

Subgroup Results from KARDIA-2: Impact of Demographic and Baseline Disease Characteristics on Zilebesiran Response in Patients with Hypertension Uncontrolled by a Standard Oral Antihypertensive

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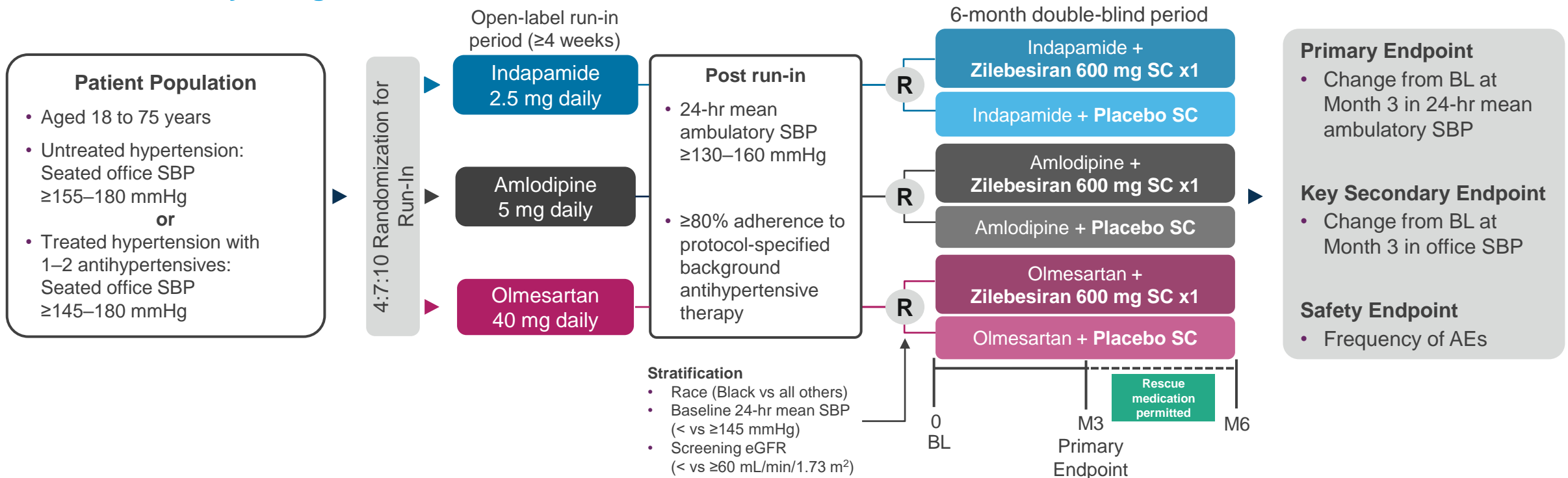
Presented at the European Society of Cardiology Congress, August 30–September 2, 2024, London, UK



Zilebesiran: An Investigational RNAi Therapeutic with Potential to Address Unmet Needs for Patients with Uncontrolled Hypertension

- Zilebesiran is designed to target hepatic synthesis of AGT, the most upstream precursor of RAS
- In the KARDIA-1 and KARDIA-2 studies, zilebesiran demonstrated clinically significant reductions in 24-hour mean ambulatory and office SBP versus placebo, enduring to 6 months in most cases^{1,2}

KARDIA-2 Study Design



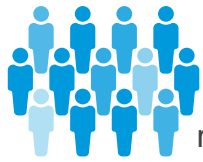
NCT05103332.

AE, adverse event; AGT, angiotensinogen; BL, baseline; eGFR, estimated glomerular filtration rate; hr, hour; M, month; R, randomization; RAS, renin–angiotensin system; RNAi, RNA interference; SBP, systolic blood pressure; SC, subcutaneous.

1. Bakris GL *et al.* *JAMA* 2024;331:740–9; 2. Bakris GL *et al.* Oral presentation presented at the American College of Cardiology Annual Scientific Session & Expo, April 7, 2024, Atlanta, GA, USA.

KARDIA₂ : Overview

Baseline Characteristics



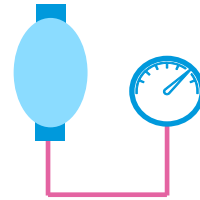
658
patients
randomized and
received treatment



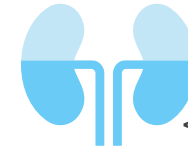
42.9%
Female

58.5
years
(mean age)

28.4%
Black/African
American

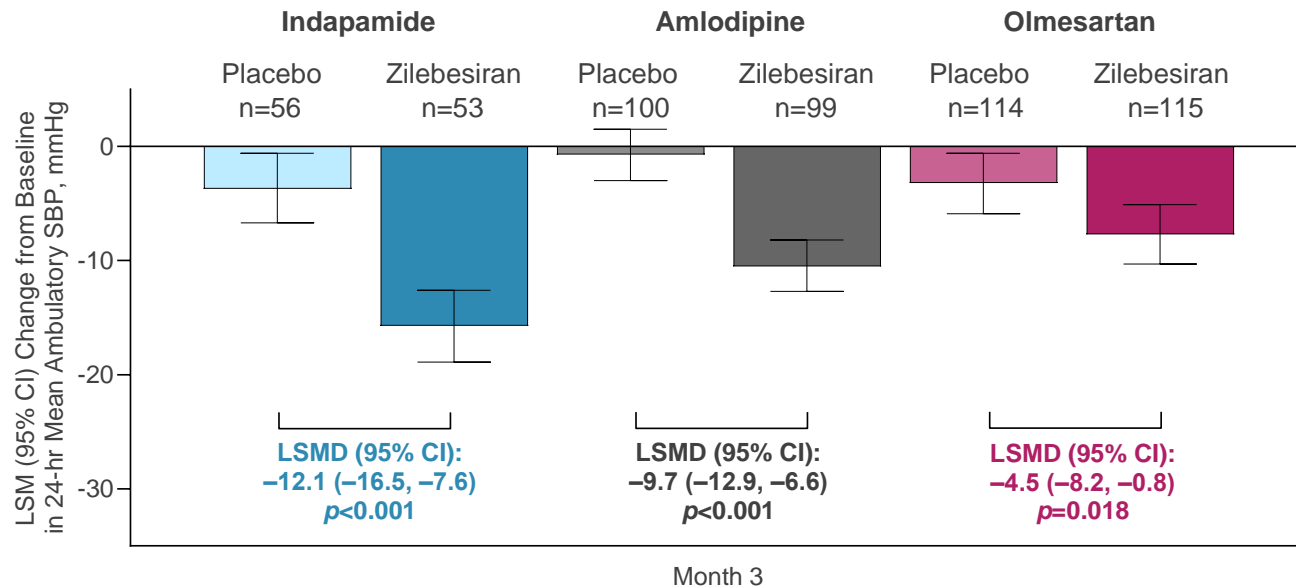


43.9%
of patients had
24-hour mean
ambulatory SBP
≥145 mmHg



10%
of patients
had eGFR
<60 mL/min/1.73m²

Primary Endpoint Results: 24-Hour Mean Ambulatory SBP at Month 3



Predefined Patient Subgroups

- Age (<65 or ≥65 years)
- Sex
- Race (Black or other)
- Baseline 24-hour mean ambulatory SBP (<145 or ≥145 mmHg)
- Baseline eGFR (<60 or ≥60 mL/min/1.73m²)
- Baseline BMI (<30 or ≥30 kg/m²)
- Diabetes mellitus status (yes or no)

Olmesartan cohort only:

- Run-in Visit 1 plasma renin concentration (≤ or > median)

Efficacy and safety analyses are based on patients who received any amount of study drug without critical GCP violations.

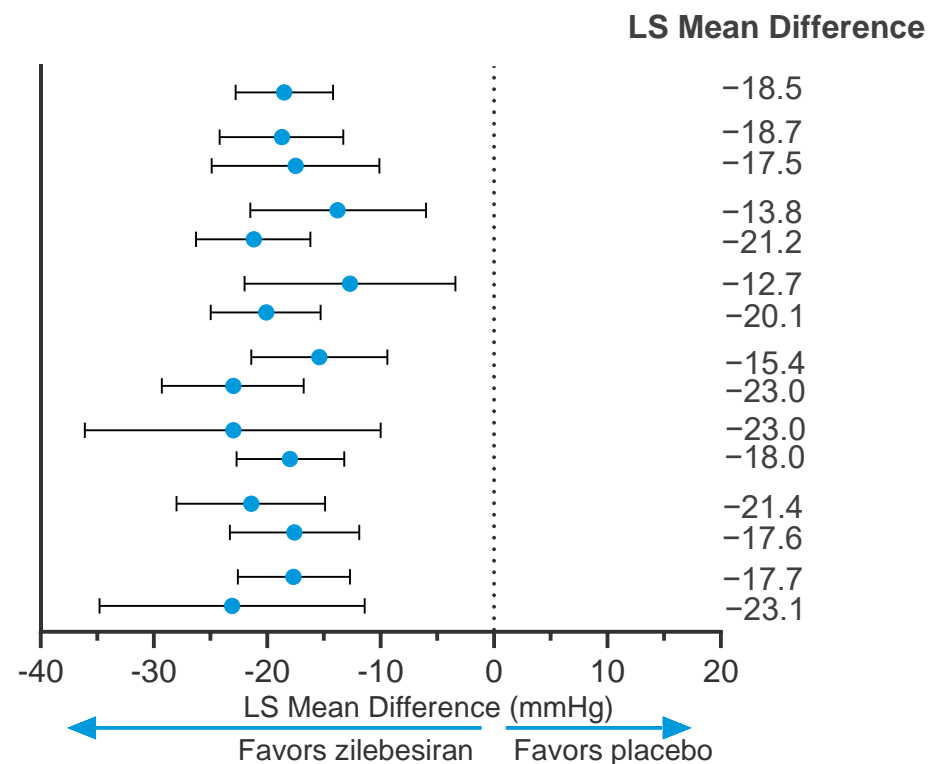
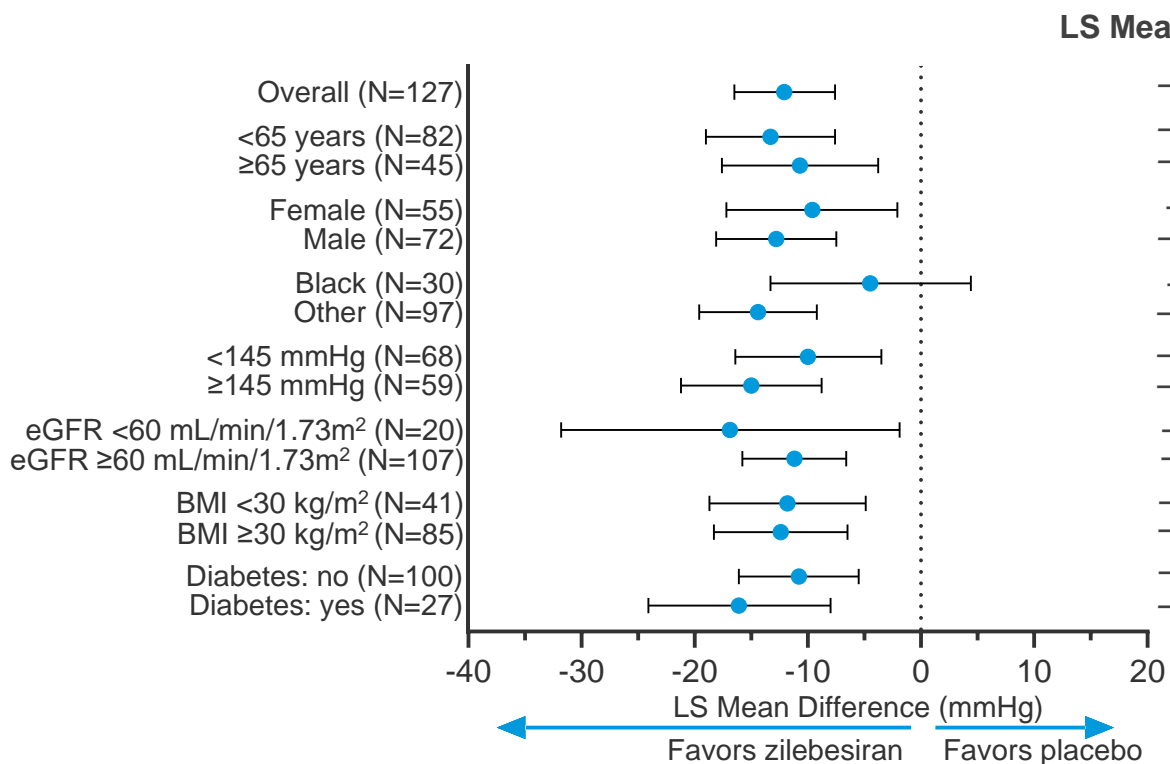
BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; hr, hour; LSM, least-squares mean; LSMD, least-squares mean difference; mFAS, modified full analysis set; SBP, systolic blood pressure.

1. Bakris GL *et al.* Oral presentation presented at the American College of Cardiology Annual Scientific Session & Expo, April 7, 2024, Atlanta, GA, USA.

Indapamide Cohort: Consistent Placebo-Adjusted SBP Reductions Were Observed Across Subgroups

Primary Endpoint: Change in 24-Hour Mean Ambulatory SBP at Month 3 (mFAS, N=127)

Secondary Endpoint: Change in Office SBP at Month 3 (mFAS, N=127)

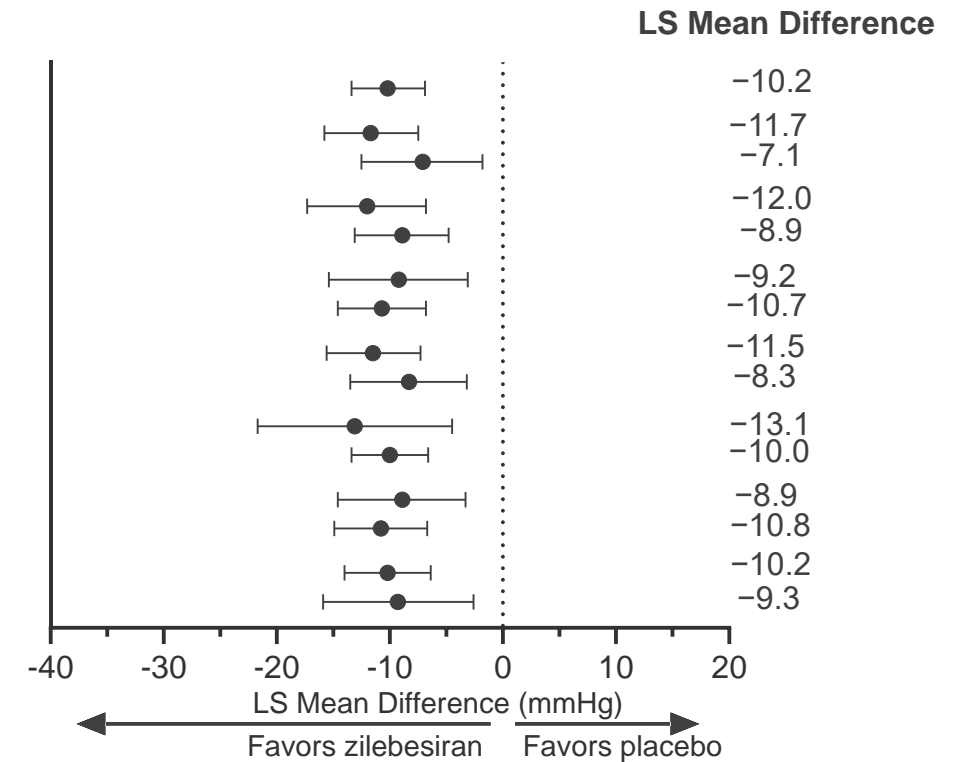
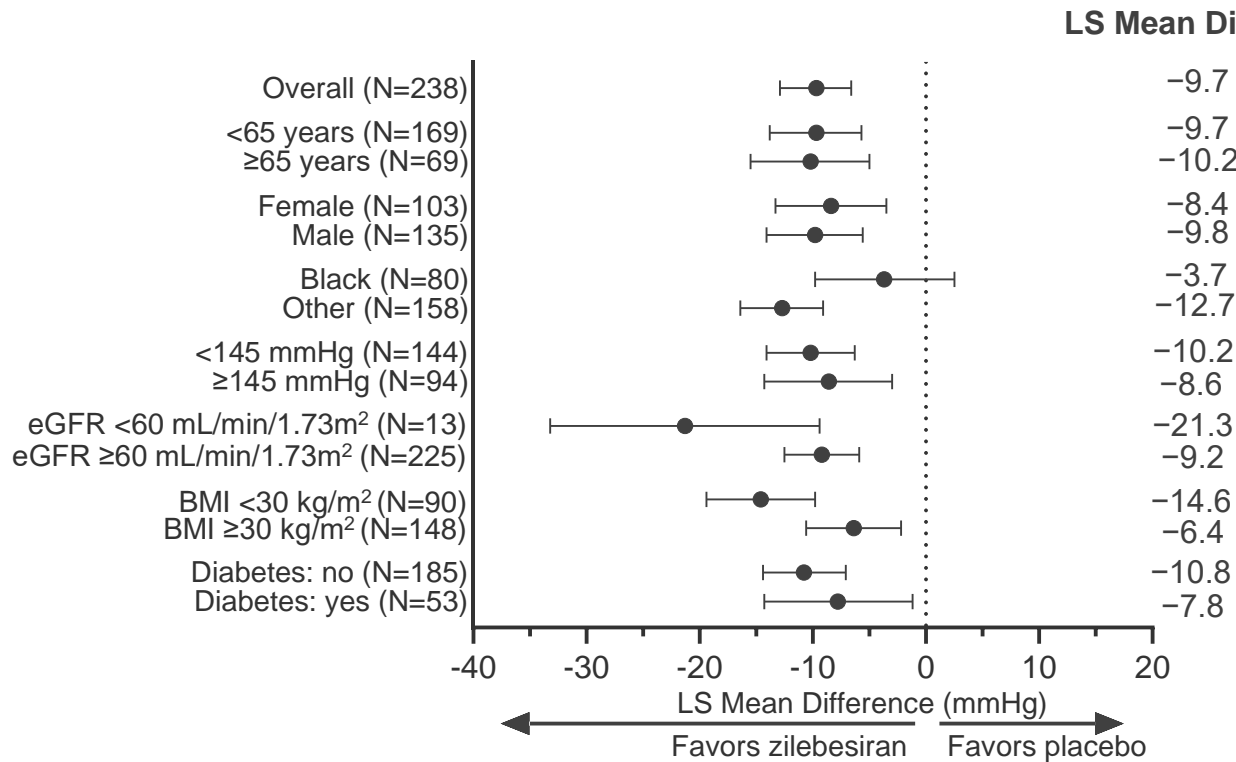


Data censored for rescue medication. The primary and secondary endpoints were evaluated as the LS mean difference in change from baseline treatment groups derived from a mixed model for repeated measures including treatment, visit, treatment-by-visit, and race (Black; all other races) as fixed factors and corresponding baseline SBP and baseline eGFR as covariates. 95% confidence intervals shown. BMI, body mass index; eGFR, estimated glomerular filtration rate; LS, least-squares; mFAS, modified full analysis set; SBP, systolic blood pressure.

Amlodipine Cohort: Consistent Placebo-Adjusted SBP Reductions Were Observed Across Subgroups

Primary Endpoint: Change in 24-Hour Mean Ambulatory SBP at Month 3 (mFAS, N=238)

Secondary Endpoint: Change in Office SBP at Month 3 (mFAS, N=238)

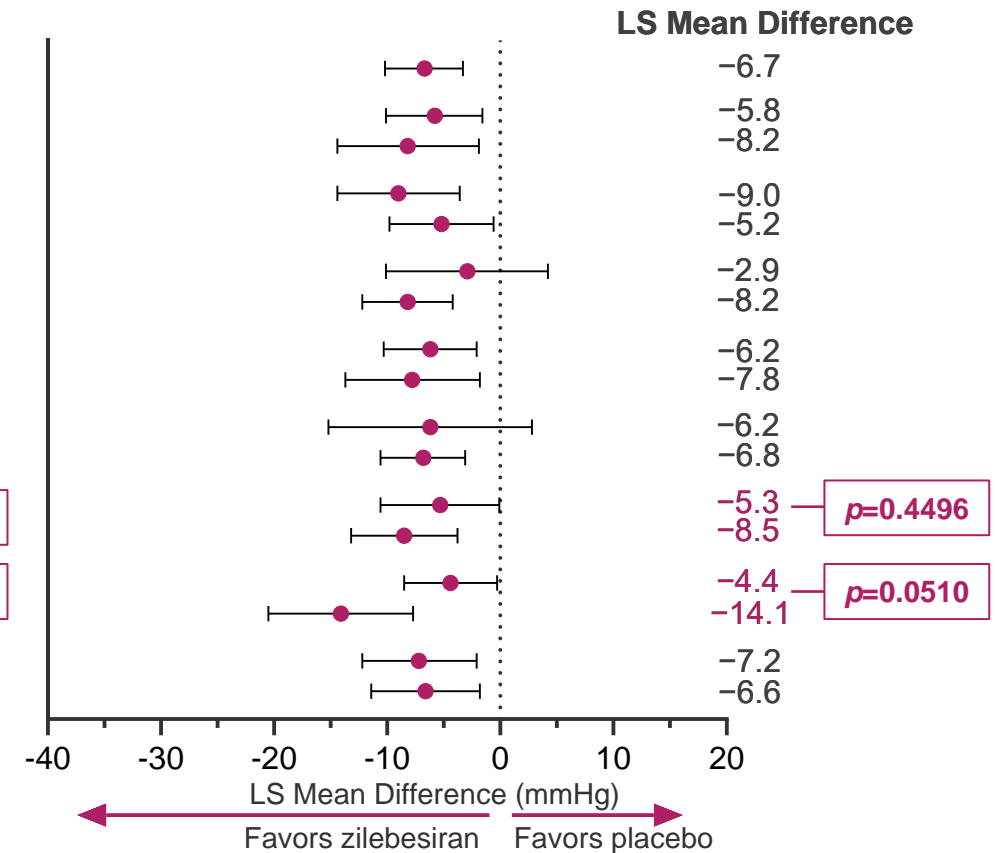
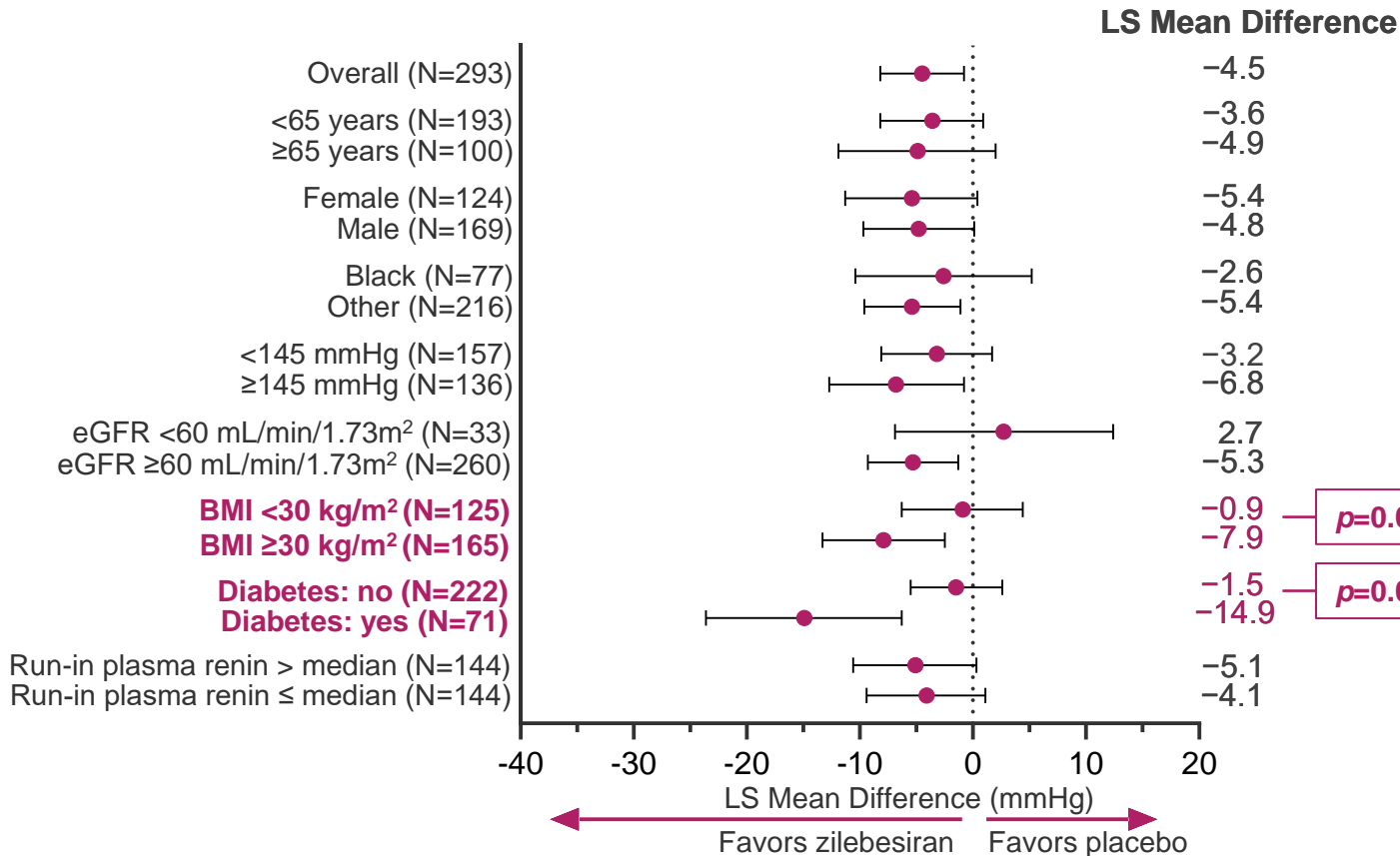


Data censored for rescue medication. The primary and secondary endpoints were evaluated as the LS mean difference in change from baseline treatment groups derived from a mixed model for repeated measures including treatment, visit, treatment-by-visit, and race (Black; all other races) as fixed factors and corresponding baseline SBP and baseline eGFR as covariates. 95% confidence intervals shown. BMI, body mass index; eGFR, estimated glomerular filtration rate; LS, least-squares; mFAS, modified full analysis set; SBP, systolic blood pressure.

Olmесartan Cohort: Consistent Placebo-Adjusted SBP Reductions Were Observed Across Most Subgroups

Primary Endpoint: Change in 24-Hour Mean Ambulatory SBP at Month 3 (mFAS, N=293)

Secondary Endpoint: Change in Office SBP at Month 3 (mFAS, N=293)



Data censored for rescue medication. The primary and secondary endpoints were evaluated as the LS mean difference in change from baseline treatment groups derived from a mixed model for repeated measures including treatment, visit, treatment-by-visit, and race (Black; all other races) as fixed factors and corresponding baseline SBP and baseline eGFR as covariates. 95% confidence intervals shown. BMI, body mass index; eGFR, estimated glomerular filtration rate; LS, least-squares; mFAS, modified full analysis set; SBP, systolic blood pressure.

Safety Profile Through Month 6 in the Overall Study Population

n (%)	Background Medication, mSAS					
	Indapamide		Amlodipine		Olmesartan	
	Placebo (N=64)	Zilebesiran (N=63)	Placebo (N=120)	Zilebesiran (N=118)	Placebo (N=145)	Zilebesiran (N=148)
At least 1 AE	25 (39.1)	31 (49.2)	56 (46.7)	64 (54.2)	69 (47.6)	87 (58.8)
At least 1 serious AE	2 (3.1)	0	1 (0.8)	3 (2.5)	4 (2.8)	4 (2.7)
Hypotension/orthostatic hypotension AE	0	0	4 (3.3)	7 (5.9)	3 (2.1)	7 (4.7)
Potassium >5.5 mmol/L	0	2 (3.2)	1 (0.8)	8 (6.8)	3 (2.1)	10 (6.8)
Confirmed by repeat measure	0	1 (1.6)	0	2 (1.7)	0	2 (1.4)
≥30% decrease from baseline in eGFR (mL/min/1.73m ²)	1 (1.6)	8 (12.7)	5 (4.2)	10 (8.5)	4 (2.8)	10 (6.8)
Confirmed by repeat measure	0	3 (4.8)	2 (1.7)	1 (0.8)	1 (0.7)	4 (2.7)

- Most hypotension AEs were mild and transient, and resolved without intervention
- Most laboratory abnormalities of interest occurred in the first 3 months and resolved upon repeat measurement within 1–2 weeks without intervention
- No apparent safety trends were observed by subgroup

KARDIA₂: Summary of Subgroup Analyses

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- Treatment with a single subcutaneous dose of zilebesiran was associated with clinically significant reductions in 24-hour mean ambulatory and office SBP compared with placebo at Month 3 when added to a thiazide-like diuretic, calcium channel blocker, or maximum-dose angiotensin receptor blocker, with consistency of treatment effect observed across most subgroups
- Zilebesiran had a favorable safety and tolerability profile over the 6-month study period when added to a standard-of-care antihypertensive, with no apparent safety trends observed by subgroup analysis
- Zilebesiran may be an effective treatment strategy for a broad population of patients with hypertension uncontrolled on monotherapy with a standard-of-care antihypertensive

The authors and sponsor would like to recognize and thank Dr George Bakris for his lifelong dedication to advancing the field of cardiometabolic medicine and his significant contributions to the zilebesiran program.

Thank you also to the patients, their families, investigators, study staff, and collaborators for their participation in the KARDIA-2 study.