Zilebesiran: KARDIA-2 Study

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The safety and efficacy of zilebesiran are currently being investigated in clinical studies and have not been evaluated by FDA or any health authority.

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SUMMARY

- Zilebesiran is an investigational subcutaneously administered RNAi therapeutic designed to target hepatic synthesis of AGT and is currently being studied for the treatment of hypertension in adults.[1]
- KARDIA-2 was a phase 2 study designed to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients with hypertension not adequately controlled by a standard-of-care antihypertensive medication.[1]
  - At Month 3, clinically significant reductions in 24-hour mean ambulatory SBP and office SBP were observed when zilebesiran treatment was added to a standard-of-care antihypertensive medication (indapamide, amlodipine, or olmesartan).[1] A consistent treatment effect was observed across most predefined patient subgroups among the three background medication cohorts.[2]
  - AEs of hyperkalemia, hypotension, and decreased eGFR were observed in the zilebesiran add-on treatment group at a higher rate than placebo with standard-of-care antihypertensives.[1]

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STUDY DESIGN

The KARDIA-2 study (NCT05103332) was a phase 2, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients aged 18 to 75 years with hypertension that was not adequately controlled by a standard-of-care antihypertensive medication.[1]

The study included an open-label run-in period of at least 4 weeks and a 6-month DB treatment period. Following discontinuation of antihypertensive therapies, eligible patients with a screening eGFR < 45 mL/min/1.73 m^2 or urine albumin:creatinine ratio ≥ 300 mg/g were preferentially assigned to the olmesartan run-in cohort. The remaining patients were randomized in a 4:7:10 ratio to receive open-label treatment of the following antihypertensive agents: indapamide (diuretic) 2.5 mg daily,

amlodipine (CCB) 5 mg daily, or olmesartan (ARB) 40 mg daily (20 mg daily for patients with creatinine clearance ≤60 mL/min at screening enrolled outside of the US, consistent with local labeling). After the run-in period, patients in each cohort with 24-hour mean ambulatory SBP between 130 and 160 mmHg and at least 80% adherence to the protocol-specified background therapy were randomized 1:1 to receive a single subcutaneous injection of either zilebesiran 600 mg or placebo as an add-on treatment during the 6-month DB period.[1]

Patients eligible for the study included those with[1]:

- An office SBP at screening ≥155 mmHg and ≤180 mmHg for patients with untreated hypertension
- An office SBP at screening ≥145 mmHg and ≤180 mmHg for patients on 1-2 antihypertensive medications
- 24-hour mean SBP >130 mmHg and ≤160 mmHg by ABPM after at least 4 weeks of run-in on protocol-specified background antihypertensive medication

Patients excluded from the study included those with[1]:

- Known secondary hypertension
- Symptomatic orthostatic hypotension
- Serum potassium > 5.0 mmol/L
- eGFR < 30 mL/min/1.73 m^2 calculated by the MDRD method
- Symptomatic heart failure
- Type 1, poorly controlled type 2, or newly diagnosed diabetes

The primary endpoint was the difference in the change from baseline at Month 3 in 24-hour mean ambulatory SBP.[1]

Secondary endpoints assessed hierarchically in the following order included[1]:

- Between-group difference in change from baseline at Month 3 in office SBP
- Time-adjusted change from baseline through Month 6 in office SBP and 24-hour mean ambulatory SBP
- Proportion of patients meeting the protocol-defined BP response criterion at Month 6 (defined as 24-hour mean ambulatory SBP <130 mmHg and/or a reduction from baseline ≥20 mmHg without rescue antihypertensive medication)

Other secondary endpoints included the change from baseline in serum AGT. Safety outcomes included rates of investigator-reported AEs and occurrence of protocol-defined laboratory abnormalities.[1]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

At the end of the run-in period and before dosing of zilebesiran or placebo, the mean (SD) changes in office SBP were -15.5 (15.6) mm Hg with indapamide, -14.7 (15.2) mm Hg with amlodipine, and -13.0 (18.0) mm Hg with olmesartan.[1]

In the overall population, the mean (SD) age was 58.5 (10.3) years, mean (SD) 24-hour ambulatory SBP was 143.4 (8.2) mm Hg, and mean (SD) office BP was 144.5 (12.2) mm Hg. Of the 658 patients, 376 (57.1%) were male, 187 (28.4%) were self-reported as Black or African American, 151 (22.9%) had diabetes, 398 (60.5%) had a BMI ≥30, 66 (10.0%) had eGFR < 60mL/min/1.73 m^2, and 77 (11.7%) were previously untreated for hypertension. Of the 581 patients previously treated for hypertension, 304 (46.2%) were

treated with 1 antihypertensive treatment, 239 (36.3%) were treated with 2, and 38 (5.8%) were treated with more than 2. The baseline characteristics of patients by each background therapy cohort are shown in **Table 1**.[1]

Table 1. Baseline Characteristics by Background Therapy Cohort in KARDIA-2.[1,a]

Characteristic	Indapamide		Amlodipine		Olmesartan	
	Zilebesiran (n=63)	Placebo (n=64)	Zilebesiran (n=118)	Placebo (n=120)	Zilebesiran (n=147)	Placebo (n=146)
Age, mean (SD), y	57.9 (10.7)	60.6 (10.2)	57.6 (10.2)	58.4 (9.8)	59.3 (10.4)	57.7 (10.6)
Male, n (%)	33 (52.4)	39 (60.9)	65 (55.1)	70 (58.3)	87 (59.2)	82 (56.2)
Female, n (%)	30 (47.6)	25 (39.1)	53 (44.9)	50 (41.7)	60 (40.8)	64 (43.8)
Country of enrollment, n (%)						
US	55 (87.3)	50 (78.1)	97 (82.2)	94 (78.3)	119 (81.0)	116 (79.5)
Canada	1 (1.6)	5 (7.8)	7 (5.9)	7 (5.8)	7 (4.8)	12 (8.2)
UK	3 (4.8)	6 (9.4)	11 (9.3)	15 (12.5)	13 (8.8)	10 (6.8)
Other	4 (6.3)	3 (4.7)	3 (2.5)	4 (3.3)	8 (5.4)	8 (5.5)
Race, n (%)[b]						
Asian	4 (6.3)	0	8 (6.8)	4 (3.3)	3 (2.0)	13 (8.9)
Black or African American	16 (25.4)	14 (21.9)	39 (33.1)	41 (34.2)	38 (25.9)	39 (26.7)
Multiracial	0	0	0	0	0	1 (0.7)
Native Hawaiian or Other Pacific Islander	1 (1.6)	0	0	0	0	0
White	41 (65.1)	48 (75.0)	71 (60.2)	74 (61.7)	106 (72.1)	93 (63.7)
Other	1 (1.6)	1 (1.6)	0	0	0	0
Not reported	0	1 (1.6)	0	1 (0.8)	0	0
24-h Ambulatory SBP, mean (SD), mm Hg	143.4 (8.5)	143.2 (8.4)	143.3 (7.8)	142.6 (8.2)	143.6 (8.2)	144.2 (8.3)
24-h mean Ambulatory SBP ≥145 mm Hg, n (%)	31 (49.2)	28 (43.8)	46 (39.0)	48 (40.0)	67 (45.6)	69 (47.3)
Office SBP, mean (SD), mm Hg	143.9 (12.1)	145.4 (11.5)[c]	142.8 (11.5)	144.1 (11.5)	144.8 (12.2)	145.8 (13.6)[d]
BMI >30, n (%)	46 (73.0)	39 (60.9)[c]	69 (58.5)	79 (65.8)	80.0 (54.4)[d]	85 (58.2)[c]
eGFR <60 mL/min/1.73 m^2, n (%)e	10 (15.9)	10 (15.6)	6 (5.1)	7 (5.8)	17 (11.6)	16 (11.0)
Type 2 diabetes, n (%)[f]	14 (22.2)	13 (20.3)	26 (22.0)	27 (22.5)	38 (25.9)	33 (22.6)
Any prior antihypertensive treatment, n (%)[g]	56 (88.9)	61 (95.3)	98 (83.1)	102 (85.0)	132 (89.2)	132 (91.0)
Number of prior antihypertensives, n (%)[h]						
0	7 (11.1)	3 (4.7)	20 (16.9)	18 (15.0)	16 (10.9)	13 (8.9)
1	33 (52.4)	33 (51.6)	57 (48.3)	55 (45.8)	63 (42.9)	63 (43.2)
2	19 (30.2)	25 (39.1)	37 (31. 4)	41 (34.2)	61 (41.5)	56 (38.4)
>2	4 (6.3)	3 (4.7)	4 (3.4)	6 (5.0)	7 (4.8)	14 (9.6)

Abbreviations: BMI = body-mass index; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; SBP = systolic blood pressure; SD = standard deviation.

[a]Analyses are presented for the full analyses set unless otherwise specified.

[b]Race was self-reported by study participants based on fixed categories. Race and ethnicity data were collected to assess the diversity and generalizability of the study and because there are well-recognized differences in response to antihypertensive medications by ethnicity.

[c]Assessment missing for 1 patient.

[d]Assessment missing for 2 patients.

[e]eGFR was calculated based on the MDRD equation. Patients with screening eGFR <45 mL/min/1.73 m^2 or urine albumin:creatinine ratio ≥300 mg/g were preferentially assigned to receive olmesartan.

[f]Type 2 diabetes was defined as a medical history of diabetes (excluding gestational diabetes) based on review of electronic medical chart data.

[g]Analysis presented in the safety analysis set: indapamide + placebo, n = 64; indapamide + zilebesiran, n = 63; amlodipine + placebo, n = 120; amlodipine + zilebesiran, n = 118; olmesartan + placebo, n = 145; olmesartan + zilebesiran, n = 148.

[h]Prior antihypertensive medications were any medications taken prior to randomization to background medication.

PRIMARY ENDPOINT

Change in 24-hour Mean Ambulatory SBP at Month 3

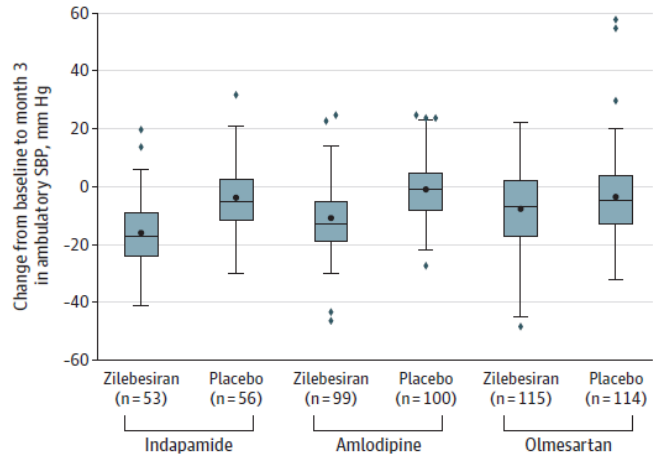
At Month 3, treatment with a single subcutaneous dose of zilebesiran 600 mg demonstrated significant reductions in 24-hour mean ambulatory SBP compared with placebo when added to indapamide, amlodipine, or olmesartan (**Figure 1**).[1]

In the indapamide cohort, the LS mean change from baseline in 24-hour mean ambulatory SBP was -15.7 (95% CI, -18.9 to -12.6) in the zilebesiran group and -3.7 (95% CI, -6.7 to -0.6) in the placebo group, resulting in a LS mean difference of -12.1 mm Hg (95% CI, -16.5 to -7.6; P<0.001).[1]

In the amlodipine cohort, the LS mean change from baseline in 24-hour mean ambulatory SBP was -10.5 (95% CI, -12.7 to -8.2) in the zilebesiran group and -0.7 (95% CI, -3.0 to 1.5) in the placebo group, resulting in a LS mean difference of -9.7 mm Hg (95% CI, -12.9 to -6.6; P<0.001).[1]

In the olmesartan cohort, the LS mean change from baseline in 24-hour mean ambulatory SBP was -7.7 (95% CI, -10.3 to -5.1) in the zilebesiran group and -3.2 (95% CI, -5.9 to -0.6) in the placebo group, resulting in a LS mean difference of 4.5 mm Hg (95% CI, -8.2 to -0.8; P<0.018) .[1]

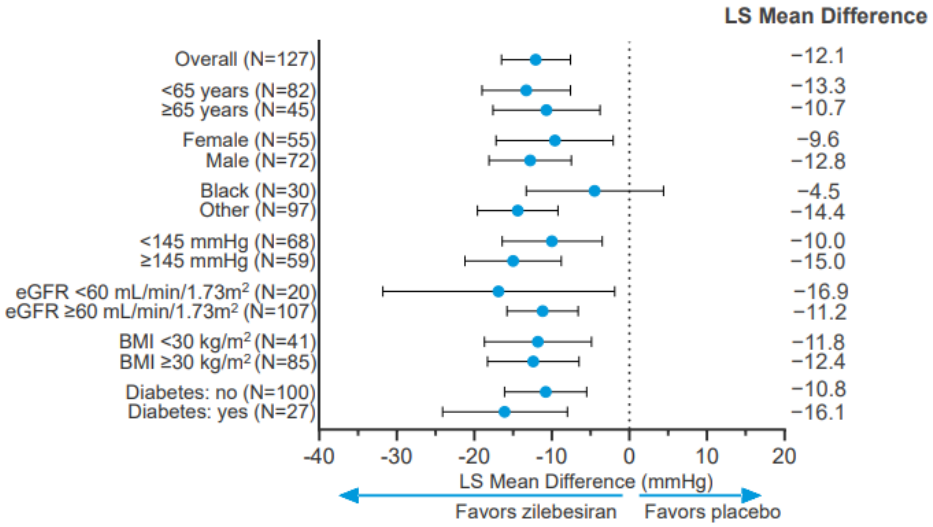
Figure 1. Change in 24-hour Mean Ambulatory SBP at Month 3.[1,a]



Abbreviations: IQR = interquartile range; SBP = systolic blood pressure.
[a]Analyses are presented for the full analysis set. Box plots demonstrate median (horizontal line), mean (circle), IQR (box upper and lower boundary), highest and lowest values within 1.5 x the IQR (whiskers), and more extreme values (diamonds).
From Desai et al.[1]

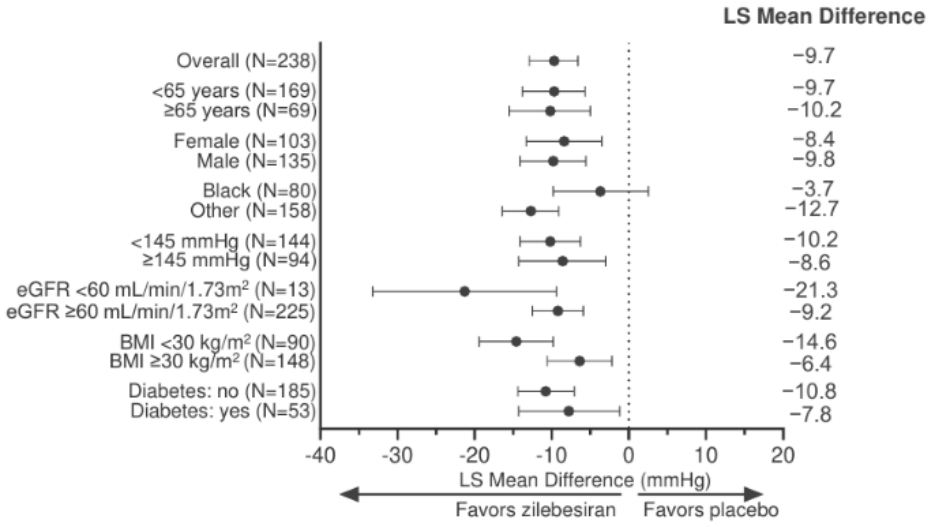
Figures 2A-2C show the change from baseline to Month 3 in 24-hour mean ambulatory SBP across predefined subgroups for each cohort.[2]

Figure 2A. Indapamide Cohort: Change in 24-hour Mean Ambulatory SBP at Month 3 Subgroup Analysis.[2,a]



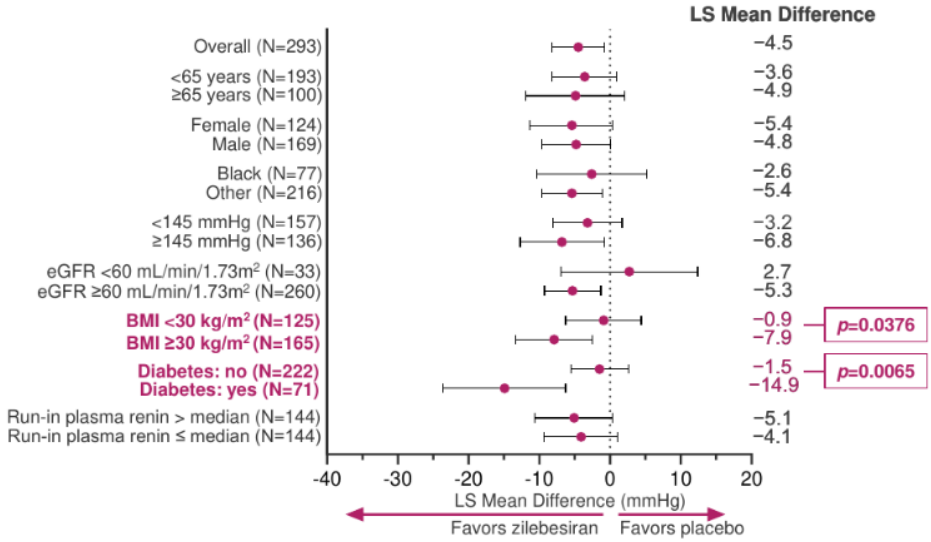
Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=127.
From Saxena et al.[2]

Figure 2B. Amlodipine Cohort: Change in 24-hour Mean Ambulatory SBP at Month 3 Subgroup Analysis.[2,a]



Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=238
From Saxena et al.[2]

Figure 2C. Olmesartan Cohort: Change in 24-hour Mean Ambulatory SBP at Month 3 Subgroup Analysis.[2,a]



Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=293
From Saxena et al.[2]

SECONDARY ENDPOINTS

Change in Office SBP at Month 3

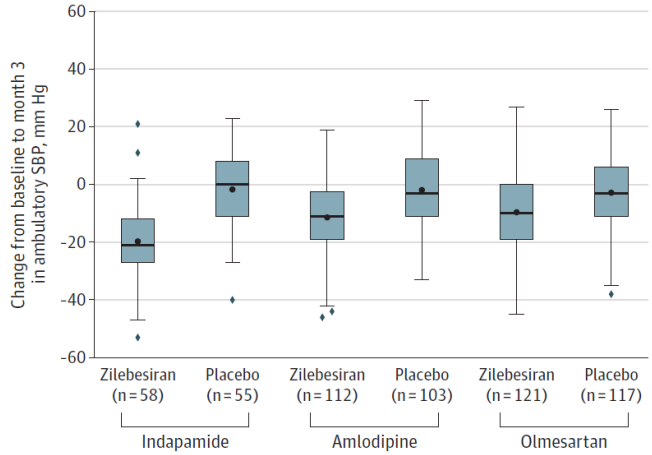
At Month 3, treatment with a single subcutaneous dose of zilebesiran 600 mg demonstrated significant reductions in office SBP compared with placebo when added to indapamide, amlodipine, or olmesartan (**Figure 3**).[1]

In the indapamide cohort, the LS mean change from baseline in office SBP was -19.3 mm Hg (95% CI, -22.3 to -16.2) in the zilebesiran group and -0.8 mm Hg (95% CI, -3.8 to 2.3) in the placebo group, resulting in a LS mean difference of -18.5 mm Hg (95% CI, -22.8 to 14.2; p<0.001).[1]

In the amlodipine cohort, the LS mean change from baseline in office SBP was -11.5 (95% CI, -13.8 to -9.2) in the zilebesiran group and -1.4 (95% CI, -3.7 to 1.0) in the placebo group, resulting in a LS mean difference of -10.2 mm Hg (95% CI, -13.4 to -6.90; P<0.001).[1]

In the olmesartan cohort, the LS mean change from baseline in office SBP was -9.3 (95% CI, -11.8 to -6.9) in the zilebesiran group and -2.6 (95% CI, -5.1 to -0.1) in the placebo group, resulting in a LS mean difference of -6.7 mm Hg (95% CI, -10.2 to -3.3; P<0.001).[1]

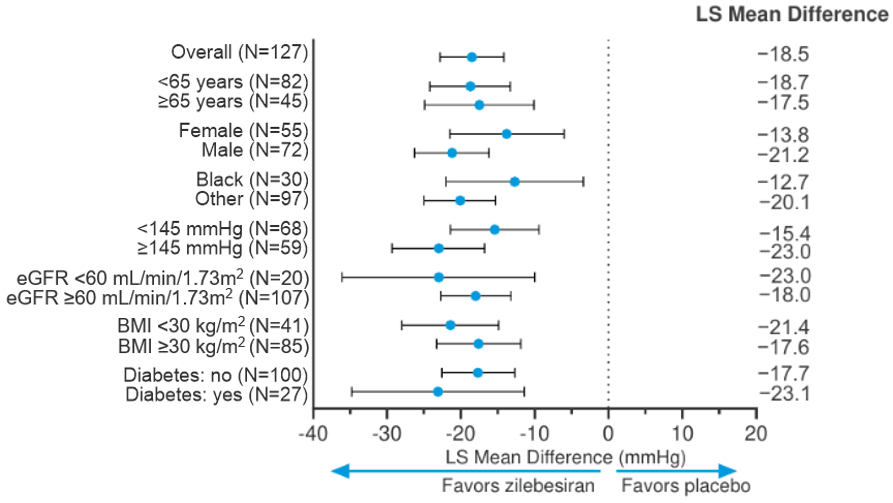
Figure 3. Change in Office SBP at Month 3.[1,a]



Abbreviations: IQR = interquartile range; SBP = systolic blood pressure.
[a]Analyses are presented for the full analysis set. Box plots demonstrate median (horizontal line), mean (circle), IQR (box upper and lower boundary), highest and lowest values within 1.5 x the IQR (whiskers), and more extreme values (diamonds).
From Desai et al.[1]

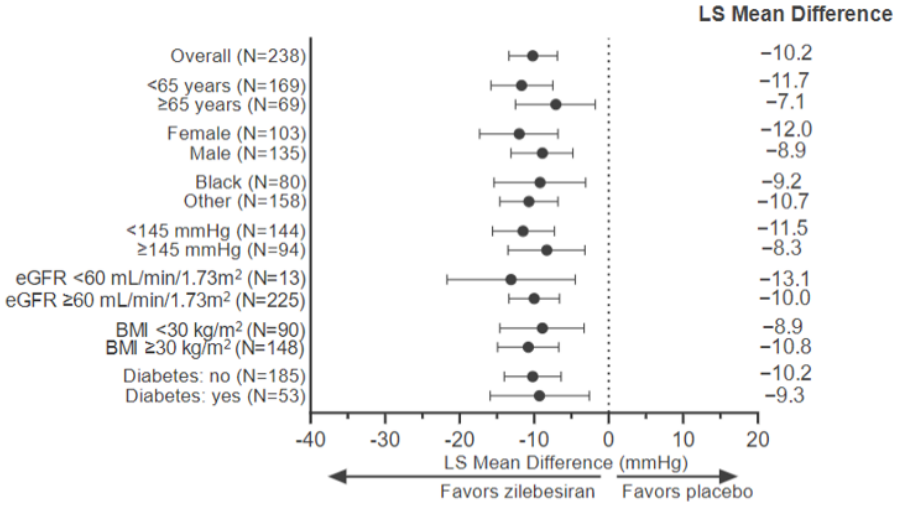
Figures 4A-4C show the change from baseline to Month 3 in office SBP across predefined subgroups for each cohort.[2]

Figure 4A. Indapamide Cohort: Change in Office SBP at Month 3 Subgroup Analysis.[2,a]



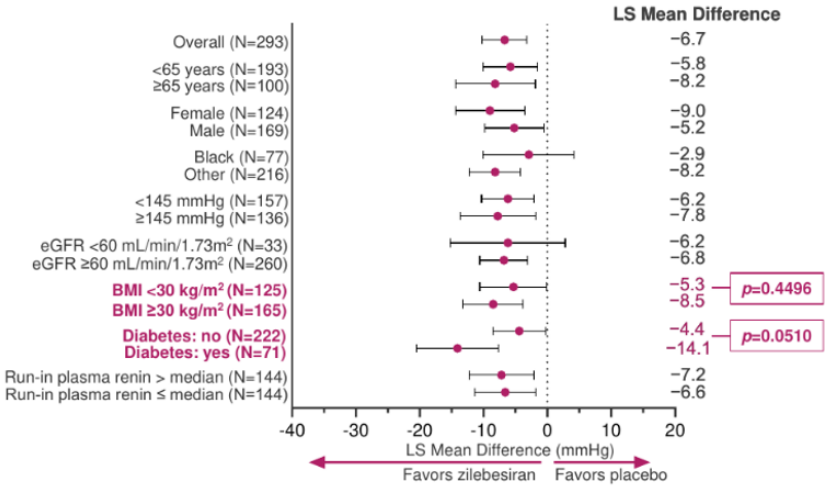
Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=127.
From Saxena et al.[2]

Figure 4B. Amlodipine Cohort: Change in Office SBP at Month 3 Subgroup Analysis.[2,a]



Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=238
From Saxena et al.[2]

Figure 4C. Olmesartan Cohort: Change in Office SBP at Month 3 Subgroup Analysis.[2,a]



Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=293
From Saxena et al.[2]

Time-Adjusted Change in Office SBP and 24-hour Mean Ambulatory SBP Through Month 6

The time-adjusted changes from baseline in SBP through Month 6 by treatment cohorts are summarized in **Table 2**.[1]

In the indapamide cohort, 25 patients (41.7%) in the placebo group and 9 patients (15.5%) in the zilebesiran group received rescue antihypertensive therapy at Month 6. In the amlodipine cohort, 55 patients (48.7%) in the placebo group and 28 patients (25.2%) in the zilebesiran group received

rescue antihypertensive therapy at Month 6. In the olmesartan cohort, 75 patients (54.0%) in the placebo group and 57 patients (42.5%) in the zilebesiran group received rescue antihypertensive therapy at Month 6.[1]

Table 2. Time-Adjusted Change from Baseline Through Month 6 in SBP.[1,a]

	Indapamide		Amlodipine		Olmesartan	
	Zilebesiran (n=63)	Placebo (n=64)	Zilebesiran (n=118)	Placebo (n=120)	Zilebesiran (n=147)	Placebo (n=118)
24-hour Ambulatory SBP						
LS mean change from baseline (95% CI), mm Hg	-15.6 (-18.3, -13.0)	-4.6 (-7.2, -2.0)	-9.7 (-11.6, -7.8)	-1.8 (-3.6, 0.1)	-7.6 (-9.5, -5.6)	-5.8 (-7.7, -3.8)
LSMD from baseline, zilebesiran vs placebo (95% CI), mmHg	-11.0 (-14.7, -7.3)		-7.9 (-10.6, -5.3)		-1.8 (-4.6, 1.0)	
P value	<0.001		<0.001		0.21	
Office SBP						
LS mean change from baseline (95% CI), mm Hg	-18.1 (-20.4, -15.7)	-4.5 (-6.8, -2.2)	-11.5 (-13.1, -9.9)	-2.9 (-4.5, -1.2)	-10.8 (-12.4, -9.2)	-6.3 (-7.9, -4.7)
LSMD from baseline, zilebesiran vs placebo (95% CI), mmHg	-13.6 (-16.9, -10.3)		-8.6 (-10.9, -6.3)		-4.5 (-6.8, -2.3)[b]	
P value	<0.001		<0.001		-	

Abbreviations: AUC = area under the curve; CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least squares; LSMD = least squares mean difference; MMRM = mixed model for repeated measures; SBP = systolic blood pressure.

[a]Analyzed by MMRM including treatment, visit, treatment x visit, and Race (Black; all other races) as fixed factors and corresponding baseline SBP and baseline eGFR as covariates. Uninstructured covariance matrix was used. Time-adjusted change from baseline is AUC divided by the duration of time between time points. All collected blood pressure measurements were analyzed through Month 6 as predefined in the statistical analysis plan.

[b]Statistical comparison presented for descriptive purposes only in line with prespecified statistical testing hierarchy.

SBP Response at Month 6 Without Rescue Medication

At Month 6, treatment with zilebesiran resulted in a larger proportion of patients achieving a SBP response without rescue medication. The response criterion was defined as a 24-hour mean ambulatory SBP <130 mmHg and/or reduction ≥20 mmHg without additional antihypertensives.[1]

In the indapamide cohort, 34 patients (64.2%) receiving zilebesiran compared with 8 patients (14.0%) receiving placebo met the prespecified BP response criterion at 6 months (OR, 12.4; 95% CI, 4.6 to 33.3; P<0.001).[1]

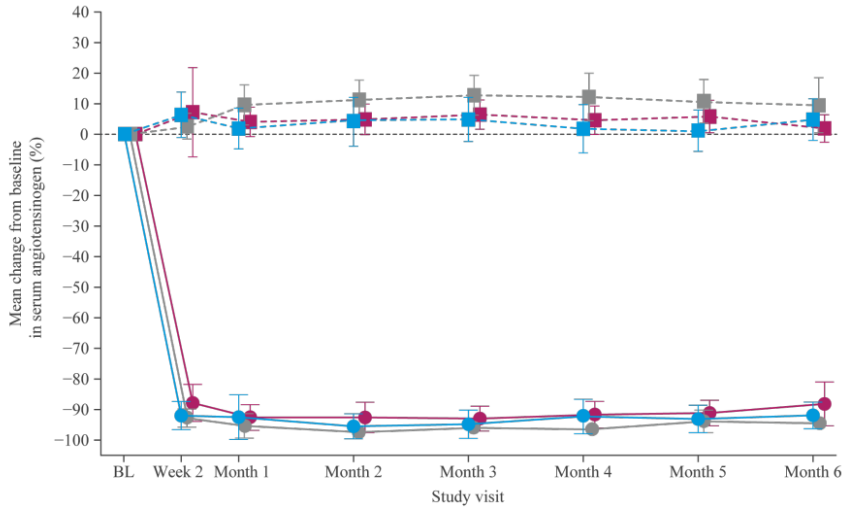
In the amlodipine cohort, 41 patients (39.8%) receiving zilebesiran compared with 14 patients (13.7%) receiving placebo met the prespecified BP response criterion at 6 months (OR, 5.1; 95% CI, 2.4 to 10.6; P<0.001).[1]

In the olmesartan cohort, the between-group difference in time-adjusted change from baseline in ambulatory SBP was not statistically significant through 6 months. Accordingly, by the prespecified testing hierarchy, formal statistical comparisons of the percentage of patients who met BP response criterion are presented for descriptive purposes. Thirty patients (25.9%) receiving zilebesiran compared with 22 patients (17.2%) receiving placebo met the prespecified BP response criterion at 6 months (OR, 1.7; 95% CI, 0.9 to 3.2).[1]

Change in Serum AGT at Month 6

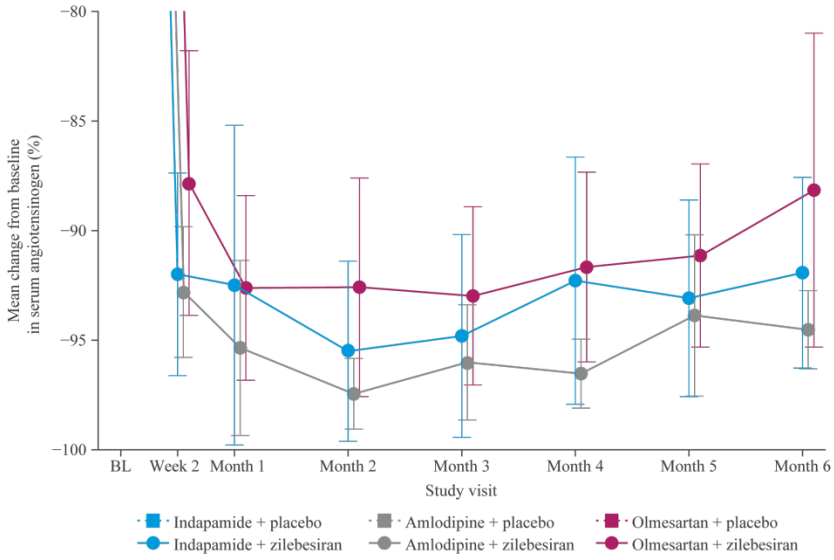
Figures 5A and 5B show the change in AGT from baseline to Month 6.[3] Across all 3 cohorts, the mean (SD) percent changes from baseline in serum AGT levels at Week 2 ranged from -87.8% (36.0) to -92.8% (16.0) in patients receiving zilebesiran. At Month 6, the mean (SD) percent changes from baseline in serum AGT levels ranged from -88.2% (41.6) to -94.5% (9.4). No change in serum AGT levels was noted in patients receiving placebo.[1]

Figure 5A. Change from Baseline to Month 6 in Serum AGT in All Arms.[3]



Abbreviations: AGT = angiotensinogen; BL = baseline.
From Desai et al.[3]

Figure 5B. Change from Baseline to Month 6 in Serum AGT in Zilebesiran Arms.[3]



Abbreviations: AGT = angiotensinogen; BL = baseline.
From Desai et al.[3]

SAFETY RESULTS

During the 6-month double-blind treatment period, a greater percentage of patients receiving zilebesiran than placebo had at least 1 AE. The rate of SAEs was similar between both groups, and there were no deaths reported. Laboratory abnormalities of interest were mild, occurred in the first 3 months, and resolved upon repeat measurement within 1-2 weeks without intervention (**Table 3**).[1,4] No apparent safety trends were observed by subgroup.[2]

Table 3. Zilebesiran Safety Summary Over 6 Months.[1,a]

Outcome, n (%)	Indapamide		Amlodipine		Olmesartan	
	Zilebesiran (n=63)	Placebo (n=64)	Zilebesiran (n=118)	Placebo (n=120)	Zilebesiran (n=148)	Placebo (n=145)
At least 1 AE	31 (49.2)	25 (39.1)	64 (54.2)	56 (46.7)	87 (58.8)	69 (47.6)
At least 1 SAE[b]	0	2 (3.1)	3 (2.5)	1 (0.8)	4 (2.7)	4 (2.8)
Injection-site reaction AE	4(6.3)	0	2 (1.7)	0	4 (2.7)	1 (0.7)
Hypotension/orthostatic hypotension AE[c]	0	0	7 (5.9)	4 (3.3)	7 (4.7)	3 (2.1)
Hyperkalemia AE[d]	2 (3.2)	0	6 (5.1)	2 (1.7)	10 (6.8)	4 (2.8)
Potassium >5.5 nmol/L	2 (3.2)	0	8 (6.8)	1 (0.8)	10 (6.8)	3 (2.1)
Confirmed on repeat measure[e]	1 (1.6)	0	2 (1.7)	0	2 (1.4)	0
Hepatic AE[f]	0	3 (4.7)	6 (5.1)	1 (0.8)	5 (3.4)	3 (2.1)
ALT >3x ULN	0[g]	0	3 (2.5)	1 (0.8)[g]	4 (2.7)[g]	1 (0.7)
AST >3x ULN	0[g]	1 (1.6)	2 (1.7)	1 (0.8)[g]	3 (2.0)[g]	3 (2.1)
Acute kidney failure AE[h]	4 (6.3)	1 (1.6)	4 (3.4)	1 (0.8)	8 (5.4)	3 (2.1)
≥30% decrease from baseline in eGFR (mL/min/1.73m^2)	8 (12.7)[1]	1 (1.6)	10 (8.5)	5 (4.2)	10 (6.8)	4 (2.8)
Confirmed on repeat measure[e]	3 (4.8)	0	1 (0.8)	2 (1.7)	4 (2.7)	1 (0.7)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; ULN = upper limit of the normal.

[a]AEs were reported by investigators based on clinical judgment and defined according to MedDRA terminology. Laboratory assessments were evaluated at a central laboratory. Analyses are presented in the safety analysis set.

[b]Included AEs that were life-threatening, required hospitalization, prolonged existing hospitalization, or resulted in disability, birth defect, or death.

[c]Included AEs mapped to the FDA MedDRA Query for hypotension (narrow terms).

[d]Included AEs mapped to the customized query of hyperkalemia, blood potassium increased, and blood potassium abnormal.

[e]Repeated typically within 1-2 weeks.

[f]Included AEs mapped to the Standardized MedDRA Query for drug-related hepatic disorders (both narrow and broad terms).

[g]Assessment missing for 1 patient.

[h]Included AEs mapped to the Standardized MedDRA Query for acute kidney failure (both narrow and broad terms).

ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring; AE = adverse event; AGT = angiotensinogen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ARB = angiotensin receptor blocker; BL = baseline; BMI = body mass index; CCB = calcium channel blocker; CI = confidence interval; DB = double-blind; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; IQR = interquartile range; LS = least squares; LSM = least squares mean; LSMD = least squares mean difference; MDRD = Modification of Diet in Renal Disease; MedDRA = Medical Dictionary for Regulatory Activities; RD = Modification of Diet in Renal Disease; OLE = open-label extension; OR = odds ratio; RNAi = RNA

interference; SAE = serious adverse event; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; ULN = upper limit of the normal.

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