zilebesiran		
	(N=26)	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)

SAFETY PROFILE THROUGH MONTH 6
COHORT B (eGFR 30–44 mL/min/1.73 m²)

n (%)	Placebo	Zilebesiran			
	(N=27)	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)

- 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; this resolved and the patient fully recovered
- One death by cardiac arrest on Day 85 reported in a patient who received zilebesiran 150 mg was not considered treatment-related by the investigator

HYPERKALEMIA
COHORT B (eGFR 30–44 mL/min/1.73 m²)

n (%)	Placebo (N=27)	Zilebesiran 150 mg (N=24)	Zilebesiran 300 mg (N=26)	Zilebesiran 600 mg (N=26)	Zilebesiran Pooled (N=76)
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

- Most elevations were transient and occurred by Month 2
- None required hospitalization or dialysis
- One patient (zilebesiran 150 mg) had one background antihypertensive discontinued, one patient (zilebesiran 600 mg) had one background antihypertensive downtitrated and three patients (n=1 placebo, n=2 zilebesiran 600 mg) required treatment with potassium binders

eGFR DECLINE
COHORT B (eGFR 30–44 mL/min/1.73 m²)

n (%)	Placebo (N=27)	Zilebesiran 150 mg (N=24)	Zilebesiran 300 mg (N=26)	Zilebesiran 600 mg (N=26)	Zilebesiran Pooled (N=76)
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)

- Most reductions were transient
- None required hospitalization or dialysis
- Kidney dysfunction was managed by discontinuation of one background medication for two patients receiving zilebesiran 150 mg and one patient receiving zilebesiran 300 mg

HYPOTENSION AND ASSOCIATED EVENTS
COHORT B (eGFR 30–44 mL/min/1.73 m^2)

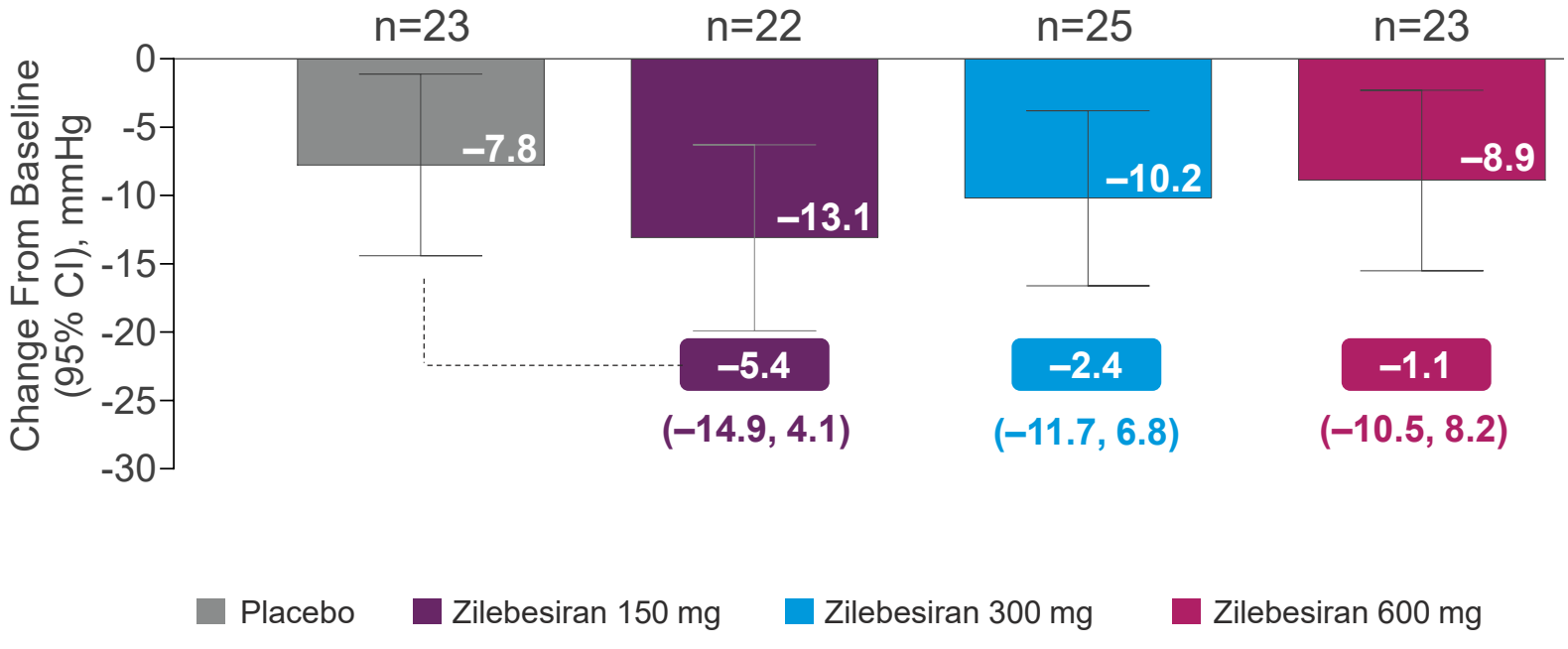
n (%)	Placebo (N=27)	Zilebesiran 150 mg (N=24)	Zilebesiran 300 mg (N=26)	Zilebesiran 600 mg (N=26)	Zilebesiran Pooled (N=76)
At least 1 hypotension AE	0	0	0	0	0
At least 1 AE potentially related to hypotension	1 (3.7)	0	1 (3.8)	0	1 (1.3)
Dizziness	1 (3.7)	0	0	0	0
Syncope	0	0	1 (3.8)	0	1 (1.3)

- Both events were transient and not serious

OFFICE SYSTOLIC BP AT MONTH 3

COHORT B (eGFR 30–44 mL/min/1.73 m²)

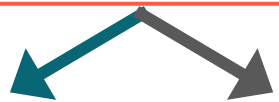
Placebo-Adjusted Change From Baseline



ZENITH CV Outcomes Trial Design

Study Population

- Adult patients with uncontrolled HTN and established CV disease or at high risk
- Office systolic BP ≥140 mmHg on stable treatment (≥2 antihypertensive medications, one of which is a diuretic)
- eGFR ≥30 mL/min/1.73 m^2, potassium ≤4.8 mEq/L



Randomize (n≈11,000)

Zilebesiran SC 300 mg Q6M + standard of care	Placebo SC Q6M + standard of care

Minimum follow-up: 2 years

Primary Outcome: CV death, nonfatal MI, nonfatal stroke, or HF event

ClinicalTrials.gov: NCT07181109.

For US HCPs Only

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KARDIA-3 CONCLUSIONS

- Among individuals with CV disease or at high CV risk who have uncontrolled HTN on multiple antihypertensives and CKD (eGFR 30–44 mL/min/1.73 m^2), single doses of zilebesiran 150, 300, and 600 mg had an acceptable safety profile
  - Most AEs were mild to moderate and transient
  - Low rates of kidney dysfunction, hyperkalemia, and hypotension
- There was no evidence of dose-dependent adverse effects, and the totality of Phase 2 data supports using the 300 mg zilebesiran dose, irrespective of kidney function
- The ZENITH trial is now enrolling and will evaluate the impact of this novel, long-acting RNAi therapy on CV outcomes in patients with HTN and established CV disease or high CV risk, with eGFR ≥30 mL/min/1.73 m^2

Thank you to the investigators and especially the participants who made the KARDIA-3 trial possible