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

George L Bakris[1], **Akshay S Desai[2],** Ahmad Aswad[3], Jolita Badariene[4], Farhana Kazi[5], Adam D Karns[6], Joel M Neutel[7], Wansu Park[8], Daniel Stiglitz[8], Nune Makarova[8], Andrea Havasi[8], Dion Zappe[8], Manish Saxena[9,10]

[1]University of Chicago Medicine, Chicago, IL, USA; [2]Brigham and Women's Hospital, Boston, MA, USA; [3]Gonzalez MD and Aswad MD Health Care Services, Miami, FL, USA; [4]Medical Faculty, Vilnius University, Vilnius, Lithuania; [5]Prime Revival Research Institute LLC, Coppell, TX, USA; [6]Entertainment Medical Group, Beverly Hills, CA, USA; [7]Orange County Research Center, Tustin, CA, USA; [8]Alnylam Pharmaceuticals, Cambridge, MA, USA; [9]Barts Health NHS Trust, London, UK; [10]Queen Mary University of London, London, UK

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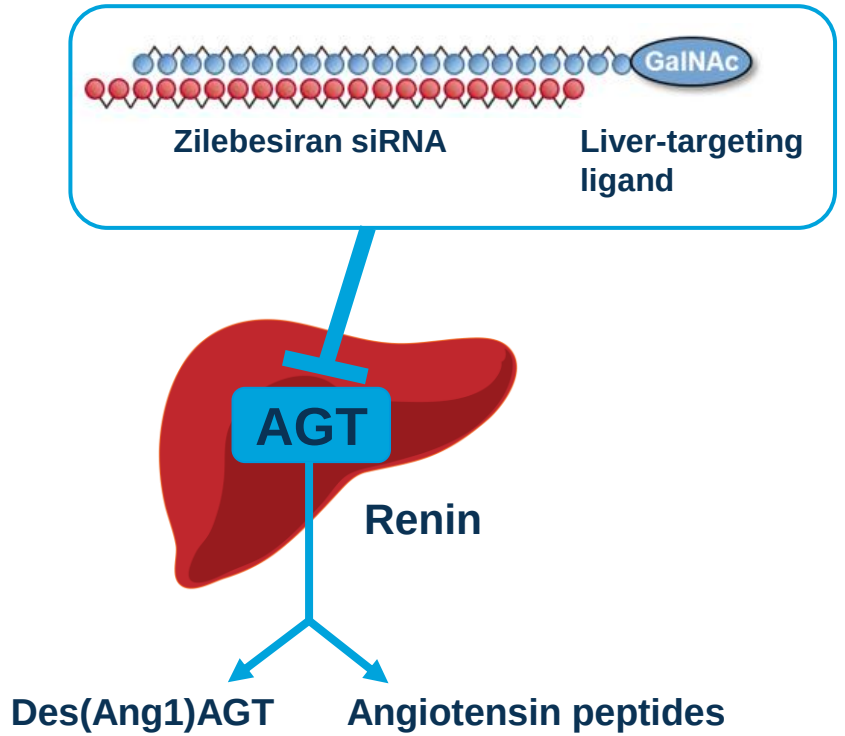
Hypertension and Zilebesiran

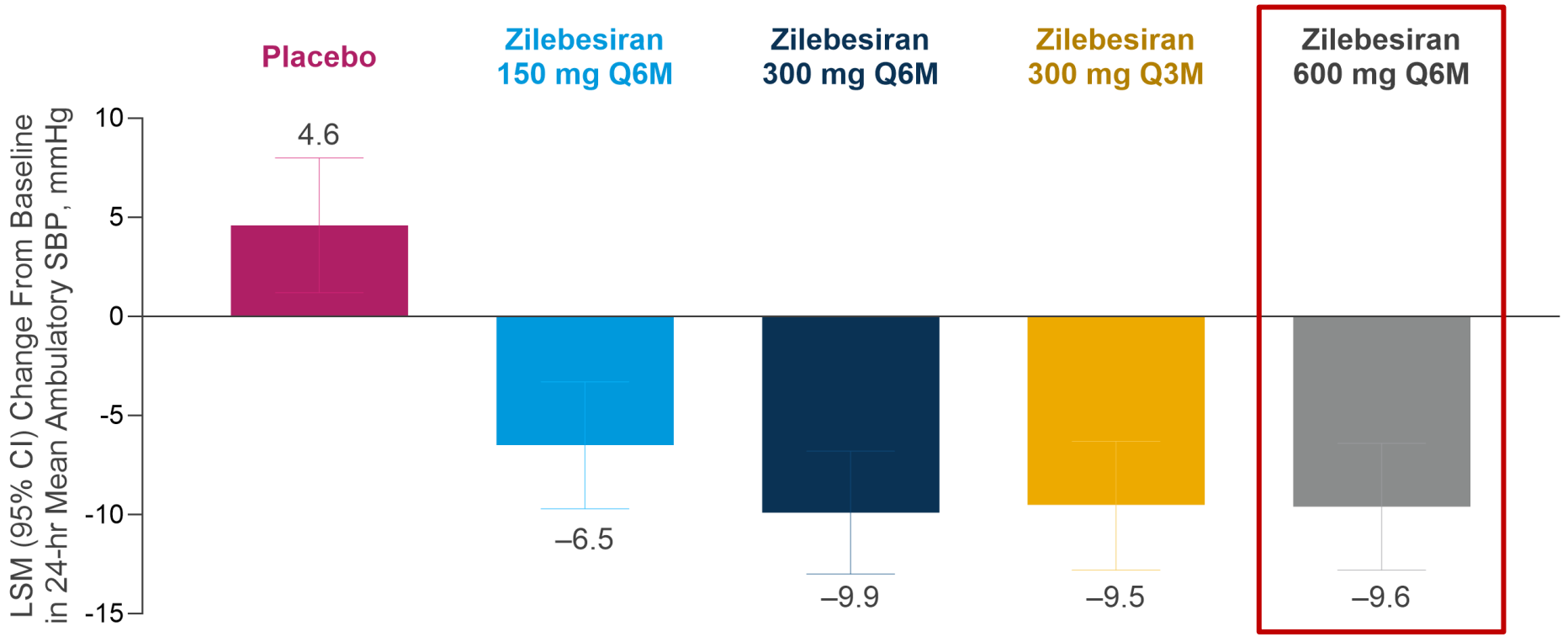
- Despite the availability of effective therapies, many patients with hypertension do not meet guideline-recommended BP targets, leaving them with unattended risk for CV events
- Poor adherence to complex, multidrug oral regimens may contribute to inadequate BP control
- Even in those who are treated, 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



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

Million Hearts Foundation. Estimated hypertension prevalence, treatment, and control among US adults: tables. https://millionhearts.hhs.gov/files/Estimated-Hypertension-Prevalence-tables-508.pdf (Accessed March 19, 2024); Desai AS et al. N Engl J Med 2023;389:228–38

KARDIA$_1$: Significant SBP Reductions Sustained to Month 6 in Patients with Mild-to-Moderate Hypertension



	Zilebesiran 150 mg Q6M	Zilebesiran 300 mg Q6M	Zilebesiran 300 mg Q3M	Zilebesiran 600 mg Q6M
LSMD vs placebo, mmHg (95% CI)	**−11.1** (−15.8, −6.4)	**−14.5** (−19.1, −9.9)	**−14.1** (−18.9, −9.4)	**−14.2** (−18.9, −9.5)

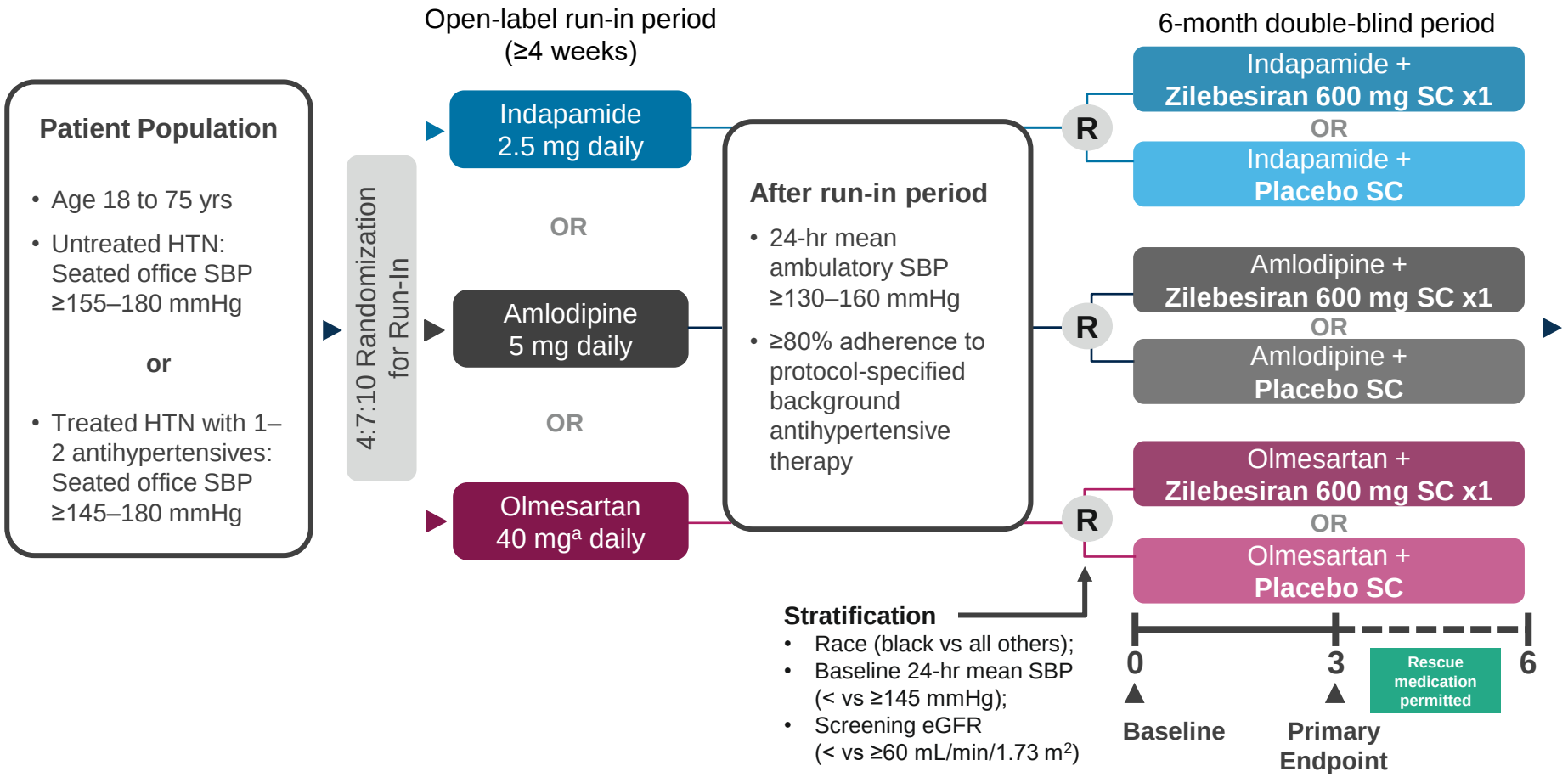
KARDIA$_2$

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

NCT04936035.

Bakris GL *et al. JAMA* 2024;331:740–9. AGT, angiotensinogen; CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; Q3M, every 3 months; Q6M, every 6 months.

KARDIA$_2$: 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



Primary Endpoint

- Change from baseline at Month 3 in 24-hr mean ambulatory SBP

Select Secondary Endpoints

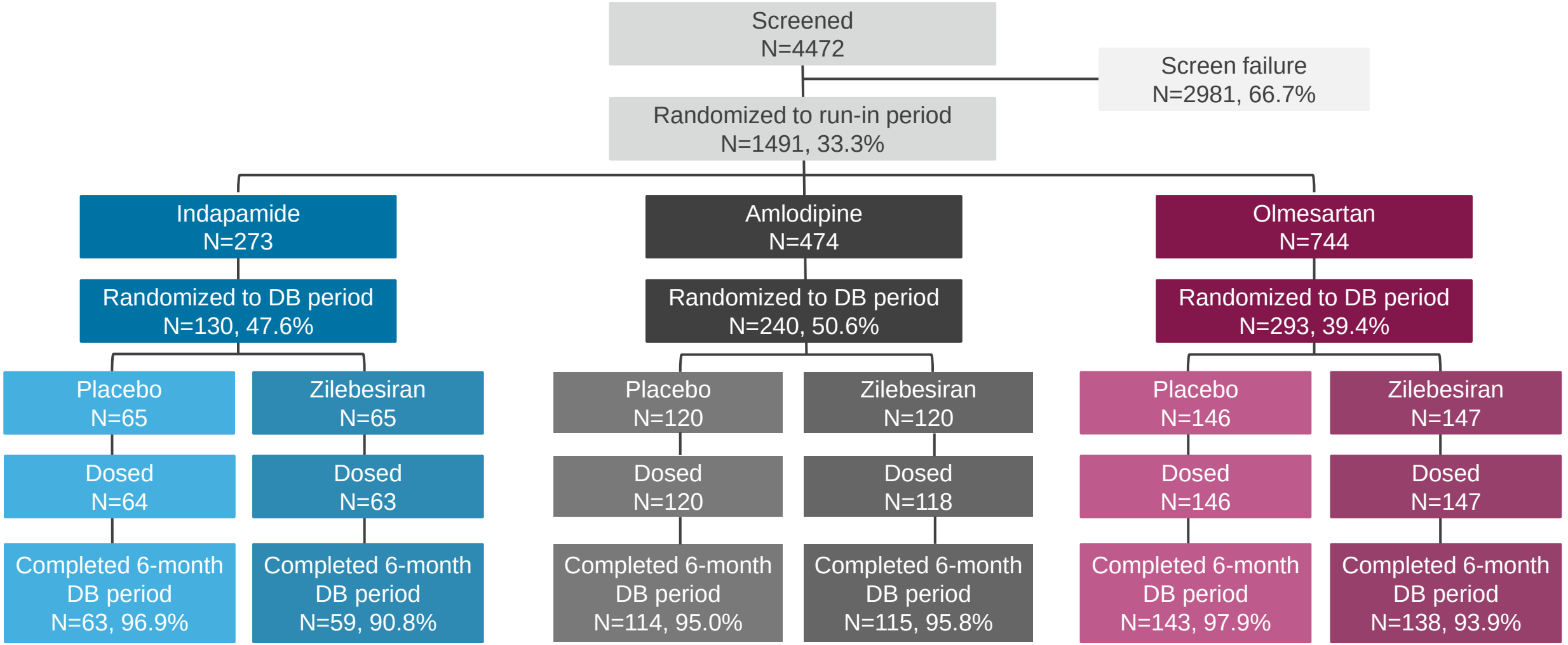
- Change from baseline in serum AGT
- Change from baseline at Month 3 in office SBP
- Time-adjusted change from baseline at Month 6 in 24-hr mean ambulatory SBP
- Time-adjusted change from baseline at Month 6 in office SBP
- Proportion of patients achieving SBP response at Month 6 without rescue medication

Safety Endpoint

- Frequency of AEs

NCT05103332. [a]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



After the original data presentation, it was detected that several patients were randomized simultaneously at multiple trial sites. This led to the exclusion of 9 patient IDs; updated data are presented here. Data presented in the full analysis set. One patient assigned to the placebo arm of the olmesartan cohort accidentally received 100 mg zilebesiran, and is therefore included in the placebo arm of the full analysis set, and the zilebesiran arm of the safety analysis set. Denominator for randomized to run-in period and screen failure is based on total number of screened patients. Denominator for randomized to DB period is based on total number of run-in patients. Denominator for completed 6-month DB period is based on total number of patients randomized to DB period.
DB, double-blind. DB, double-blind.

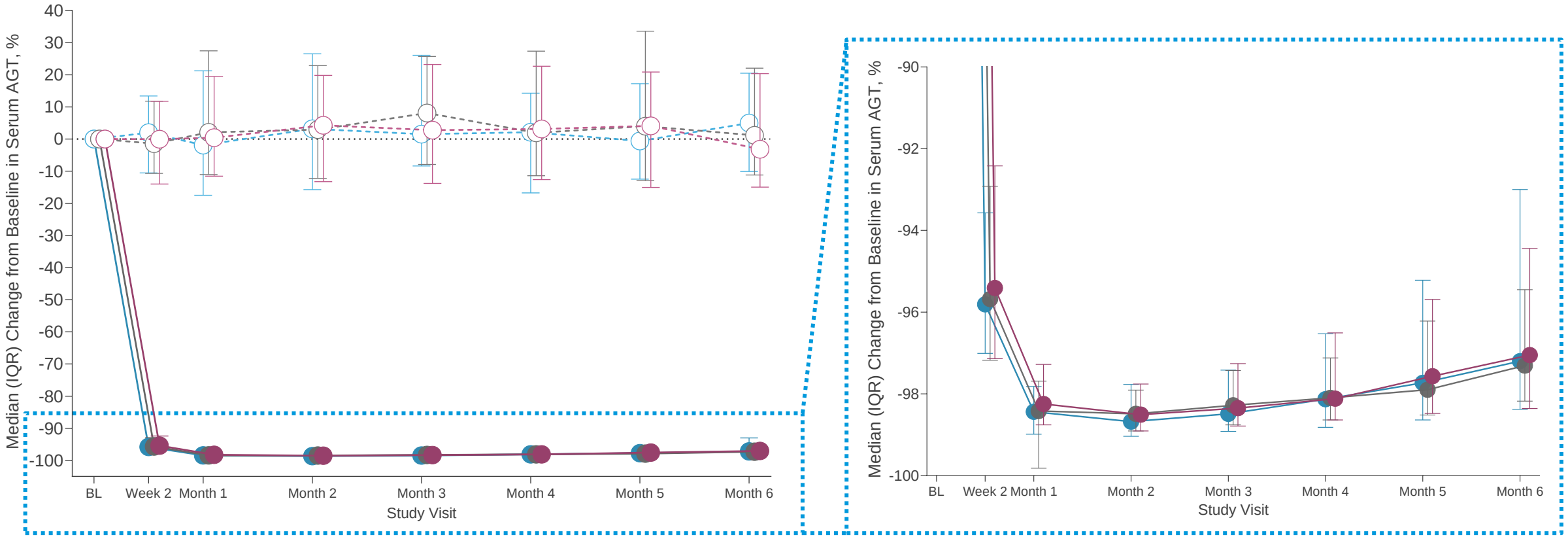
Baseline Demographics Across Cohorts

	Background Medication		
	Indapamide	Amlodipine	Olmesartan
	Placebo or Zilebesiran (N=127)	Placebo or Zilebesiran (N=238)	Placebo or Zilebesiran (N=293)
Mean age, years (SD)	59.2 (10.5)	58.0 (10.0)	58.5 (10.5)
Male, %	56.7	56.7	57.7
Dosed in the United States, %	82.7	80.3	80.2
Race, %			
White	70.1	60.9	67.9
Black or African American	23.6	33.6	26.3
24-hr mean ambulatory SBP, mmHg (SD)	143.3 (8.4)	142.9 (8.0)	143.9 (8.2)
24-hr mean ambulatory SBP ≥145 mmHg, %	46.5	39.5	46.4
Mean office SBP, mmHg (SD)	144.7 (11.8)	143.5 (11.5)	145.3 (12.9)
BMI ≥30 kg/m^2, %	66.9	62.2	56.3
eGFR <60 mL/min/1.73 m^2, %	15.7	5.5	11.3
Diabetes, %	21.3	22.3	24.2

After the original data presentation, it was detected that several patients were randomized simultaneously at multiple trial sites. This has led to the exclusion of 9 patient IDs; updated data are presented here. Percentages are based on the number of patients randomized to and dosed with zilebesiran or placebo. Data presented in the full analysis set.

Change From Baseline in Serum AGT

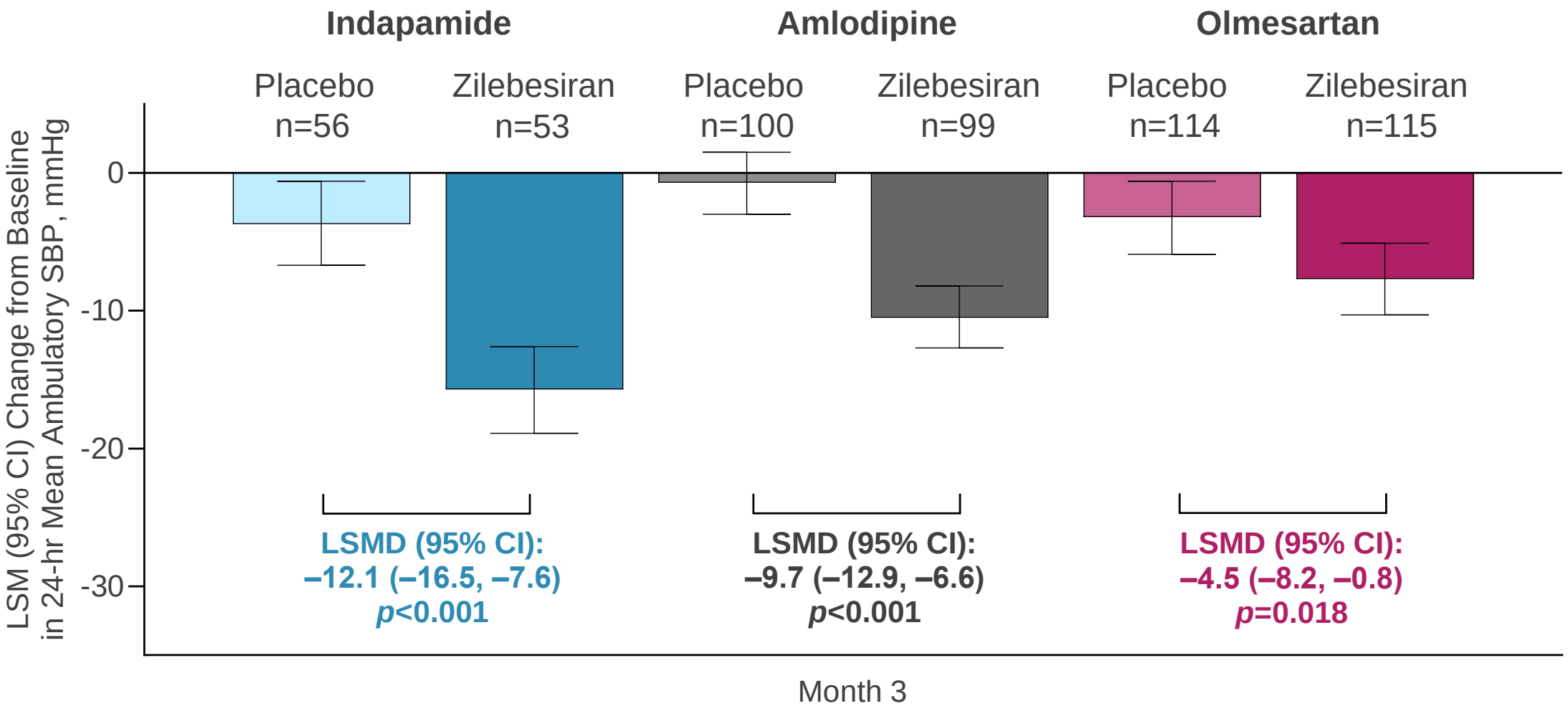
Rapid median reductions in serum AGT >95% sustained through Month 6 with zilebesiran



After the original data presentation, it was detected that several patients were randomized simultaneously at multiple trial sites. This has led to the exclusion of 9 patient IDs; updated data are presented here. Data presented in the pharmacodynamic analysis set.

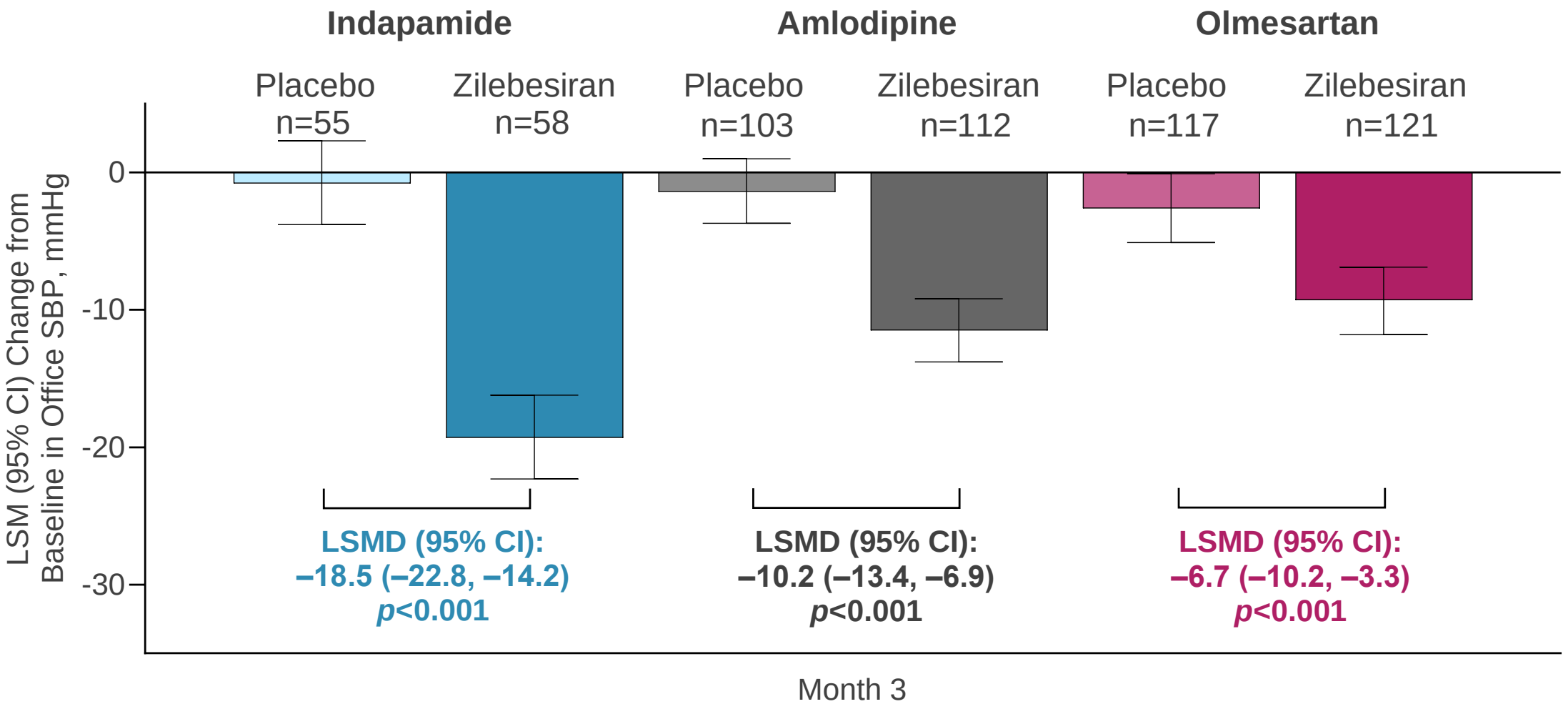
AGT, angiotensinogen; BL, baseline; IQR, interquartile range.

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



After the original data presentation, it was detected that several patients were randomized simultaneously at multiple trial sites. This has led to the exclusion of 9 patient IDs; updated data are presented here. **Ambulatory blood pressure assessed while patients were receiving or within 2 weeks of stopping any rescue medication is censored.** Data presented in the full analysis set.
CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference.

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



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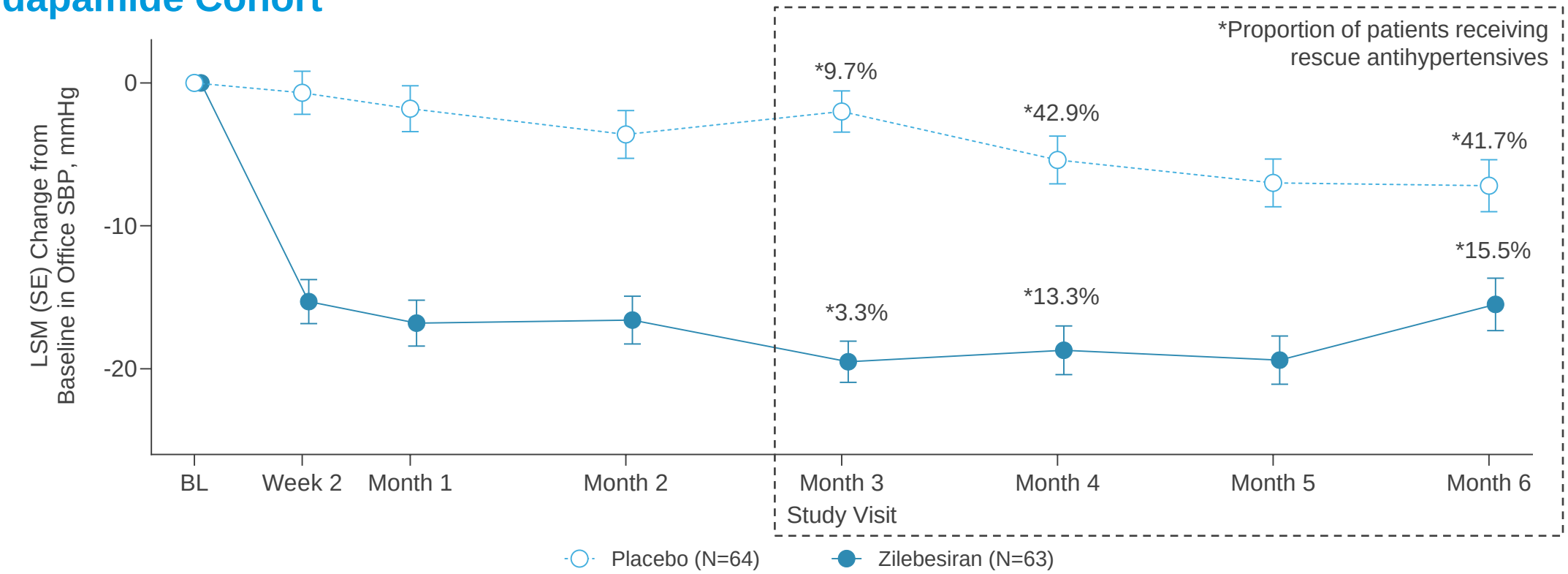
CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference.

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**

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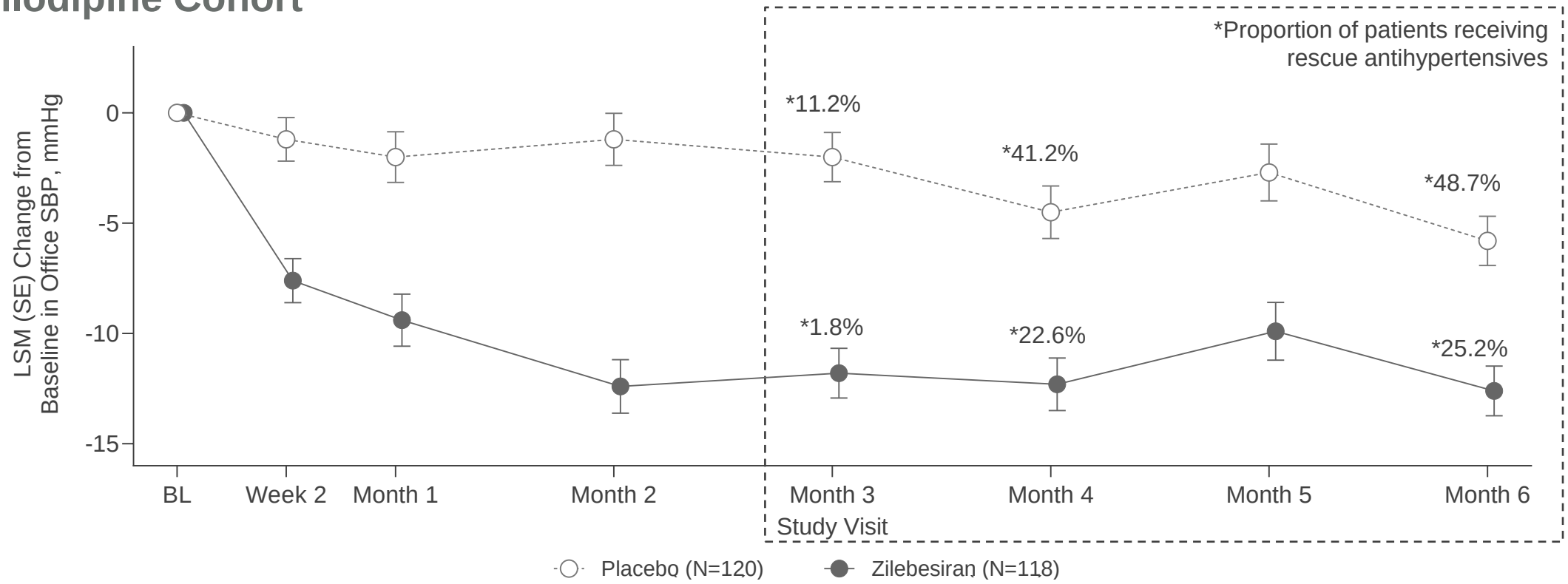
BL, baseline; CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; SE, standard error.

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

Amlodipine Cohort



No. of Patients

Placebo	120	117	118	117	116	114	114	113
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)	**−7.9 (−10.6, −5.3), *p*<0.001**	**−8.6 (−10.9, −6.3), *p*<0.001**

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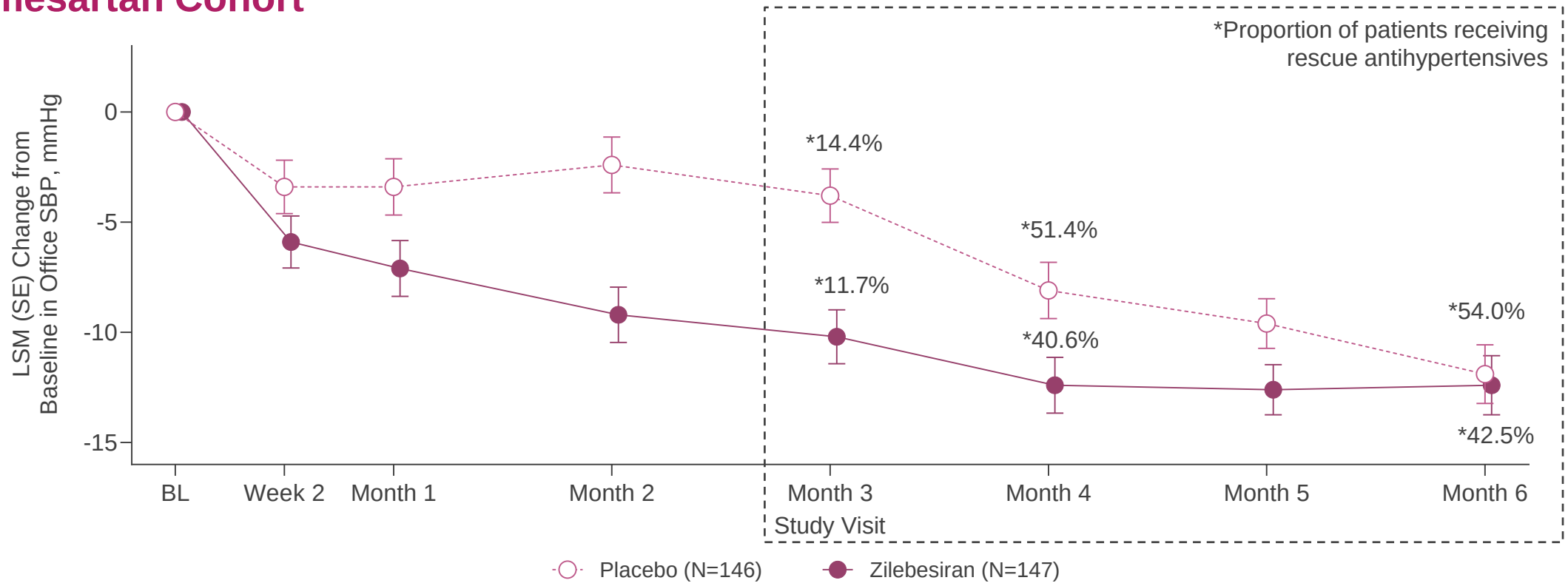
BL, baseline; CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; SE, standard error.

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

Olmesartan Cohort



No. of Patients

Placebo	144	137	142	136	137	138	139	137
Zilebesiran	147	145	143	140	137	138	135	134

	Time-Adjusted 24-hr Mean Ambulatory SBP	Time-Adjusted Office SBP
LSMD vs placebo, mmHg (95% CI)	**−1.8 (−4.6, 1.0), *p*=0.210**	**−4.5 (−6.8, −2.3), *p*<0.001**

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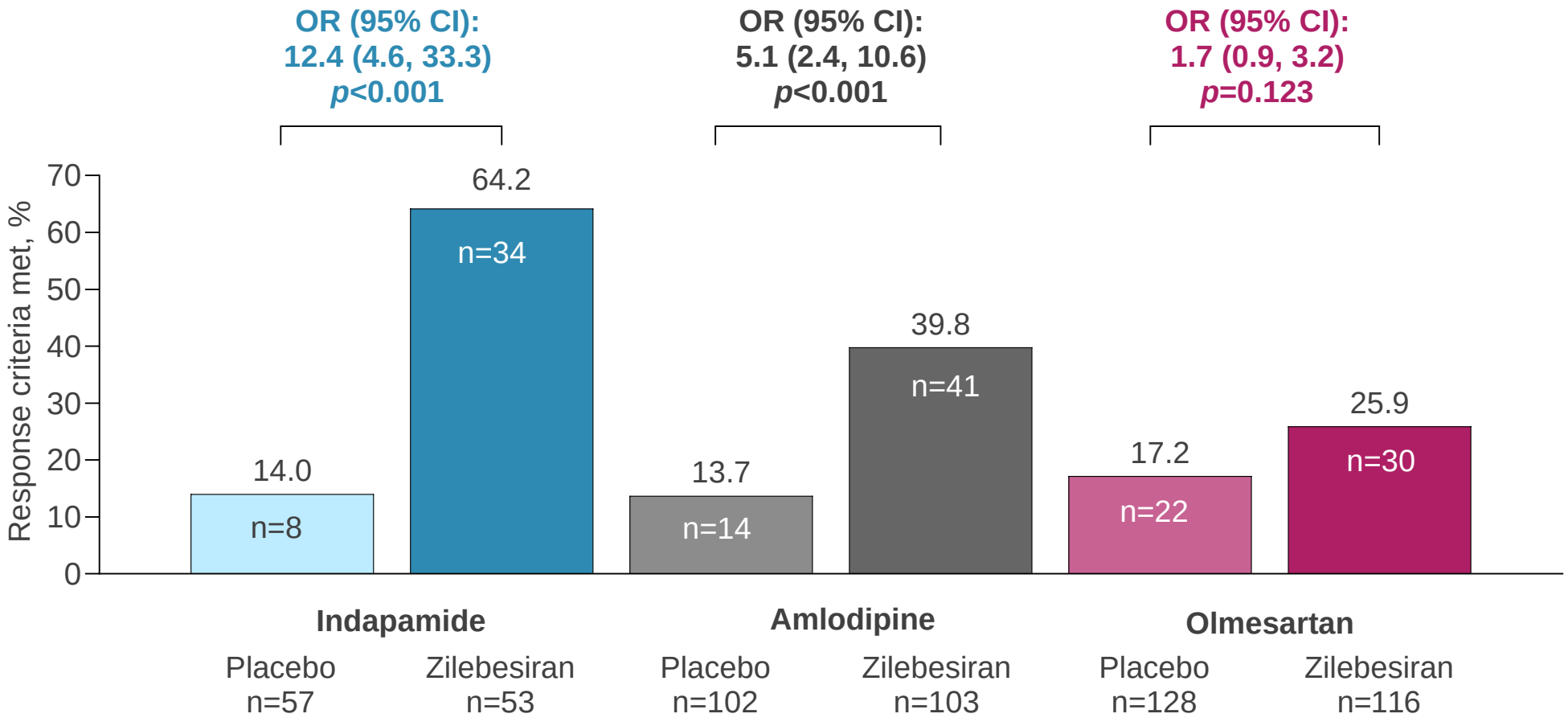
Data presented in the full analysis set. BL, baseline; CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; SE, standard error.

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 ≥20 mmHg without additional antihypertensives



After the original data presentation, it was detected that several patients were randomized simultaneously at multiple trial sites. This has led to the exclusion of 9 patient IDs; updated data are presented here. Data presented in the full analysis set.
CI, confidence interval; OR, odds ratio.

Safety Profile Through Month 6

n (%)	Background Medication					
	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)
>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

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Adverse event definitions are based on MedDRA terminology. AE, adverse event, MedDRA, Medical Dictionary for Regulatory Activities.

KARDIA-2 Summary

For US HCPs Only

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- 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