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Zilebesiran as Add-on Treatment to RAAS Inhibitors for Patients with Hypertension: Data from KARDIA-2 and KARDIA-3 Phase 2 Trials

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Disclosure for David C Wheeler

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Conflict	Disclosure - if conflict of interest exists
Research Support	
Director, Officer, Employee	
Shareholder	
Honoraria	Alnylam, Amgen, AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, CSL Vifor, Dimerix, Emerald Clinical, Mineralys, MSD, Purespring, Pathalys, Roche, Sana, Senya, Silence, ThermoFisher, and Vertex.
Advisory Committee	
Consultant	

Unlabeled/Unapproved Use Disclosure:
Zilebesiran is an investigational product in development for treatment of patients with hypertension.

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

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The Problem: Uncontrolled Hypertension

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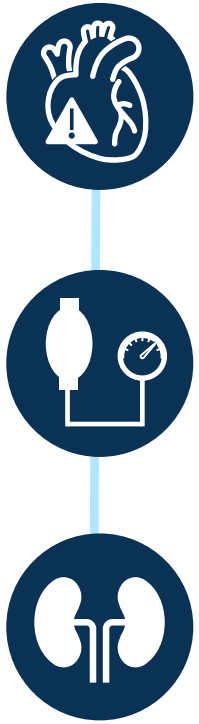


Uncontrolled HTN is the greatest contributor to CV morbidity and mortality worldwide[1]

Despite the availability of effective therapies, many patients do not achieve and maintain BP goals[2]

Treatment options for patients with CKD may be further limited as kidney function declines[3,4]

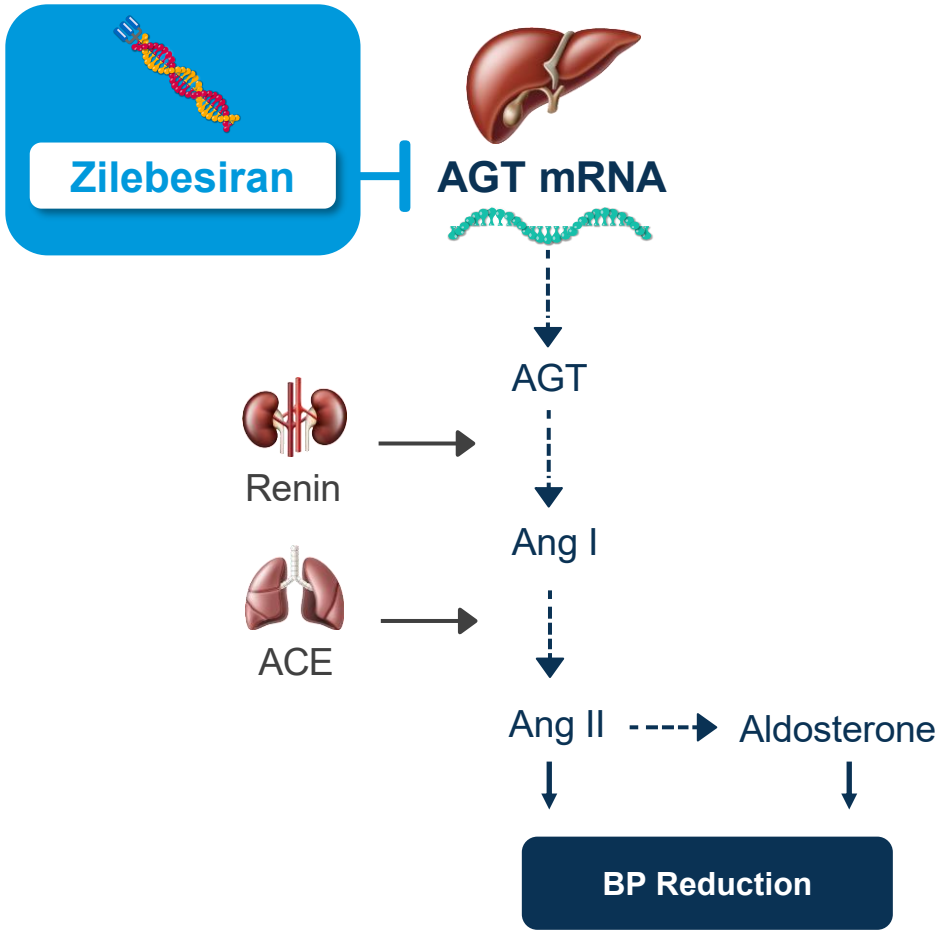
An effective, long-acting therapy that provides continuous control of BP may help to reduce the burden of uncontrolled HTN and associated morbidity and mortality

BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; HTN, hypertension; RAAS, renin–angiotensin–aldosterone system. 1. Magnussen C *et al. N Engl J Med* 2023;389:1273–85. 2. Choudhry NK *et al. Hypertension* 2022;79:e1–e14. 3. Jones *DW et al. Circulation* 2025;152:e114–e218. 4. McEvoy JW *et al. Eur Heart J* 2024;45:3912–4018.

Zilebesiran

- An investigational RNA interference therapeutic
- Reduces hepatic production of AGT, the most upstream precursor in the RAAS pathway
- Has the potential to provide continuous control of BP with subcutaneous dosing every 6 months

Zilebesiran Suppresses the RAAS Pathway



ACE, angiotensin-converting enzyme; AGT, angiotensinogen; Ang, angiotensin; BP, blood pressure; RAAS, renin–angiotensin–aldosterone system.

Zilebesiran Phase 2 Summary

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	Phase 2		
	KARDIA-1	KARDIA-2	KARDIA-3
Trial Setting	N=394 randomized[1] **Monotherapy in adults with mild-to-moderate HTN**	N=663 randomized[2] **Add-on therapy in adults with HTN inadequately controlled with amlodipine, indapamide, or olmesartan**	N=375 randomized[3,4] **Add-on therapy in adults with uncontrolled HTN on 2–4 antihypertensives and CVD or high CV risk**
Efficacy at Month 3	Placebo-adjusted office systolic BP: up to ↓ 12.0 mmHg	Placebo-adjusted office systolic BP: ↓ 18.5 mmHg with diuretic ↓ 10.2 mmHg with CCB ↓ 6.7 mmHg with ARB	Placebo-adjusted office systolic BP: up to ↓ 5.0 mmHg in **Cohort A**[a] (eGFR ≥45 mL/min/1.73 m^2) up to ↓ 5.4 mmHg in **Cohort B**[b] (eGFR 30–44 mL/min/1.73 m^2)
Safety to Month 6	Manageable safety profile	Manageable safety profile	Manageable safety profile

[a]Statistical significance was not reached after multiplicity control. [b]Cohort B was not powered to assess efficacy. 1. Bakris GL *et al*. *JAMA* 2024;331:740–9. 2. Desai AS *et al*. *JAMA* 2025;334:46–55. 3. Pagidipati N *et al*. European Society of Cardiology Congress, August 29–September 1, 2025, Madrid, Spain. [Oral presentation]. 4. Pagidipati N *et al*. American Heart Association Scientific Sessions, November 7–10, 2025, New Orleans, LA, USA. [Oral presentation]. ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HTN, hypertension.

KARDIA$_3$: BP-Lowering Potential of Zilebesiran

Cohort A: eGFR ≥45 mL/min/1.73 m^2

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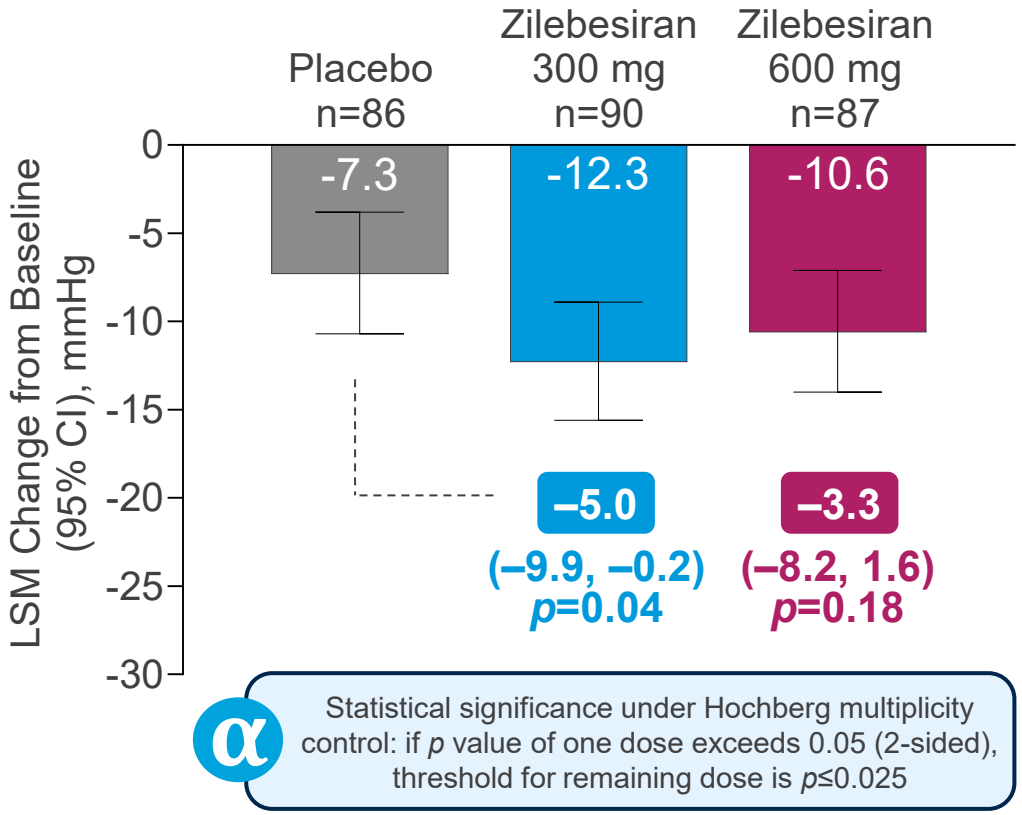
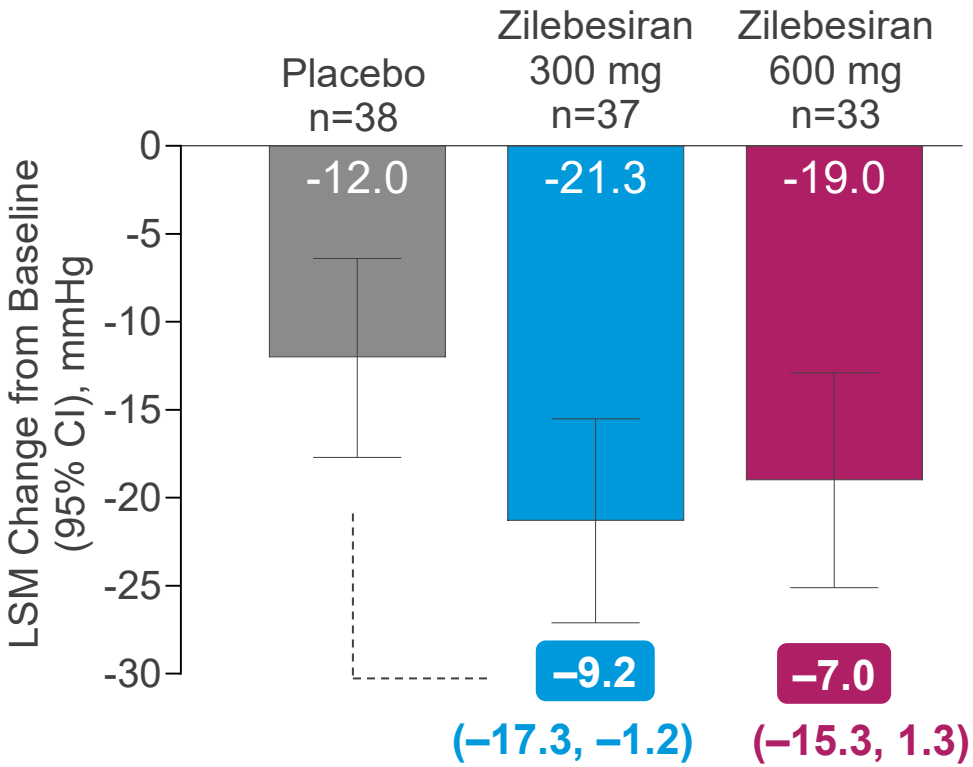
Primary Outcome:[1]

Office Systolic BP at Month 3



Post Hoc Analysis:[1]

Office Systolic BP at Month 3 in Patients on Diuretic with Baseline Systolic BP ≥140 mmHg



Proportion of patients receiving background ACEi/ARB at baseline: 90.7% in overall Cohort A, 87.3% in patients on diuretic with baseline systolic BP ≥140 mmHg. Figure annotations show LSM difference versus placebo. 1. Pagidipati N *et al*. European Society of Cardiology Congress, August 29–September 1, 2025, Madrid, Spain. [Oral presentation]. ACEi, angiotensin–converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; LSM, least-squares mean.

KARDIA-3 Safety Summary[1,2]

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	N (%)	Cohort A: eGFR ≥45 mL/min/1.73 m²			Cohort B: eGFR 30–44 mL/min/1.73 m²	
		Placebo (N=88)	Zilebesiran 300 mg (N=91)	Zilebesiran 600 mg (N=91)	Placebo (N=27)	Zilebesiran pooled doses (N=76)
TEAEs	At least 1 AE	38 (43.2)	47 (51.6)	46 (50.5)	15 (55.6)	42 (55.3)
	At least 1 serious AE	4 (4.5)	1 (1.1)	6 (6.6)	1 (3.7)	5 (6.6)
	At least 1 serious AE related to study drug	0	0	1 (1.1)	0	1 (1.3)
	Death	0	0	0	0	1 (1.3)[a]
	At least 1 hypotension AE	3 (3.4)	3 (3.3)	4 (4.4)	0	0
Laboratory measurements	Potassium >5.5 mmol/L	4 (4.5)	4 (4.4)	8 (8.8)	3 (11.1)	10 (13.2)
	Confirmed by subsequent measurement	1 (1.1)	3 (3.3)	1 (1.1)	0	3 (3.9)
	Potassium >6.0 mmol/L	0	0	0	1 (3.7)	2 (2.6)
	Confirmed by subsequent measurement	–	–	–	0	0
	eGFR ≥30% decrease from baseline **and** final eGFR <60 mL/min/1.73 m²	1 (1.1)	5 (5.5)	8 (8.8)	3 (11.1)	7 (9.2)
	Confirmed by subsequent measurement	1 (1.1)	2 (2.2)	2 (2.2)	0	2 (2.6)

[a]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. 1. Pagidipati N *et al*. European Society of Cardiology Congress, August 29–September 1, 2025, Madrid, Spain. [Oral presentation]. 2. Pagidipati N *et al*. American Heart Association Scientific Sessions, November 7–10, 2025, New Orleans, LA, USA. [Oral presentation]. AE, adverse event; eGFR, estimated glomerular filtration rate; TEAE, treatment-emergent adverse event.

Dual RAAS Targeting With RAAS Inhibitors Has Previously Demonstrated Safety Concerns and Limited Benefits

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	ONTARGET[1]	ALTITUDE[2]
	Patients with vascular disease or high-risk diabetes	Patients with type 2 diabetes
	ACEi ramipril **+ ARB** telmisartan n=8502 **VS** **ACEi** ramipril alone n=8576	**ACEi or ARB + renin inhibitor** aliskiren n=4274 **VS** **ACEi or ARB** + placebo n=4287
BP lowering	Systolic BP ↓ 2–3 mmHg vs ACEi alone	Systolic BP ↓ 2 mmHg vs ACEi/ARB alone
CV effects	No significant difference in risk for MI, stroke, hospitalization for HF, CV or non-CV death, or death from any cause	No difference in risk for MI, stroke, hospitalization for HF, death from CV disease, end-stage renal disease, death attributable to kidney failure or loss of kidney function or death from any cause
Safety	Significant ↑ risk of hypotension, syncope, renal impairment, and hyperkalemia Trend toward ↑ risk of renal dysfunction requiring dialysis	↑ risk of hypotension, hyperkalemia, and hypoglycemia

1. ONTARGET Investigators *et al. N Engl J Med* 2008;358:1547–59. 2. Parving HH *et al. N Engl J Med* 2012;367:2204–13. ACEi, angiotensin–converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; RAAS, renin–aldosterone–angiotensin system.

KARDIA Patients Receiving a Background RAAS Inhibitor: Analysis Objective

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Dual RAAS targeting with RAAS inhibitors has demonstrated safety concerns and limited benefits[1,2]

In contrast to RAAS inhibitors zilebesiran targets AGT, the most upstream substrate in the RAAS pathway

This pooled analysis of all patients receiving a RAAS inhibitor in Phase 2 KARDIA studies aimed to **assess safety and efficacy of zilebesiran on top of a RAAS inhibitor** in patients with HTN, including those with reduced kidney function

1. ONTARGET Investigators *et al. N Engl J Med* 2008;358:1547–59. 2. McMurray JJV *et al. N Engl J Med* 2016;374:1521–32.
AGT, angiotensinogen; HTN, hypertension; RAAS, renin–aldosterone–angiotensin system.

KARDIA Patients Receiving a Background RAAS Inhibitor: Methods

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KARDIA-2	KARDIA-3
Population: adults with inadequately controlled HTN and eGFR ≥30 mL/min/1.73 m^2	**Population:** adults with uncontrolled HTN and CVD or CV risk with eGFR ≥45 (Cohort A) or 30–44 mL/min/1.73 m^2 (Cohort B)
Dosing: amlodipine, indapamide, or olmesartan + zilebesiran 600 mg, or placebo	**Dosing:** standard of care + zilebesiran 150 (Cohort B only), 300, 600 mg, or placebo

Pooled analyses of all KARDIA patients receiving a background RAAS inhibitor

	Subgroup of interest: olmesartan + zilebesiran or placebo	**Subgroup of interest:** baseline ACEi or ARB + zilebesiran or placebo
Safety analysis (N=625)	All patients in subgroup of interest	All patients in subgroup of interest
Efficacy analysis (N=601)	All patients in subgroup of interest	All patients in subgroup of interest excluding zilebesiran 150 mg dose group

ACEi, angiotensin–converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; RAAS, renin–angiotensin–aldosterone system.

KARDIA Patients Receiving a Background RAAS Inhibitor: Baseline Demographics and Disease Characteristics

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	Placebo (N=246)	Zilebesiran (N=379)
Age, years, mean (SD)	61.4 (11.0)	64.5 (10.3)
Female sex, n (%)	97 (39.4)	174 (45.9)
Black, n (%)	59 (24.0)	93 (24.5)
Hispanic or Latino, n (%)	103 (41.9)	178 (47.0)
eGFR, mL/min/1.73 m^2, median (IQR)	78.0 (24.8)	75.6 (31.7)
eGFR <60 mL/min/1.73 m^2, n (%)	45 (18.3)	97 (25.6)
eGFR <30 mL/min/1.73 m^2, n (%)	4 (1.6)	6 (1.6)
UACR, mg/g, median (IQR)	16.0 (27.2)[a]	15.0 (35.0)[b]
Office systolic BP, mmHg, mean (SD)	145.3 (13.2)[c]	144.5 (13.5)

Safety analysis set. [a]n=211; [b]n=338; [c]n=244. BP, blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; RAAS, renin–angiotensin–aldosterone system; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.

KARDIA Patients Receiving a Background RAAS Inhibitor: Overall Safety Summary Through Month 6

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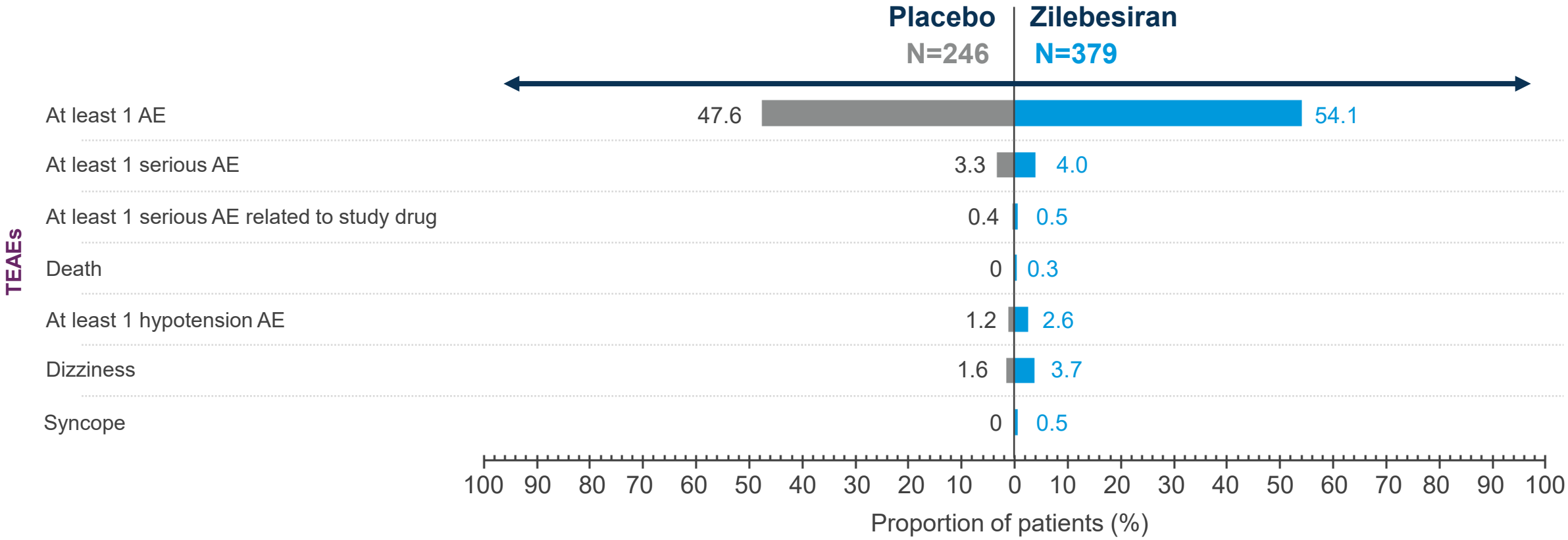

- Most AEs were mild or moderate in severity, transient, and resolved without intervention
- One death by cardiac arrest (Day 85, zilebesiran 150 mg) in KARDIA-3 was not considered treatment-related by the investigator

AE, adverse event; RAAS, renin–angiotensin–aldosterone system; TEAE, treatment-emergent adverse event.

KARDIA Patients Receiving a Background RAAS Inhibitor: Renal Safety Through Month 6

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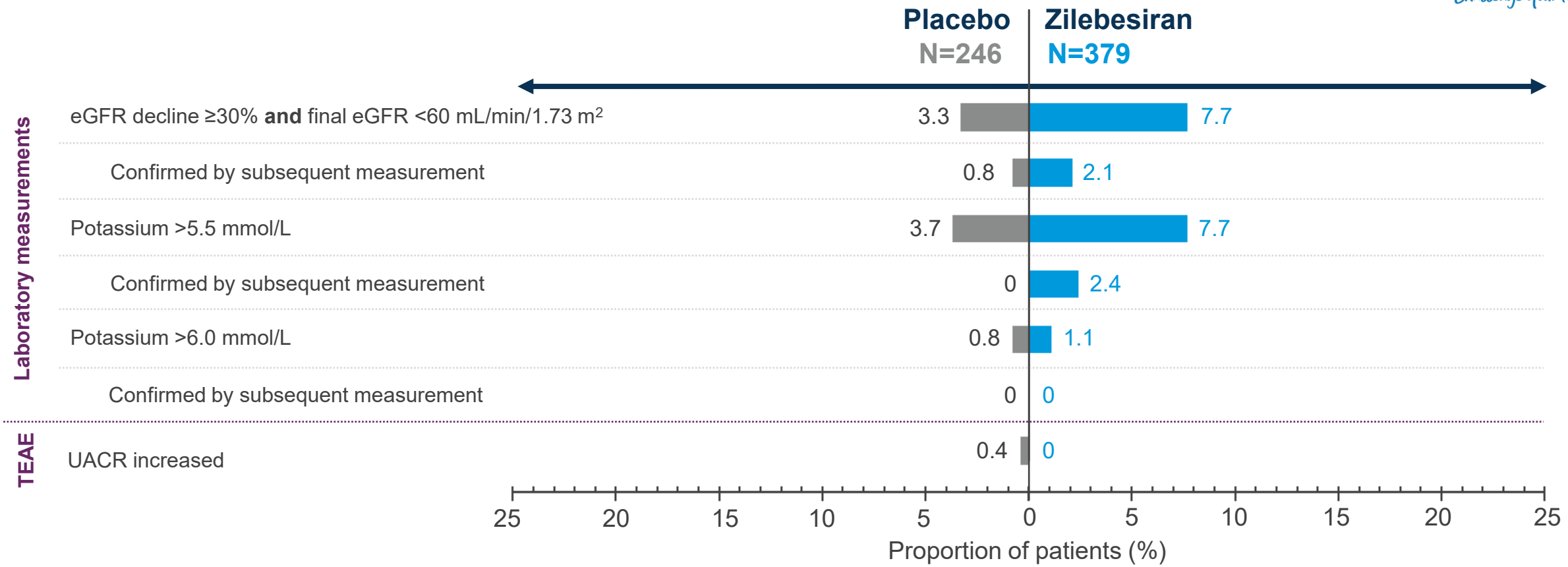

- Majority of events were mild or moderate in severity, nonserious, and resolved without intervention, including in patients with eGFR 30–44 mL/min/1.73 m^2
- Standard interventions included treatment with potassium binders and background medication adjustments

eGFR, estimated glomerular filtration rate; RAAS, renin–angiotensin–aldosterone system; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio.

KARDIA Patients Receiving a Background RAAS Inhibitor: Change from Baseline in Office Systolic BP (Descriptive)

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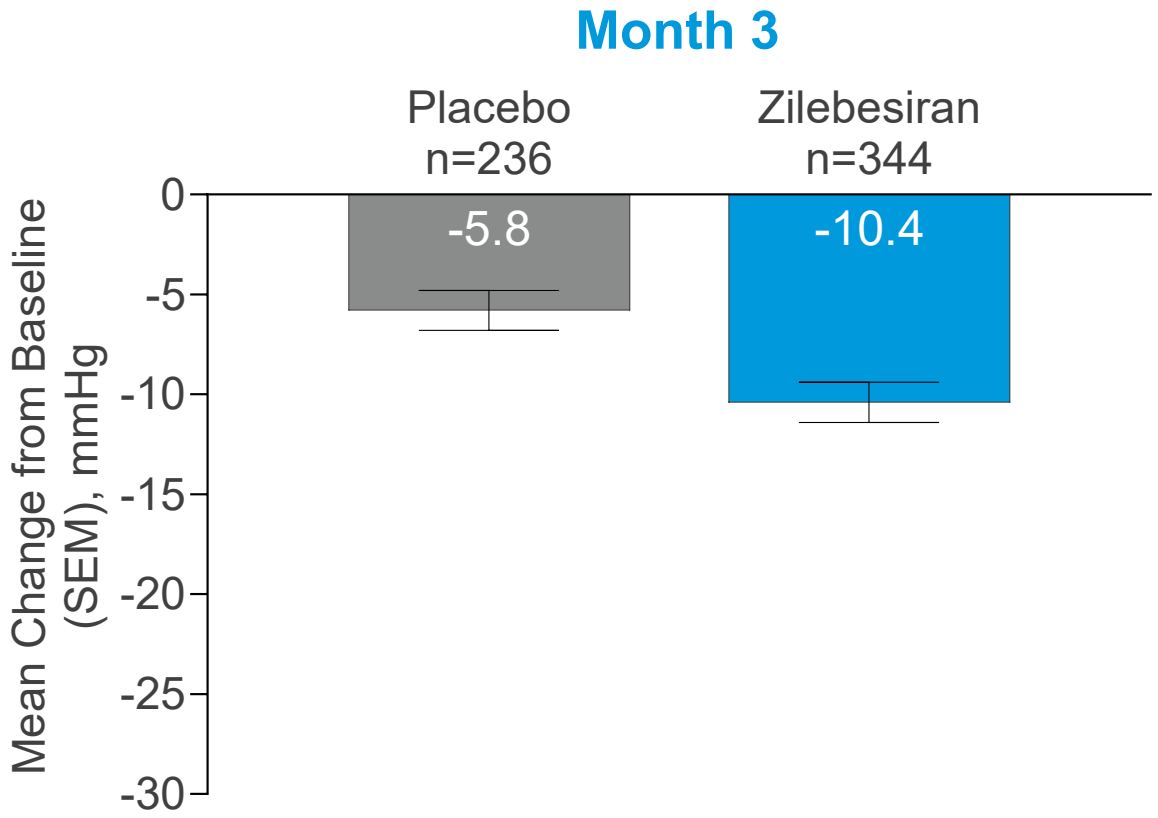

- Additional BP lowering was suggested in patients receiving zilebesiran 300 mg or 600 mg on top of a background RAAS inhibitor

BP, blood pressure; RAAS, renin–angiotensin–aldosterone system; SEM, standard error of the mean.

zenith CV Outcomes Trial Design

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Trial Population

- Adult patients with uncontrolled HTN and established CVD (≥18 years of age) or at high CV risk (≥55 years of age)
- Office systolic BP ≥140 mmHg on stable treatment with a diuretic and ≥1 other standard of care antihypertensive medication
- eGFR ≥30 mL/min/1.73 m^2, potassium ≤4.8 mEq/L

Randomize (n≈11,000)

Zilebesiran 300 mg SC 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. BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; MI, myocardial infarction; Q6M, every 6 months; SC, subcutaneous.

Conclusions

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- Across Phase 2 studies, zilebesiran has led to clinically significant BP reductions in patients with HTN, with a manageable safety profile
- In subgroups of patients who received zilebesiran on top of background RAAS inhibitor, zilebesiran demonstrated low rates of hypotension, kidney dysfunction, and hyperkalemia
- Descriptive office BP data suggest a numerically greater reduction in BP with zilebesiran on top of RAAS inhibitor compared with RAAS inhibitor alone
- The totality of the Phase 2 data supports continued development of zilebesiran, including in patients receiving a background RAAS inhibitor, and those with reduced kidney function
- The Phase 3 ZENITH trial is now enrolling and will evaluate the impact of zilebesiran on top of standard-of-care antihypertensive medications on CV outcomes in patients with HTN and established CVD or high CV risk, including those with CKD

BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; CKD, chronic kidney disease; HCP, healthcare professional; HTN, hypertension; RAAS, renin–angiotensin–aldosterone system.