Consistent Antihypertensive Efficacy of the RNA Interference Therapeutic Zilebesiran: Subgroup Results from the KARDIA-1 Phase 2 Study in Patients with Hypertension

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A Novel Investigational RNAi Therapeutic with Potential to Address an Unmet Need for Hypertension

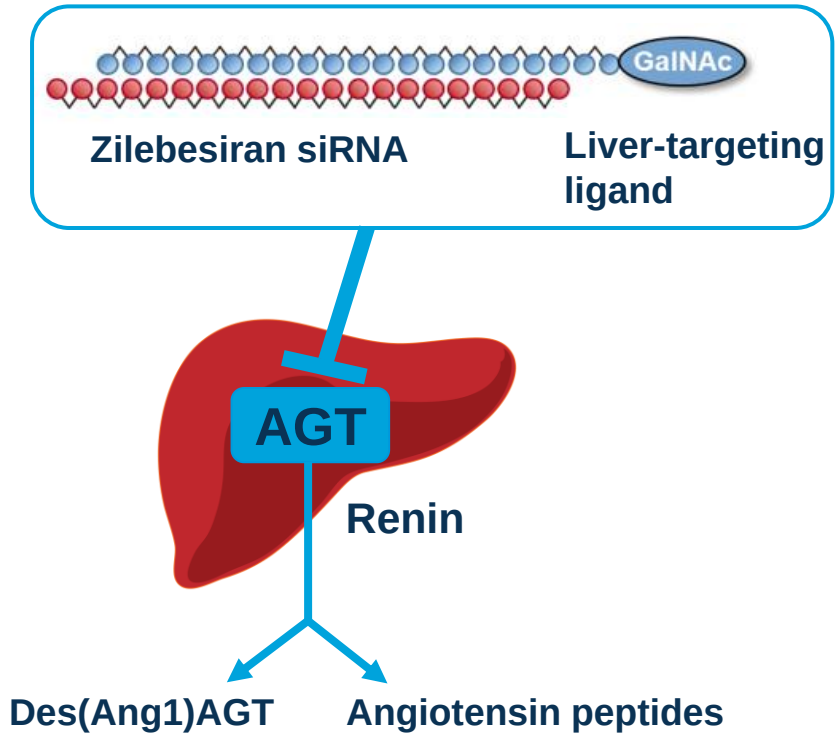
Zilebesiran

- An investigational subcutaneously administered RNA interference therapeutic targeting hepatic synthesis of AGT, the most upstream precursor of the renin–angiotensin system
- Demonstrated clinically meaningful, significant reductions in 24-hr mean ambulatory and office SBP compared to placebo at Month 3, which were sustained over 6 months in the Phase 2 KARDIA-1 study[1]

Objective

- To assess the efficacy and safety of zilebesiran across key patient subgroups from KARDIA-1

Zilebesiran Mediates Hepatic AGT Reduction



AGT, angiotensinogen; des(Ang1)AGT, des(Ang1)angiotensinogen; GalNAc, N-acetylgalactosamine; RNA, ribonucleic acid; RNAi, RNA interference; siRNA, small interfering ribonucleic acid.

1. Bakris GL, et al. *JAMA*. 2024;331(9):740-749

KARDIA-1: A Randomized, Double-Blind, Dose-Ranging Study of Zilebesiran in Patients with Mild-to-Moderate Hypertension

Patients (N=394)

- Age 18–75 years
- 2–4 week[a] washout of previous antihypertensive medication
- Daytime mean ambulatory SBP 135–160 mmHg

1:1:1:1:1 RANDOMIZATION

- Placebo Q3M SC
- OR
- Zilebesiran 150 mg Q6M SC
- OR
- Zilebesiran 300 mg Q6M SC
- OR
- Zilebesiran 300 mg Q3M SC
- OR
- Zilebesiran 600 mg Q6M SC

Primary Endpoint: Change from baseline at Month 3 in 24-hr mean ambulatory SBP[b]

Key Secondary Endpoint: Change from baseline at Month 3 in office SBP[b]

Safety Endpoint: Frequency of AEs

Subgroups[c,d]

- Age
- Sex
- Race
- Baseline 24-hr mean ambulatory SBP
- Baseline eGFR
- Baseline plasma renin concentration

NCT04936035. [a]Patients previously taking medication for hypertension must have been without antihypertensives for ≥2 weeks before randomization. Four weeks of washout was required for long-acting antihypertensive. [b]For analyses of Month 3 endpoints, zilebesiran 300 mg Q3M and Q6M data were pooled together. [c]Changes in SBP as defined by the primary endpoint and key secondary endpoints involving continuous variables were re-analyzed according to these subgroups. LSM difference in change from baseline in SBP at Month 3 were calculated. [d]Subgroup analyses defined by age (<65, ≥65), sex (male, female), race (black, other), baseline 24-hr mean ambulatory SBP (<145 mmHg, ≥145 mmHg), and baseline eGFR (<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2) were prespecified; analysis of the subgroup defined by baseline plasma renin concentration (≤11 mIU/L, >11 mIU/L) was conducted post hoc, based on median plasma renin concentration: 11 mIU/L.

AE, adverse event; eGFR, estimated glomerular filtration rate; LSM, least-squares mean; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure; SC, subcutaneous.

Baseline Demographics and Characteristics

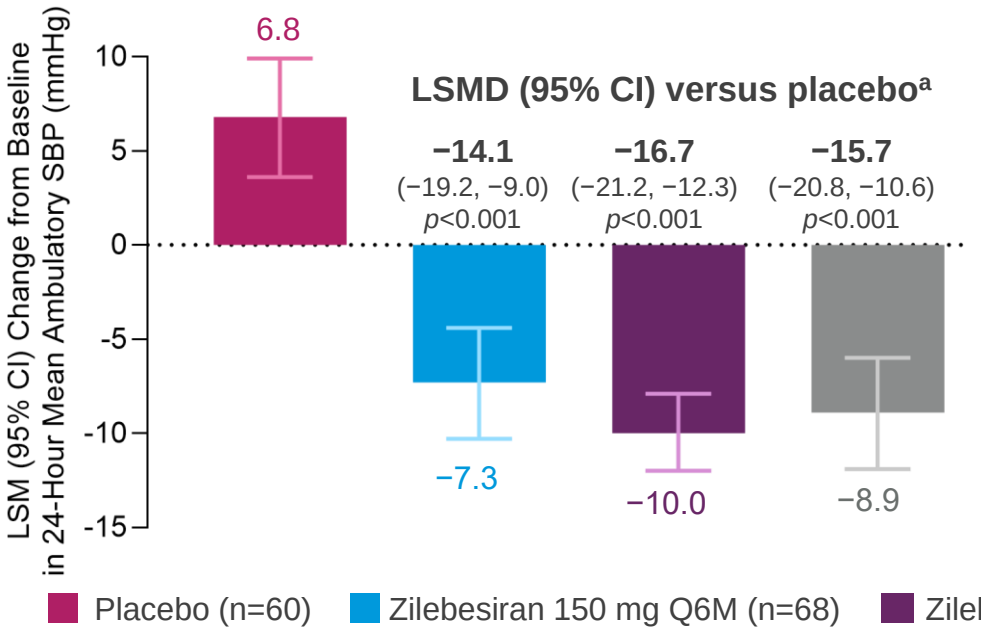
	Placebo (N=75)	Zilebesiran (all doses combined) (N=302)	Total (N=377)
Mean age, years (min, max)	56.8 (33, 75)	56.7 (22, 75)	56.8 (22, 75)
Age ≥65 years, n (%)	21 (28.0)	82 (27.2)	103 (27.3)
Male, n (%)	37 (49.3)	173 (57.3)	210 (55.7)
BMI ≥30 kg/m^2, n (%)	37 (49.3)	177 (58.6)	214 (56.8)
Race, n (%)			
Asian	5 (6.7)	18 (6.0)	23 (6.1)
Black	18 (24.0)	75 (24.8)	93 (24.7)
White	52 (69.3)	207 (68.5)	259 (68.7)
Any other race	0	2 (0.7)	2 (0.5)
Mean baseline BP, mmHg (SD)			
24-hr ambulatory SBP	141.1 (7.9)	141.9 (8.6)	141.8 (8.4)
24-hr ambulatory DBP	81.7 (7.8)	81.9 (8.4)	81.8 (8.3)
Office SBP	143.1 (13.3)	141.4 (11.0)	141.8 (11.5)
Office DBP	87.9 (10.5)	86.8 (9.1)	87.0 (9.4)
eGFR <60 mL/min/1.73 m^2, n (%)	11 (14.7)	27 (8.9)	38 (10.1)

Analysis population includes all randomized patients who received any amount of study drug and excludes patients enrolled at sites in Ukraine.

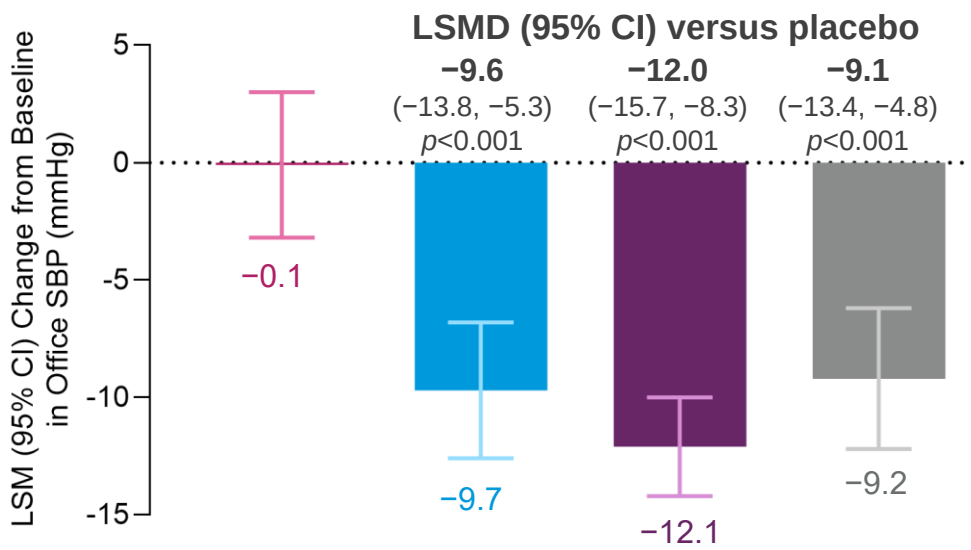
BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SD, standard deviation.

Primary Results Showed Significantly Reduced SBP at Month 3 and an Encouraging Safety Profile

24-hr Mean Ambulatory SBP
(Primary Endpoint)



Office SBP
(Key Secondary Endpoint)



Placebo (n=60) | Zilebesiran 150 mg Q6M (n=68) | Zilebesiran 300 mg Q6M and Q3M combined (n=137[b]) | Zilebesiran 600 mg Q6M (n=65[c])

- SBP reductions were sustained through Month 6

Safety

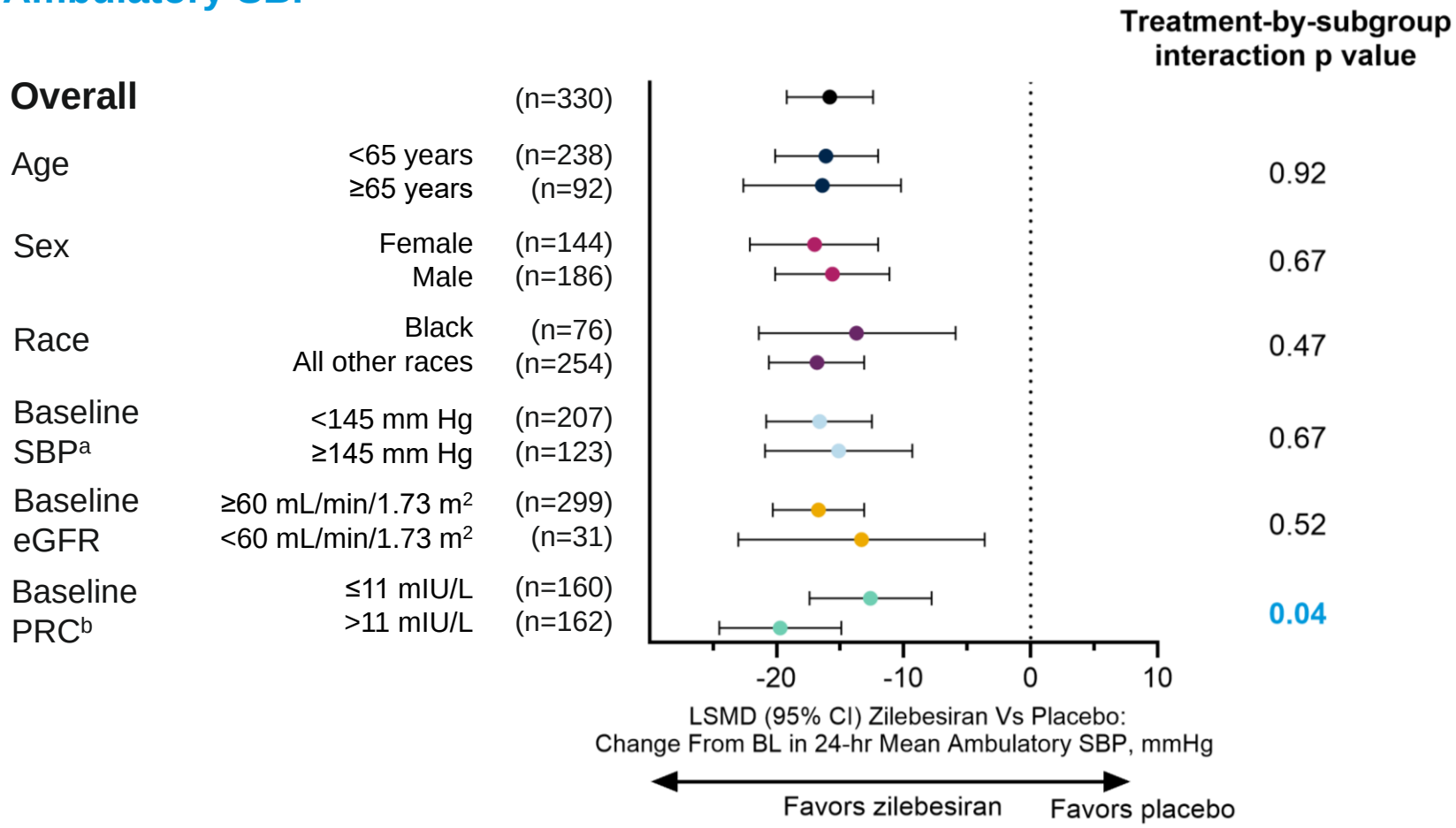
- Rates of serious or severe AEs were low; no drug-related AEs were serious or severe
- Most hyperkalemia and hypotension AEs were mild, transient, and resolved without intervention[d]

Rescue antihypertensive medication was permitted after Month 3 assessments and was discontinued by Month 5 for Month 6 assessments. Blood pressure assessments were censored if taken while patients were receiving or in the 2 weeks after stopping any rescue medication. [a]Adjusted 95% CI and p values for the Month 3 primary analysis are based on Dunnett's test. [b]n=133 for office SBP data. [c]n=64 for office SBP data. [d]One hypotension event (zilebesiran 300 mg Q3M) requiring treatment with normal saline.

AE, adverse event; CI, confidence interval; LSM, least-squares mean; LSMD, least-squares mean difference; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure. Bakris GL, et al. *JAMA*. 2024;331:740–749

Consistent Placebo-Adjusted Ambulatory SBP Reductions Were Observed Across Subgroups at Month 3

LSM Difference (95% CI) between Zilebesiran (All Doses Combined) and Placebo in Change From Baseline in 24-hr Mean Ambulatory SBP

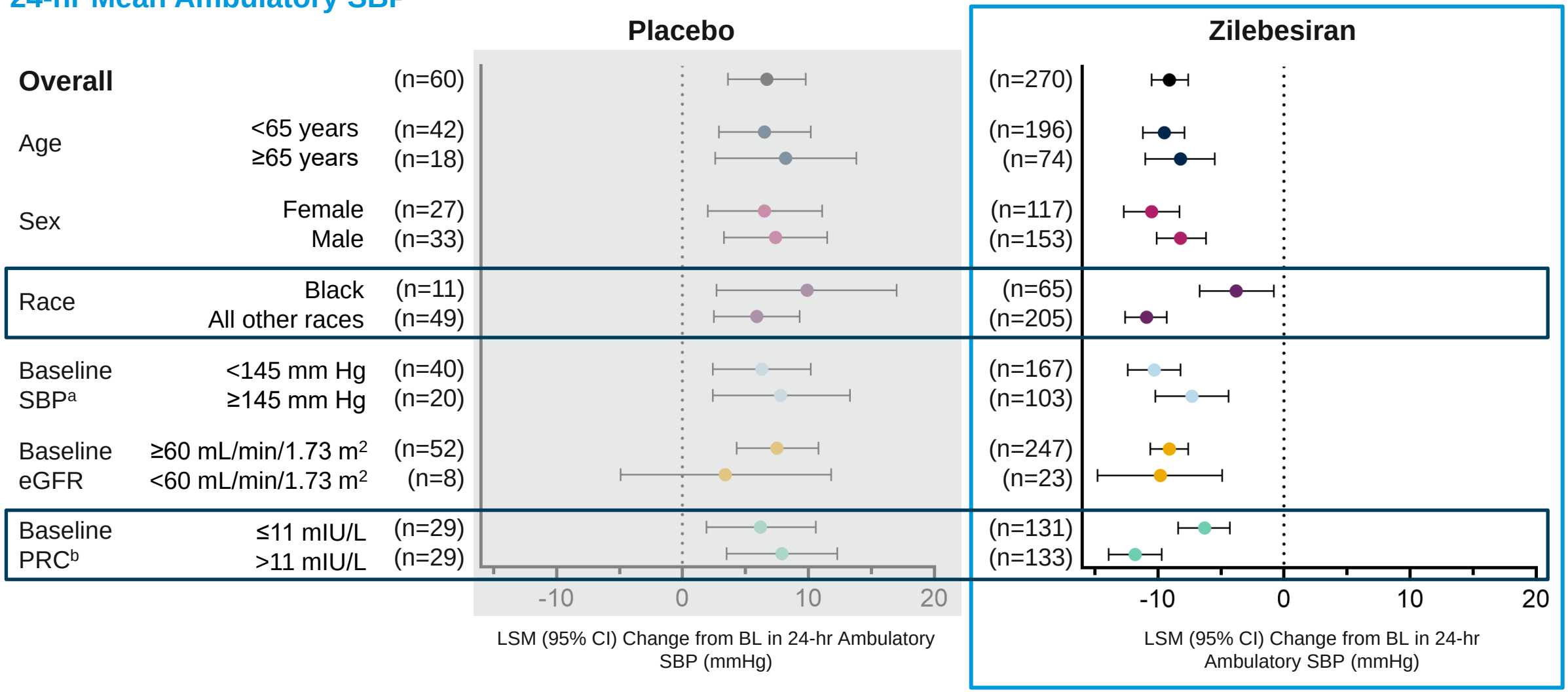


For subgroup analyses, MMRM model includes treatment, visit, subgroup and treatment-by-visit, treatment-by-subgroup, subgroup-by-visit, treatment by visit by subgroup interaction terms, race (black, all other races) when race is not the subgroup to be analyzed, as fixed factors, baseline 24-hr mean SBP assessed by ABPM as a covariate. [a]24-hr mean assessed by ABPM. [b]Baseline PRC above or below median (11 mIU/L).

ABPM, ambulatory blood pressure monitoring; BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; LSMD, least-squares mean difference; MMRM, mixed model for repeated measurements; PRC, plasma renin concentration; SBP, systolic blood pressure.

Change From Baseline in Ambulatory SBP

LSM (95% CI) Change from Baseline in Patients Treated with Zilebesiran (All Doses Combined) and Placebo in 24-hr Mean Ambulatory SBP



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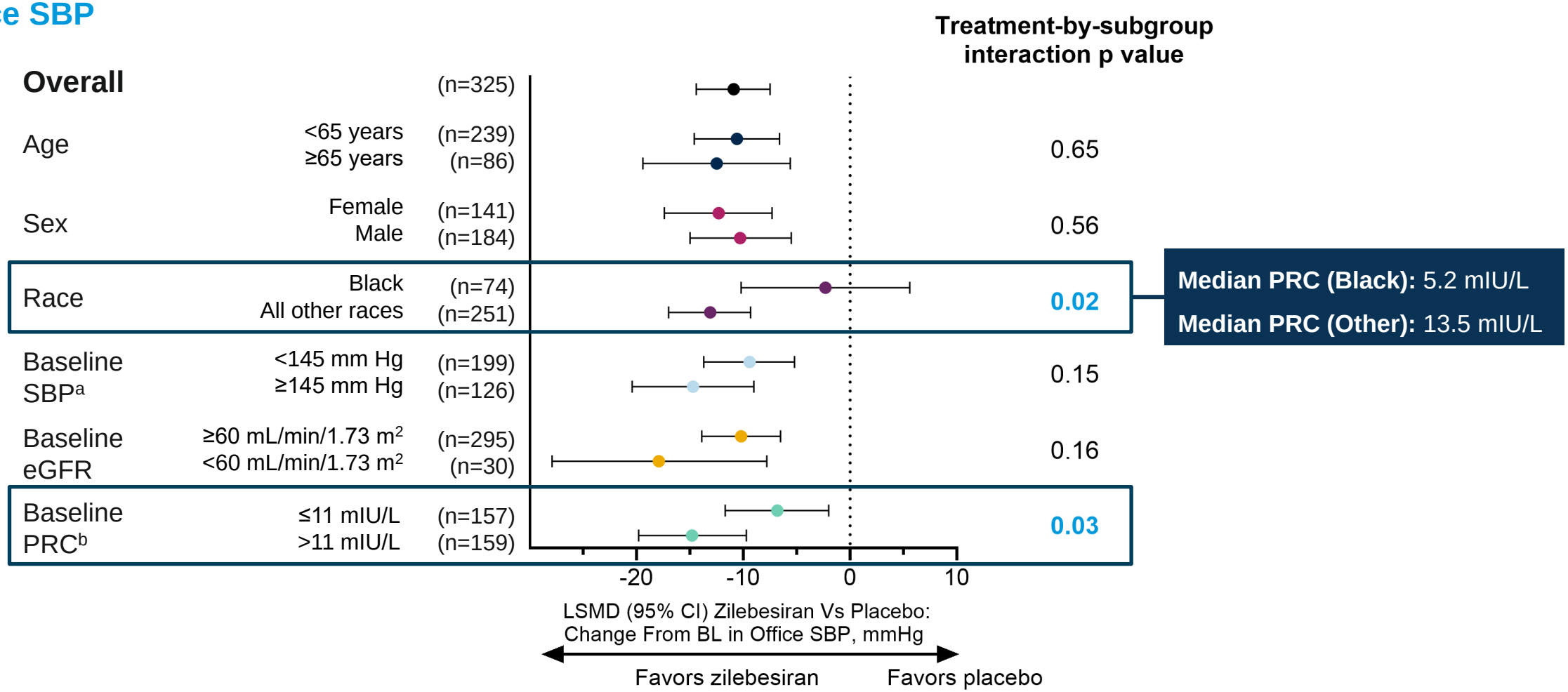
ABPM, ambulatory blood pressure monitoring; BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; LSM, least-squares mean; MMRM, mixed model for repeated measurements; PRC, plasma renin concentration; SBP, systolic blood pressure.

Consistent Placebo-Adjusted Office SBP Reductions Were Observed Across Most Subgroups at Month 3

LSM Difference (95% CI) between Zilebesiran (All Doses Combined) and Placebo in Change From Baseline in Office SBP



For subgroup analyses, MMRM model includes treatment, visit, subgroup and treatment-by-visit, treatment-by-subgroup, subgroup-by-visit, treatment by visit by subgroup interaction terms, race (black, all other races) when race is not the subgroup to be analyzed, as fixed factors, baseline office SBP as a covariate. [a]24-hr mean assessed by ABPM. [b]Baseline PRC above or below median (11 mIU/L).

ABPM, ambulatory blood pressure monitoring; BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; LSMD, least-squares mean difference; MMRM, mixed model for repeated measurements; PRC, plasma renin concentration; SBP, systolic blood pressure.

Change from Baseline in SBP at Month 3 for PRC×Race Subgroups

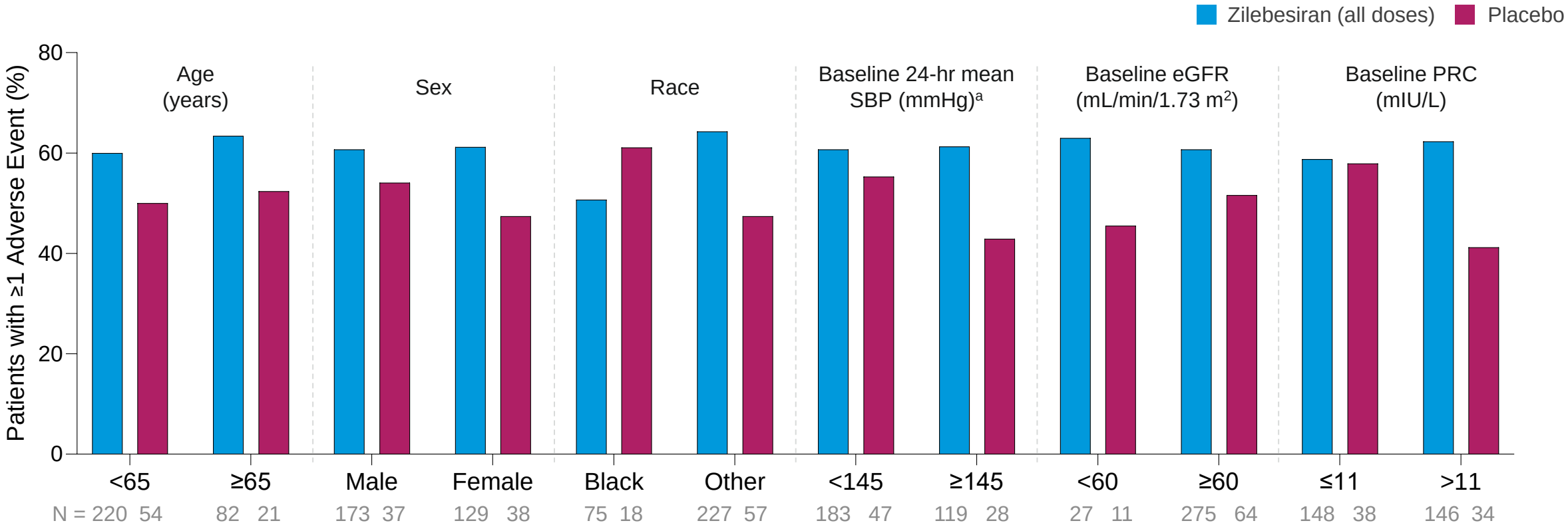
LSM Change From Baseline (SE) in Patients Treated with Zilebesiran (All Doses Combined)

Race	Baseline PRC above or below median (11 mIU/L)	Zilebesiran (all doses combined)	
		24-hr mean ambulatory SBP	Office SBP
Black Median PRC: 5.2 mIU/L	**≤11 mIU/L** (N=52)	**−0.7** (2.1)	**−2.7** (2.0)
	>11 mIU/L (N=17)	**−12.1** (3.0)	**−13.4** (2.5)
All other races Median PRC: 13.5 mIU/L	**≤11 mIU/L** (N=96)	**−8.3** (1.2)	**−10.9** (1.2)
	>11 mIU/L (N=129)	**−12.6** (1.1)	**−13.7** (1.1)

- Greater mean SBP reductions were observed in patients with higher baseline PRC, across both 24-hr mean ambulatory and office measures

MMRM model includes treatment, visit, treatment-by-visit interaction, as fixed factors, baseline SBP (24-hour mean SBP assessed by ABPM or office SBP) as a covariate. Placebo data not presented owing to small sample size.
ABPM, ambulatory blood pressure monitoring; LSM, least-squares mean; PRC, plasma renin concentration; SBP, systolic blood pressure; SE, standard error.

Consistent Safety of Zilebesiran Across Subgroups Over 6 Months



- Overall, AEs were reported in 50.7–64.3% of patients who received zilebesiran across subgroups
- Frequency of key AEs of interest[b] (acute renal failure, hypotension, and hyperkalemia) was low and mostly transient without the need for intervention, with no notable differences across most subgroups
  - Slight increases in hypotension rates were observed in patients ≥65 years or eGFR <60 mL/min/1.73m^2

[a]24-hr mean assessed by ABPM.. [b]AEs are defined per MedDRA terminology. Acute renal failure includes events of increased serum creatinine, increased blood urea, decreased glomerular filtration rate, and acute kidney injury. Hyperkalemia AEs include hyperkalemia and increased serum potassium. Hypotension AEs include decreased blood pressure, hypotension, and orthostatic hypotension.

ABPM, ambulatory blood pressure monitoring; AE, adverse event; eGFR, estimated glomerular filtration rate; MedDRA, Medical Dictionary for Regulatory Activities; PRC, plasma renin concentration; SBP, systolic blood pressure.

Conclusions

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- In KARDIA-1, efficacy and safety of zilebesiran versus placebo were generally consistent across subgroups of interest defined by baseline demographic and disease characteristics
  - Greater SBP reductions in patients with high baseline plasma renin concentration are consistent with the mechanism of action of zilebesiran
  - Variation in SBP reductions in black patients versus all other patients in KARDIA-1 is largely explained by differences in baseline plasma renin concentrations, therefore rectifying low renin profiles in black patients may augment the treatment response to zilebesiran
- Quarterly or biannual subcutaneous dosing of zilebesiran may be an effective treatment strategy in a broad population of patients with hypertension
- Further research is needed to elucidate the impact of plasma renin concentration, race, and background antihypertensives on zilebesiran treatment response

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the KARDIA-1 study

SBP, systolic blood pressure.