

# Zilebesiran in Combination with a Standard-of-care Antihypertensive in Patients with Inadequately Controlled Hypertension: Primary Results from the Phase 2 KARDIA-2 Study

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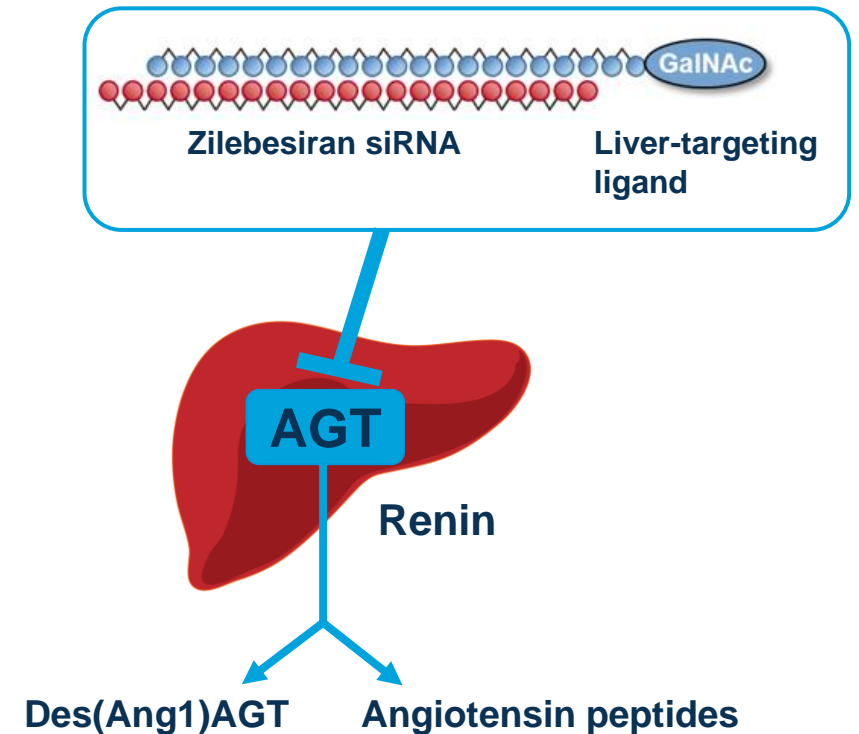
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Presented at the the American College of Cardiology Annual Scientific Session & Expo, April 6–8, 2024, Atlanta, GA, USA

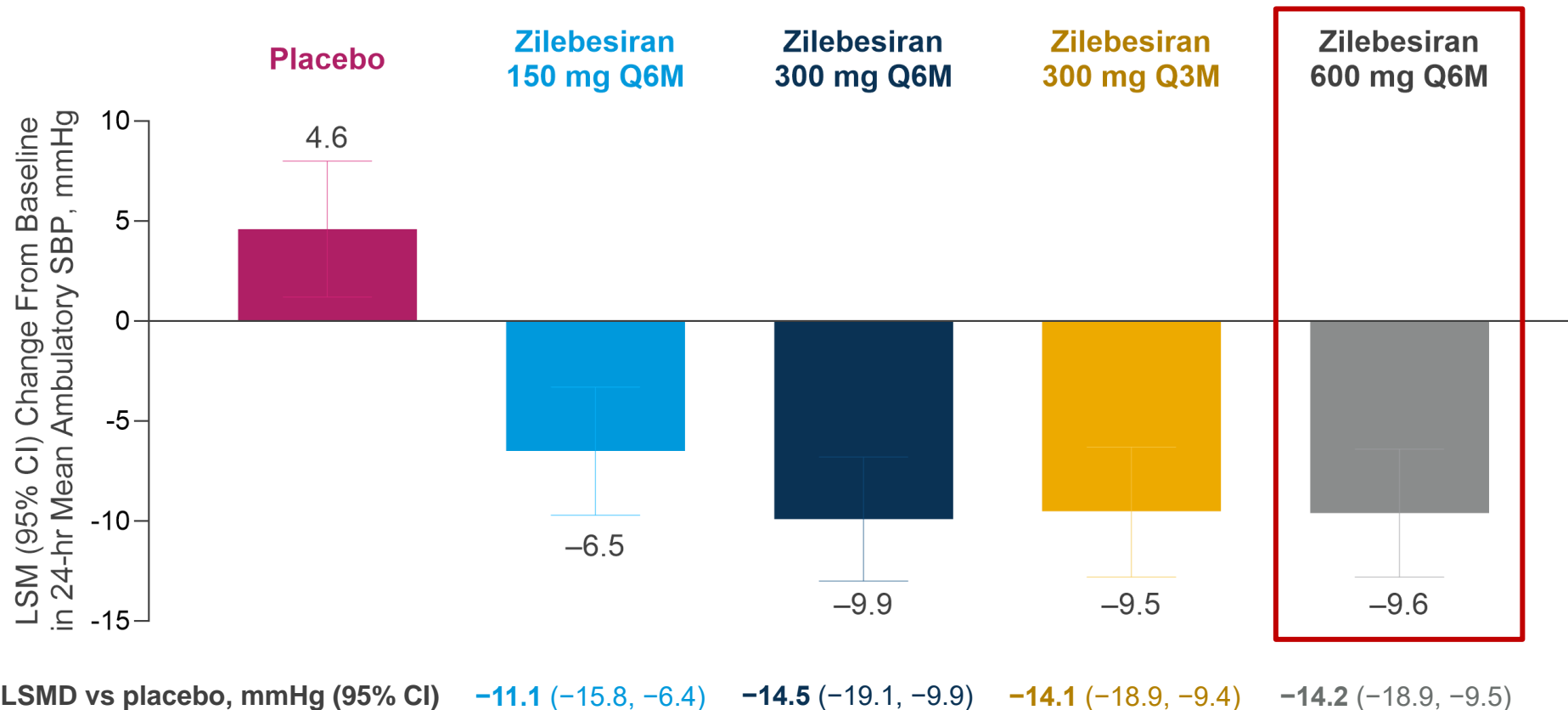


# Hypertension and Zilebesiran

- Despite the availability of effective therapies, many patients with hypertension do not meet guideline-recommended BP targets, leaving them with unattended risk for CV events
- Poor adherence to complex, multidrug oral regimens may contribute to inadequate BP control
- Even in those who are treated, residual BP variability and lack of nighttime dipping may further increase CV risk
- Zilebesiran, an investigational, subcutaneously administered RNA interference therapeutic targeting hepatic synthesis of AGT, the most upstream precursor to all angiotensin peptides, may offer an alternative treatment approach for hypertension



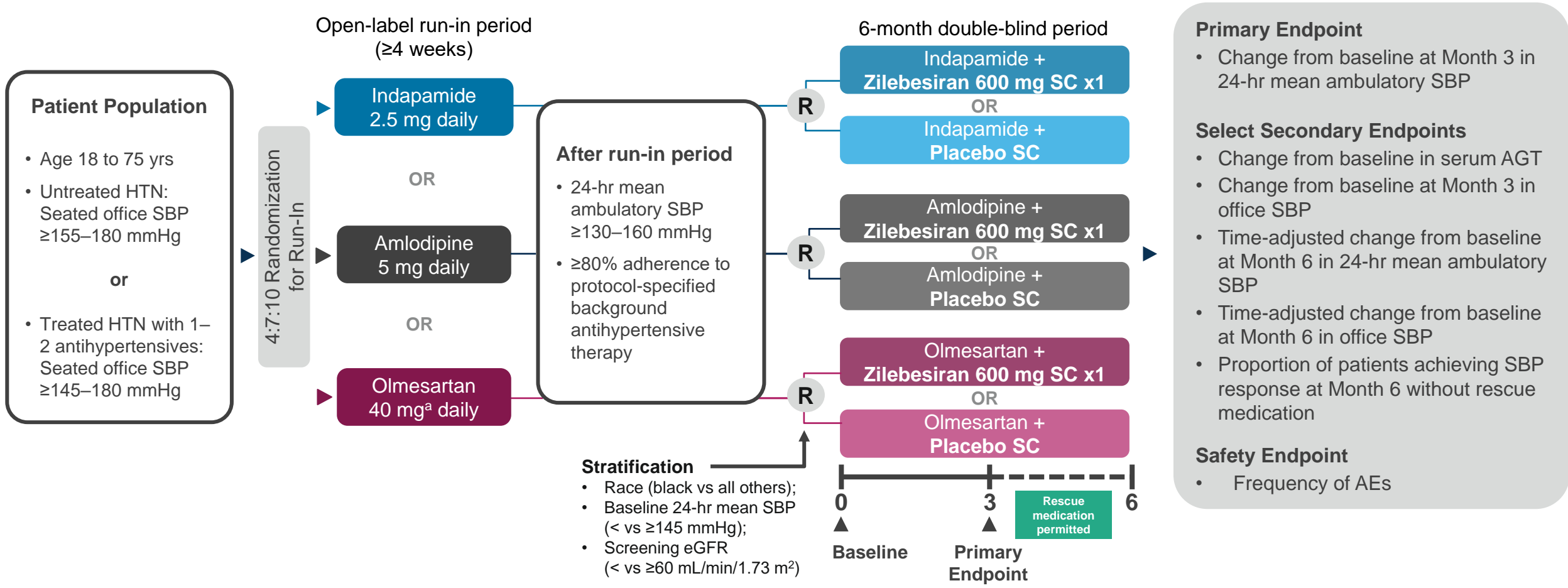
# KARDIA<sub>1</sub>: Significant SBP Reductions Sustained to Month 6 in Patients with Mild-to-Moderate Hypertension



KARDIA<sub>2</sub>

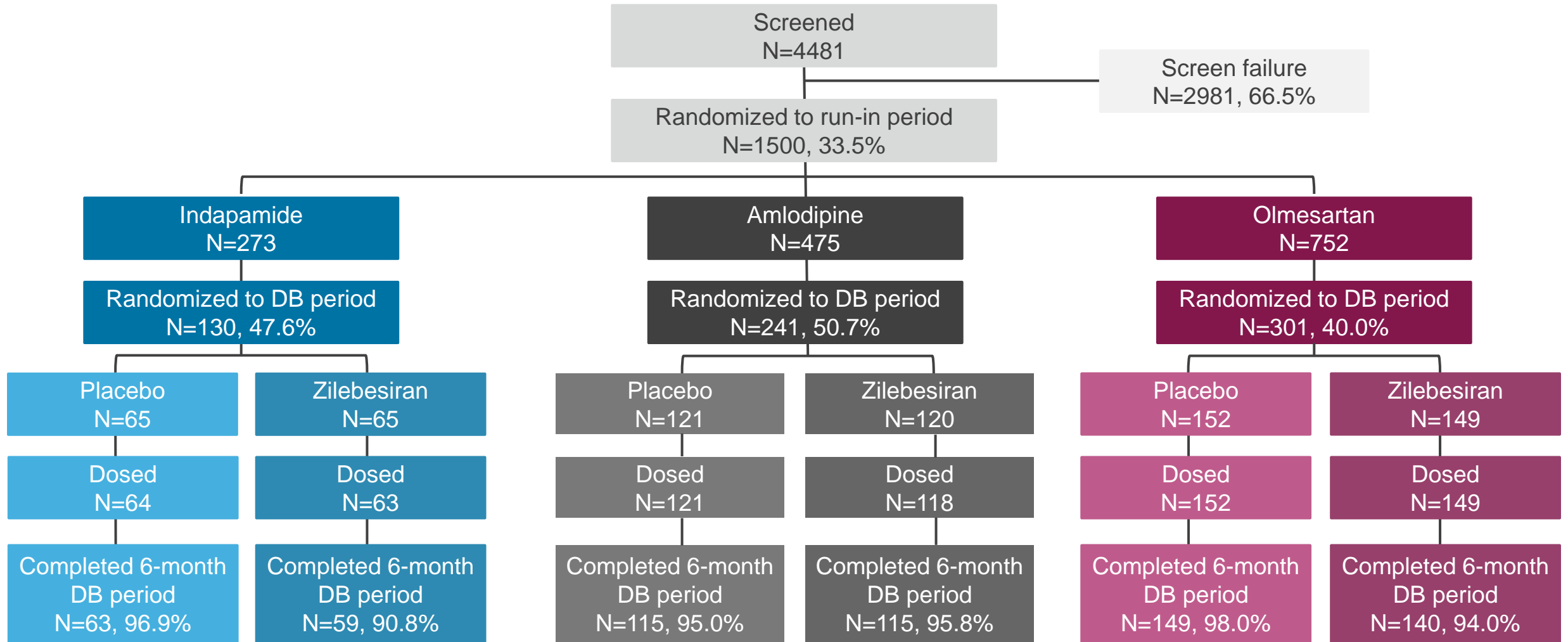
What is the efficacy, safety, and tolerability of zilebesiran when added to a standard-of-care antihypertensive in patients with inadequately controlled hypertension?

# KARDIA<sub>2</sub>: Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Zilebesiran as an Add-on Therapy in Patients with Uncontrolled Hypertension



NCT05103332. <sup>a</sup>20 mg daily for patients with creatinine clearance ≤60 mL/min at screening enrolled outside of US, consistent with local labeling. AE, adverse event; AGT, angiotensinogen; R, randomization; SBP, systolic blood pressure.

# Patient Disposition



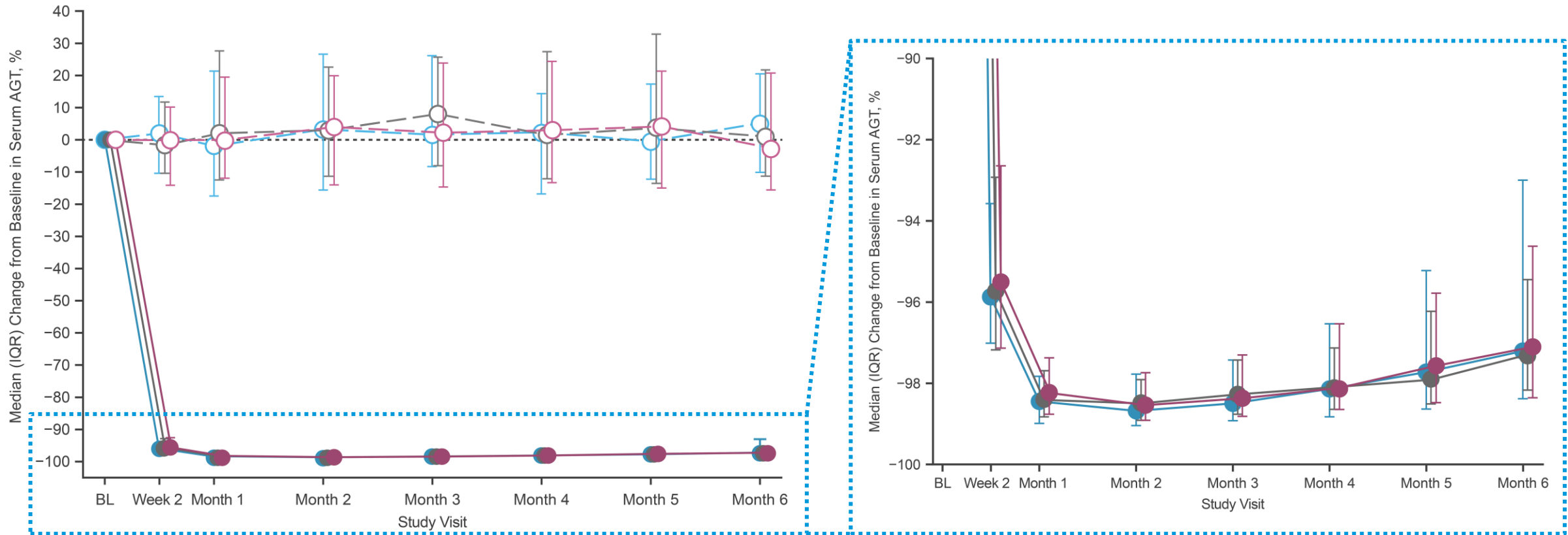
# Baseline Demographics Across Cohorts

	Background Medication		
	Indapamide	Amlodipine	Olmesartan
	Placebo or Zilebesiran (N=127)	Placebo or Zilebesiran (N=239)	Placebo or Zilebesiran (N=301)
Mean age, years (SD)	59.2 (10.5)	58.0 (10.0)	58.5 (10.4)
Male, %	56.7	56.5	57.1
Enrolled in the United States, %	82.7	80.3	80.7
Race, %			
White	70.1	61.1	68.8
Black or African American	23.6	33.5	25.6
24-hr mean ambulatory SBP, mmHg (SD)	143.3 (8.4)	142.9 (8.0)	143.8 (8.2)
24-hr mean ambulatory SBP $\geq$ 145 mmHg, %	46.5	39.3	45.5
Mean office SBP, mmHg (SD)	144.7 (11.8)	143.5 (11.5)	145.2 (12.9)
BMI $\geq$ 30 kg/m <sup>2</sup> , %	66.9	61.9	56.1
eGFR $<$ 60 mL/min/1.73 m <sup>2</sup> , %	15.7	5.4	11.6
Diabetes, %	21.3	22.6	25.2

Percentages are based on the number of patients randomized to and dosed with zilebesiran or placebo.

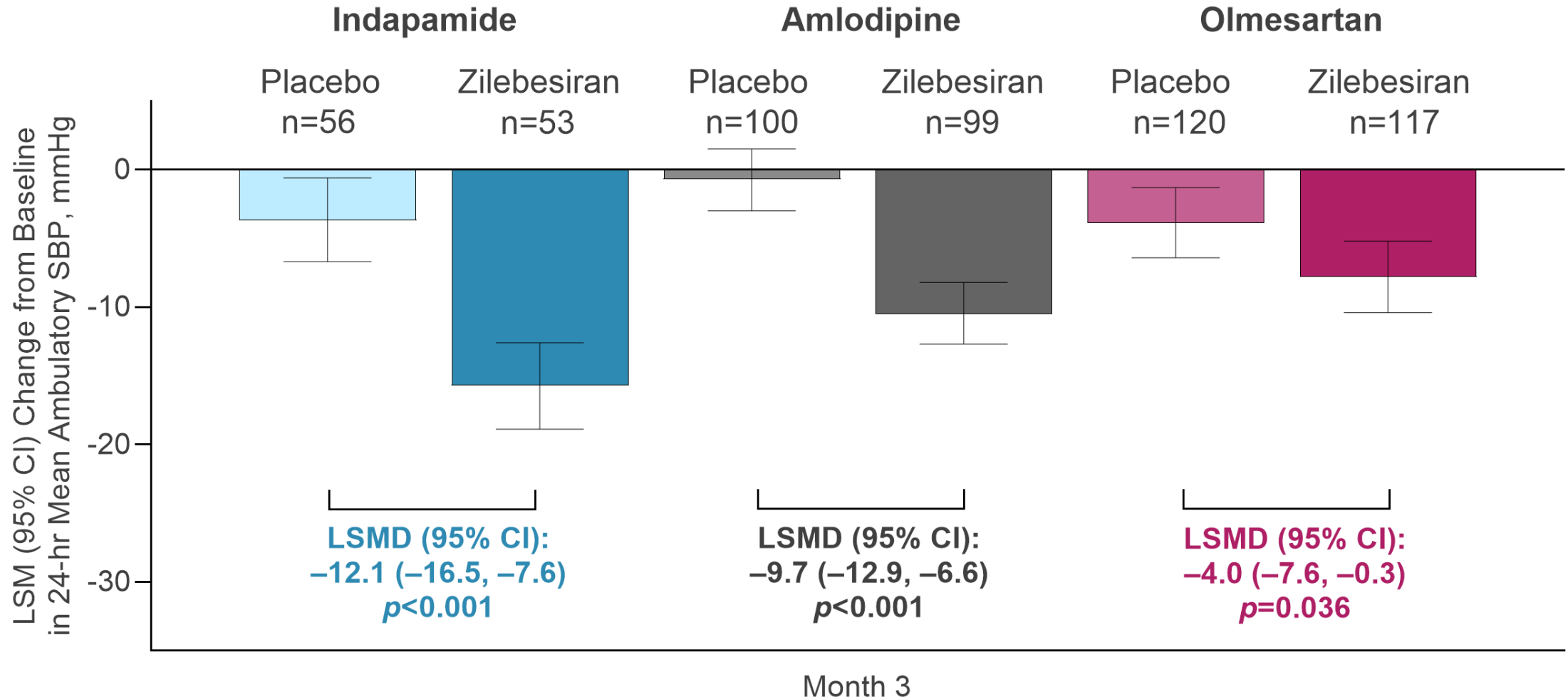
# Change From Baseline in Serum AGT

Rapid median reductions in serum AGT >95% sustained through Month 6 with zilebesiran



- Indapamide + placebo
- Amlodipine + placebo
- Olmesartan + placebo
- Indapamide + zilebesiran
- Amlodipine + zilebesiran
- Olmesartan + zilebesiran

# Primary Endpoint: Change from Baseline to Month 3 in 24-hr Mean Ambulatory SBP

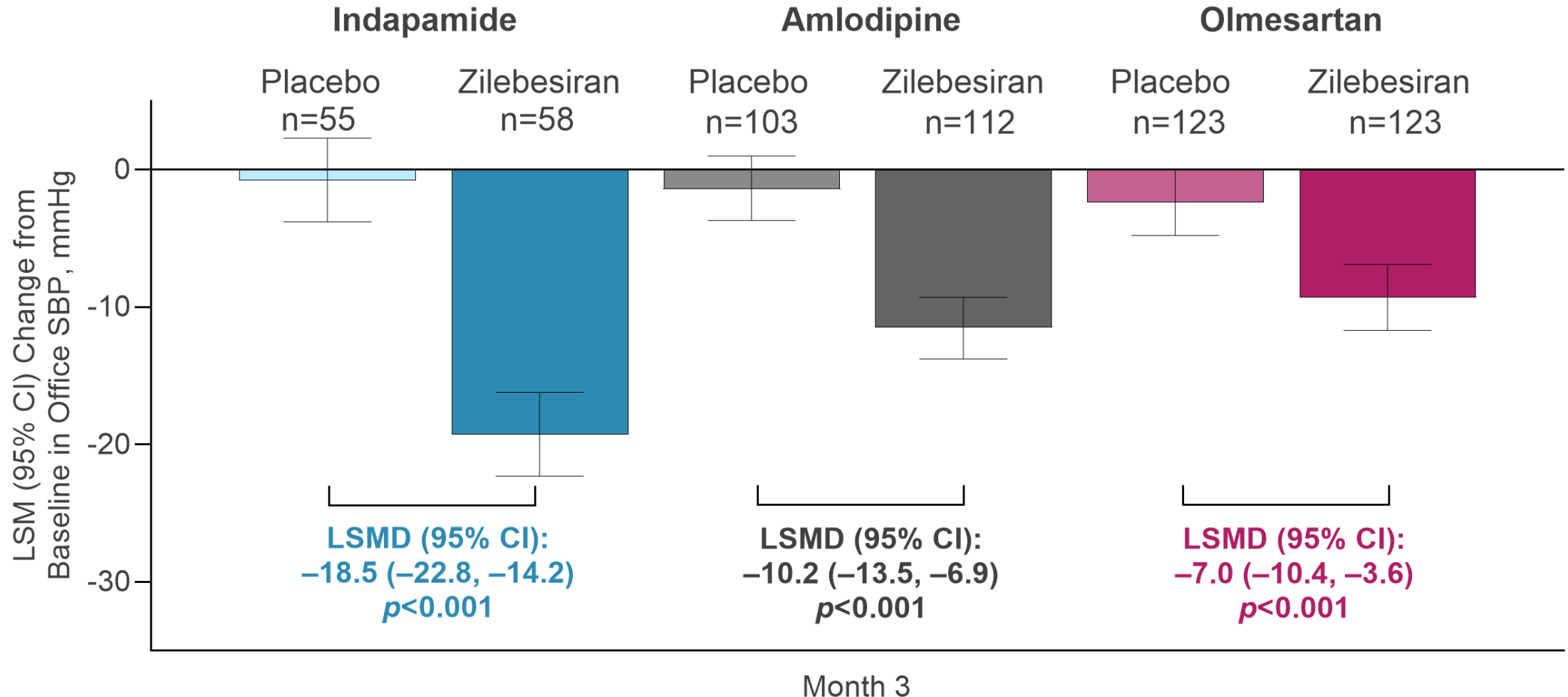


Ambulatory blood pressure assessed while patients were receiving or within 2 weeks of stopping any rescue medication is censored.

CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference.



# Secondary Endpoint: Change from Baseline to Month 3 in Office SBP

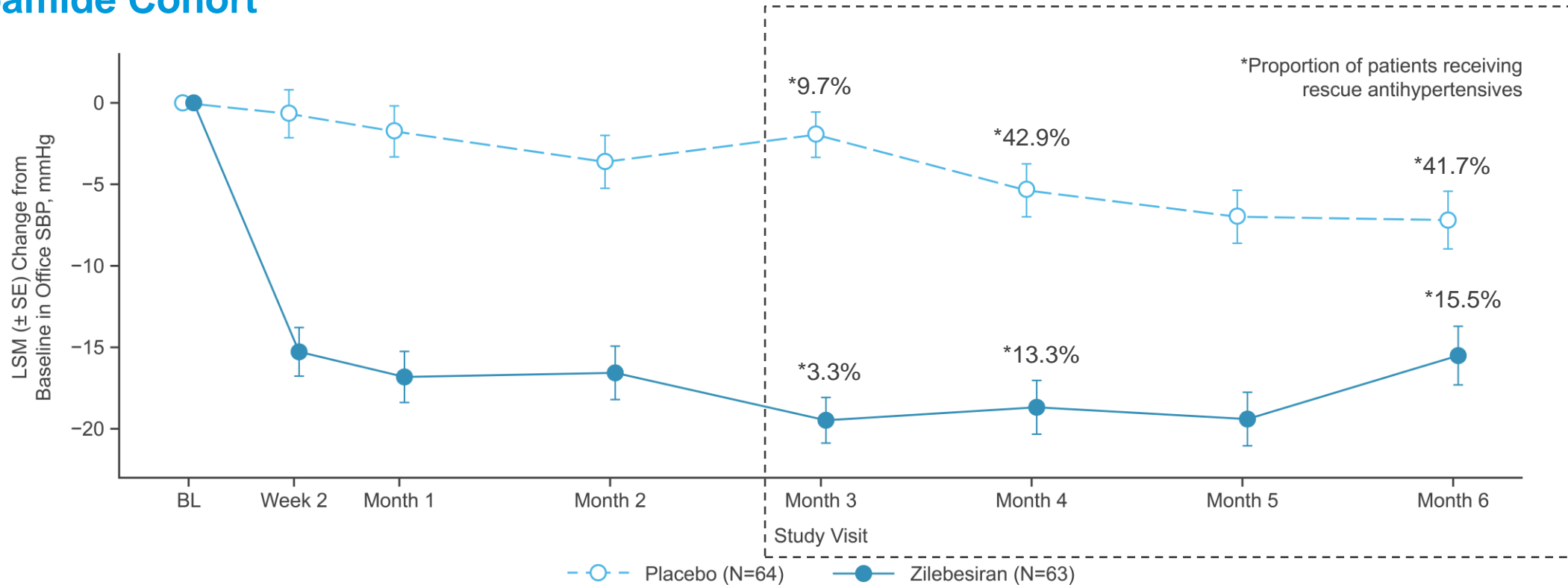


Office blood pressure assessed while patients were receiving or within 2 weeks of stopping any rescue medication is censored.

CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference.

# Secondary Endpoint: Change From Baseline Through Month 6 in Office SBP

## Indapamide Cohort



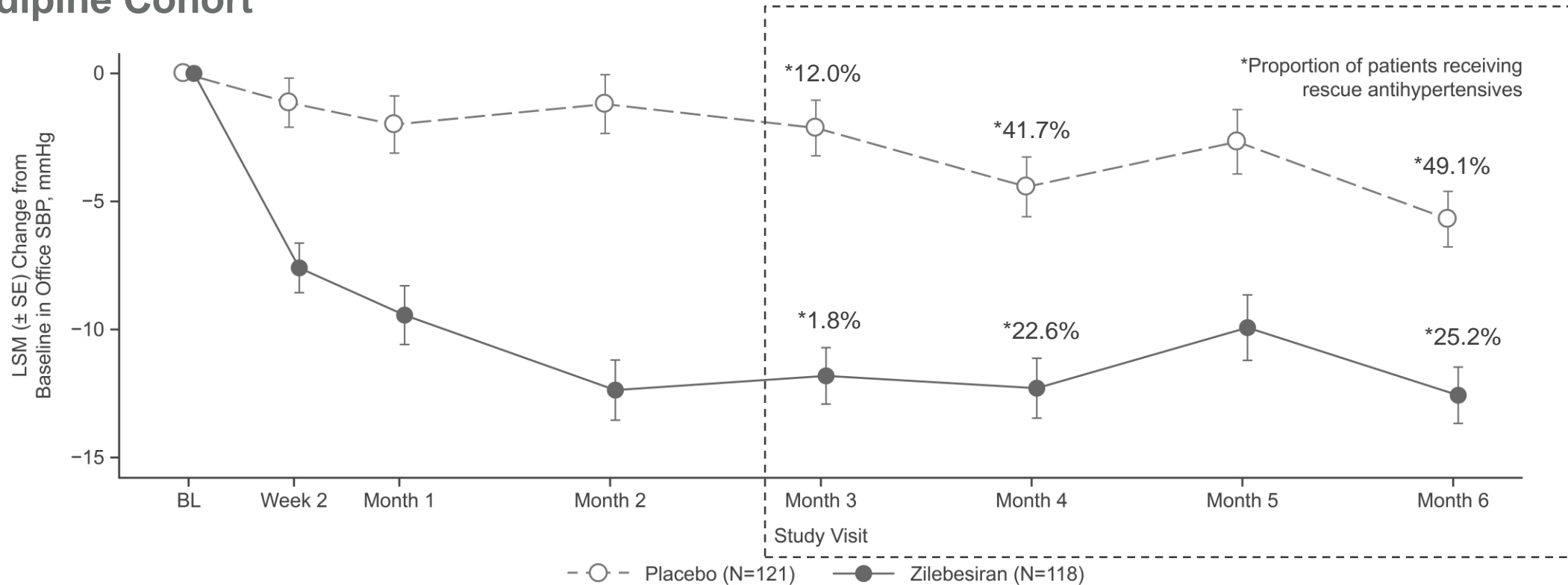
	No. of Patients							
Placebo	63	63	62	62	61	62	60	60
Zilebesiran	63	61	62	61	60	60	59	58

	Time-Adjusted 24-hr Mean Ambulatory SBP	Time-Adjusted Office SBP
LSMD vs placebo, mmHg (95% CI)	-11.0 (-14.7, -7.3), $p < 0.001$	-13.6 (-16.9, -10.3), $p < 0.001$

BL, baseline; CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; SE, standard error.

# Secondary Endpoint: Change From Baseline Through Month 6 in Office SBP

## Amlodipine Cohort



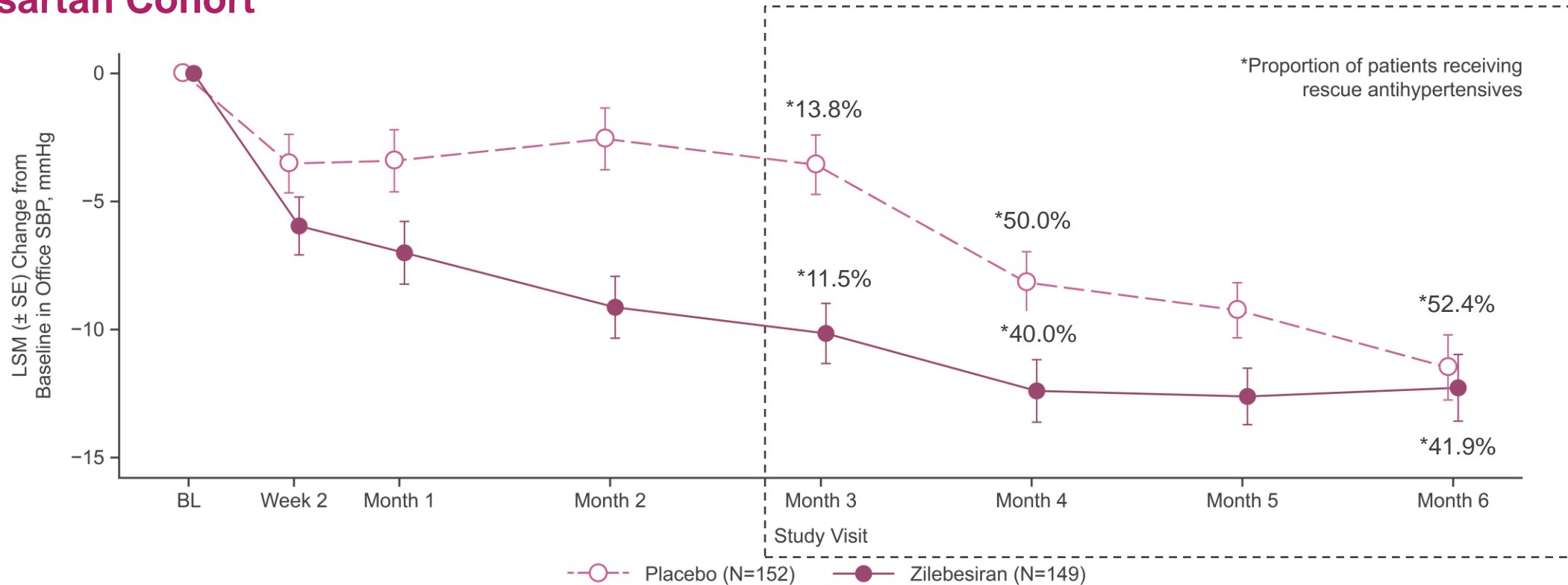
	No. of Patients							
Placebo	121	118	119	118	117	115	115	114
Zilebesiran	118	116	112	112	114	115	111	111

	Time-Adjusted 24-hr Mean Ambulatory SBP	Time-Adjusted Office SBP
LSMD vs placebo, mmHg (95% CI)	<b>-7.9 (-10.6, -5.3), <math>p &lt; 0.001</math></b>	<b>-8.6 (-10.9, -6.3), <math>p &lt; 0.001</math></b>

BL, baseline; CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; SE, standard error.

# Secondary Endpoint: Change From Baseline Through Month 6 in Office SBP

## Olmesartan Cohort



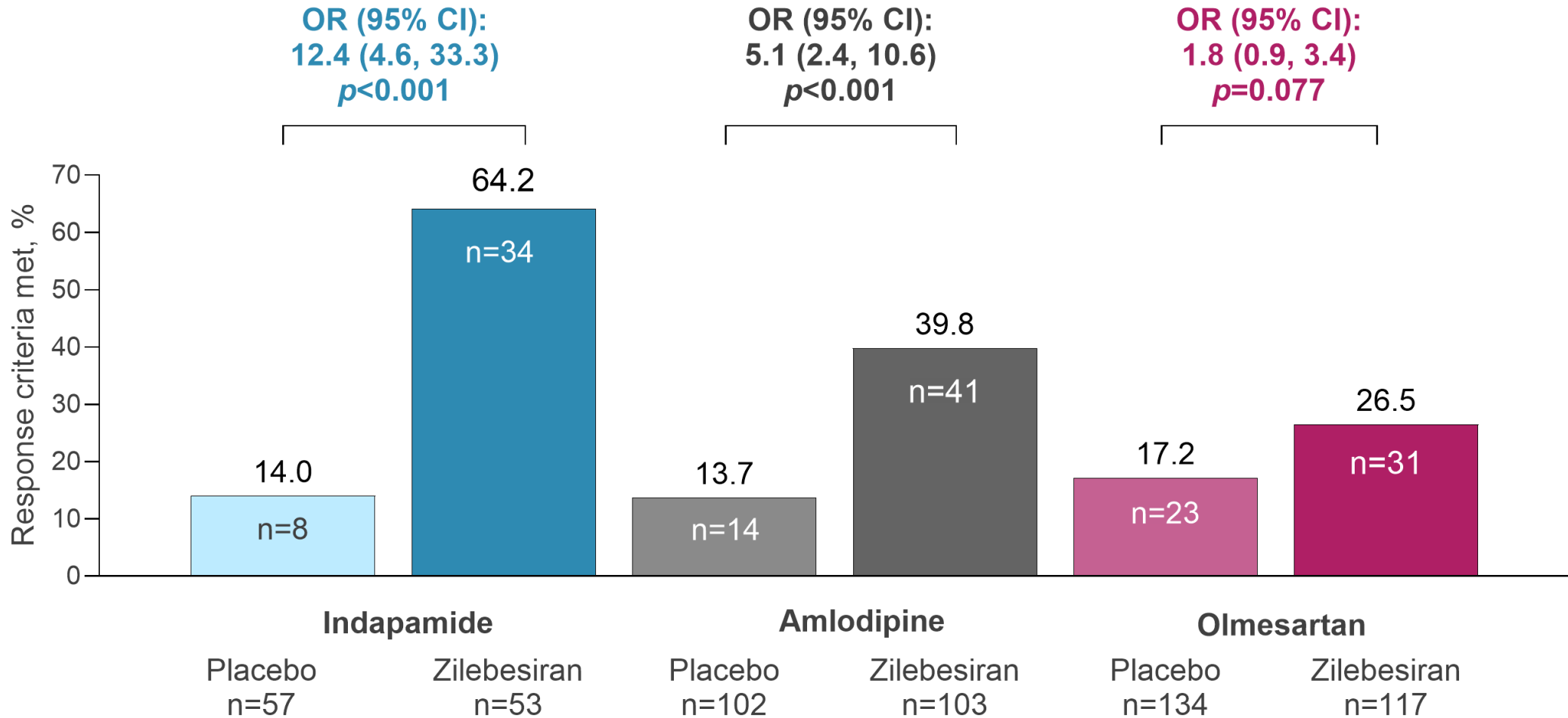
	No. of Patients							
Placebo	150	143	148	142	143	144	145	143
Zilebesiran	149	147	145	142	139	140	137	136

	Time-Adjusted 24-hr Mean Ambulatory SBP	Time-Adjusted Office SBP
LSMD vs placebo, mmHg (95% CI)	-1.6 (-4.4, 1.2), $p=0.26$	-4.6 (-6.8, -2.4), $p<0.001$

BL, baseline; CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; SE, standard error.

# Secondary Endpoint: Proportion of Patients Achieving SBP Response at Month 6 Without Rescue Medication

Response Criterion: 24-hr mean ambulatory SBP <130 mmHg and/or reduction  $\geq 20$  mmHg without additional antihypertensives



# Safety Profile Through Month 6

n (%)	Background Medication					
	Indapamide		Amlodipine		Olmesartan	
	Placebo (N=64)	Zilebesiran (N=63)	Placebo (N=121)	Zilebesiran (N=118)	Placebo (N=152)	Zilebesiran (N=149)
At least 1 AE	25 (39.1)	31 (49.2)	57 (47.1)	64 (54.2)	73 (48.0)	87 (58.4)
At least 1 serious AE	2 (3.1)	0	1 (0.8)	3 (2.5)	4 (2.6)	4 (2.7)
Hypotension/orthostatic hypotension AE	0	0	4 (3.3)	7 (5.9)	3 (2.0)	7 (4.7)
Potassium >5.5 nmol/L	0	2 (3.2)	1 (0.8)	8 (6.8)	3 (2.0)	10 (6.7)
Confirmed by repeat measure	0	1 (1.6)	0	2 (1.7)	0	2 (1.3)
≥30% decrease from baseline in eGFR (mL/min/1.73m <sup>2</sup> )	1 (1.6)	8 (12.7)	5 (4.1)	10 (8.5)	4 (2.6)	10 (6.7)
Confirmed by repeat measure	0	3 (4.8)	2 (1.7)	1 (0.8)	1 (0.7)	4 (2.7)
>2x increase from baseline in creatinine (μmol/L)	0	0	0	0	0	3 (2.0)
Confirmed by repeat measure	0	0	0	0	0	1 (0.7)

- There were no deaths or no AEs leading to study discontinuation
- Most hypotension AEs were transient and resolved without intervention
- Most laboratory abnormalities of interest were mild, occurred in the first 3 months, and resolved upon repeat measurement within 1-2 weeks without intervention

# KARDIA<sub>2</sub> Summary

For US HCPs Only  
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Material Presented



- Treatment with a single subcutaneous dose of zilebesiran 600 mg was associated with clinically significant reductions in 24-hr mean ambulatory and office SBP compared with placebo at Month 3 when added to a diuretic, calcium channel blocker, or maximum-dose angiotensin receptor blocker
- Placebo-adjusted differences in blood pressure were sustained to Month 6 despite add-on antihypertensive therapy, particularly in the indapamide and amlodipine cohorts
- Add-on treatment with zilebesiran was associated with increased rates of mild hyperkalemia, hypotension, and eGFR decline >30%, but most episodes were non-serious, transient, and resolved without intervention
- Though the trial was not adequately powered to ensure long-term safety, these results support the potential for combining biannual dosing of zilebesiran with standard-of care antihypertensives to achieve additive blood pressure reductions
- The Phase 2 KARDIA-3 study (NCT06272487) has been initiated and will evaluate patients with hypertension uncontrolled by 2-4 standard-of-care antihypertensives who have high cardiovascular risk or advanced chronic kidney disease

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