Zilebesiran: KARDIA-1 Study

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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-1 was a phase 2 study to evaluate the safety and efficacy of zilebesiran dosing regimens for adults with mild to moderate hypertension. Statistically significant decreases in both 24-hour mean ambulatory SBP and office SBP measures were observed across all zilebesiran regimens studied through Months 3 and 6.[1]
- AEs occurring in >5% of patients treated with zilebesiran were ISRs (6%, n=19/302) and hyperkalemia (5%, n=16/302), which were mild to moderate in severity and transient in nature.[1]

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STUDY DESIGN

The KARDIA-1 study (NCT04936035) was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging multicenter study to evaluate the efficacy and safety of zilebesiran in patients aged 18-75 years with mild-to-moderate hypertension (N=394). Patients included in the study had a daytime mean SBP ≥135 mmHg and ≤160 mmHg (evaluated through ABPM) without antihypertensive medication.[1]

Study participants were randomized to receive subcutaneous administration of either zilebesiran (150 mg q6m, 300 mg q6m, 300 mg q3m, or 600 mg q6m) or placebo for the first 6 months of the 12-month double-blind period. Prior to randomization, a washout period of ≥2 weeks, or 4 weeks for long-acting hypertensives (eg, long-acting diuretics or calcium channel blockers), was required for patients previously taking antihypertensive medications.[1–3]

At month 6, participants randomized to placebo were re-randomized to 1 of the 4 initial dosing regimens until the end of the 12-month double-blind treatment period. Participants originally randomized to zilebesiran regimens remained on their originally assigned treatment arm through the

remainder of the study.[2] Patients could receive rescue antihypertensives at the discretion of the Investigator between months 3 and 5 and after month 6. Washout of rescue antihypertensives was required between months 5 and 6. Blood pressure measures were censored while patients were on or within 2 weeks after stopping a rescue antihypertensive.[3]

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

Secondary endpoints assessed include[1]:

- Change from baseline at month 3 in office SBP
- Change from baseline at month 6 in 24-hour mean SBP, assessed by ABPM
- Change from baseline at month 6 in office SBP
- Proportion of patients with 24-hour mean SBP <130 mmHg and/or reduction of ≥20 mmHg from baseline without additional antihypertensive medications at month 6
- Change from baseline at month 6 in 24-hour mean DBP
- Change from baseline at month 6 in office DBP
- Change from baseline at month 6 in serum AGT
- Change from baseline at month 6 in daytime and nighttime BP

Analyses were also conducted to assess the consistency of the zilebesiran treatment effect in various prespecified subgroups by the following baseline characteristics: age (<65 or ≥65 years), sex, race (Black or other), baseline 24-hour mean ambulatory SBP (<145 or ≥145 mmHg), and eGFR (<60 or ≥60 mL/min/1.73m^2).[1]

Exploratory endpoints of the study evaluated the effect of zilebesiran over time on other measures of blood pressure reduction, such as the percentage of patients requiring rescue antihypertensives.[1,2]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

A total of 394 patients were randomized, with 377 patients included in the full analysis set. The baseline characteristics by treatment assignment are summarized in **Table 1**.[1]

Table 1. Baseline Demographics and Disease Characteristics in KARDIA-1.[1,a]

Characteristic	Zilebesiran				Placebo (n=75)
	150 mg q6m (n=78)	300 mg q6m (n=73)	300 mg q3m (n=75)	600 mg q6m (n=76)	
Mean age, years (SD)	55.5 (10.6)	56.4 (10.3)	57.7 (10.6)	57.4 (10.2)	56.8 (11.2)
Male sex, n (%)	39 (50)	44 (60)	45 (60)	45 (59)	37 (49)
Race, n (%)[b]					
American Indian or Alaska Native	1(1)	0	0	0	0
Asian	4 (5)	2 (3)	7 (9)	5 (7)	5 (7)
Black or African American	20 (26)	17 (23)	19 (25)	19 (25)	18 (24)
Native Hawaiian or Pacific Islander	0	0	1 (1)	0	0
White	53 (68)	54 (74)	48 (64)	52 (68)	52 (69)
Ethnicity, n (%)[b]					
Hispanic or Latino	19 (24)	16 (22)	10 (13)	20 (26)	9 (12)

Characteristic	Zilebesiran				Placebo (n=75)
	150 mg q6m (n=78)	300 mg q6m (n=73)	300 mg q3m (n=75)	600 mg q6m (n=76)	
BMI ≥30, n (%)	46 (59)	46 (63)	40 (53)	45 (59)	37 (49)
Type 2 diabetes, n (%)[c]	14 (18)	11 (15)	17 (23)	16 (21)	10 (13)
Receiving ≥1 hypertensive agent before study enrollment, n (%)[d]	43 (55)	55 (75)	57 (76)	63 (83)	55 (73)
24-hour ambulatory SBP/DBP, mean (SD), mmHg	140.6 (8.5)/ 81.7 (8.3)	142.5 (8.8)/ 82.3 (8.7)	141.6 (7.7)/ 82.0 (8.6)	143.1 (9)/ 81.4 (8.3)	141.1 (7.9)/ 81.7 (7.8)
Office SBP/DBP, mean (SD), mmHg	142.0 (10.9)/ 87.4 (9.6)	143.0 (11.3)/ 88.8 (8.8)	140.0 (11.0)/ 85.3 (9.1)	140.8 (10.6)/ 85.6 (8.8)	143.1 (13.3)/ 87.9 (10.5)
eGFR, mean (SD), mL/min/1.73m^2	81.7 (16.5)	82.0 (14.5)	80.2 (18.3)	81.9 (19.4)	78.7 (21.0)
eGFR ≥60 mL/min/1.73m^2, n (%)	68 (87)	70 (96)	69 (92)	68 (90)	64 (85)
Serum AGT concentration, mean (SD), ng/mL	22.1 (5.9)	23.2 (7.8)	20.8 (4.9)	21.7 (5.9)	23.9 (10.9)

Abbreviations: AGT = angiotensinogen; BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; q3m = every 3 months; q6m = every 6 months; SBP = systolic blood pressure; SD = standard deviation.

[a]All randomized patients who received any amount of study drug. Patients enrolled at sites in Ukraine (n = 16) were excluded from the analysis populations.

[b]Race and ethnicity were self-reported from patient to the investigator in closed categories. For ethnicity, categories were Hispanic or Latino, not Hispanic or Latino, not reported, or unknown. For race, categories were American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, other (please specify), or not reported.

[c]Patients who met the study inclusion criteria with at least 1 of the following: medical history of type 2 diabetes, glycated hemoglobin A1c >7% before first study drug dose, or taking diabetes medication before first study drug dose.

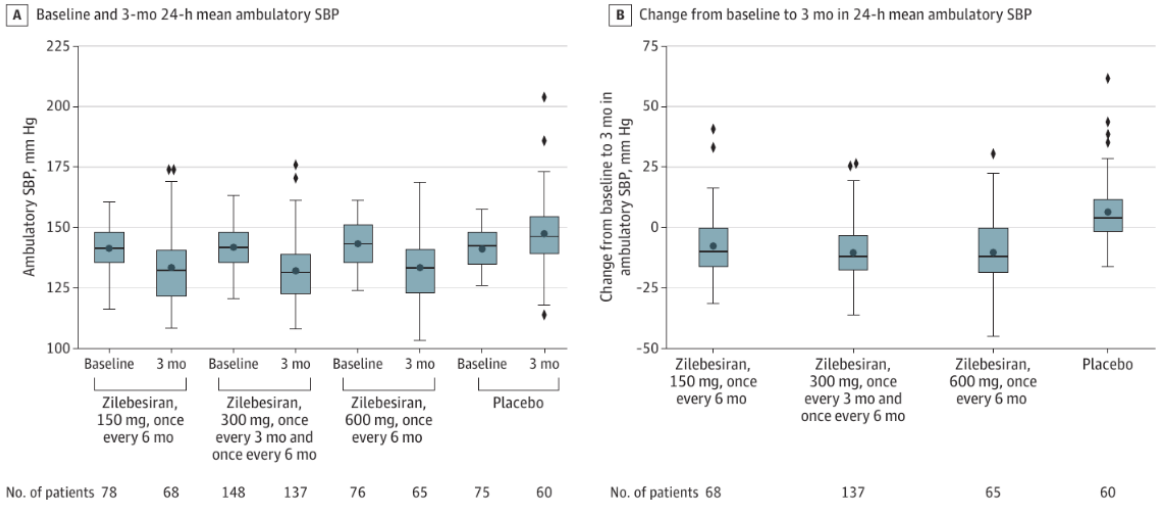
[d]Safety analysis set included all patients who received any amount of study drug, grouped according to the treatment actually received.

PRIMARY ENDPOINT

Change in 24-Hour Mean Ambulatory SBP at Month 3

At month 3, the LSM differences in the change from baseline in 24-hour mean ambulatory SBP between zilebesiran and placebo were −14.1 mmHg (95% CI, −19.2 to −9.0; P<0.001) for zilebesiran 150 mg every 6 months; −16.7 mmHg (95% CI, −21.2 to −12.3; P<0.001) for zilebesiran 300 mg every 3 months or every 6 months; and −15.7 mmHg (95% CI, −20.8 to −10.6; P<0.001) for zilebesiran 600 mg every 6 months (**Figure 1**).[1]

Figure 1. 24-Hour Mean Ambulatory SBP (Full Analysis Set).[1,a]



Abbreviations: IQR = interquartile range; mo = month; no = number; SBP = systolic blood pressure.
[a]The full analysis set included all randomized patients who received any amount of study drug, analyzed according to randomized treatment. Box plots demonstrate median (thick horizontal line), mean (circle), IQR (box top and bottom), highest and lowest values within 1.5x IQR (whiskers), and more extreme values (diamonds). For the efficacy analyses of endpoints assessed at month 3, the zilebesiran 300 mg and 600 mg groups were combined because both had received the same zilebesiran dose.
From Bakris et al.[1]

SECONDARY ENDPOINTS

Systolic Blood Pressure

The changes from baseline in office SBP at months 3 and 6 and in 24-hour mean ambulatory SBP at month 6 are summarized in **Table 2**.[1]

Table 2. Change from Baseline to Month 3 or 6 in 24-Hour Mean Ambulatory and Office SBP (Full Analysis Set).[1,a]

Outcome	Zilebesiran					Placebo (n=75)
	150 mg q6m (n=78)	300 mg q6m (n=73)	300 mg q3m (n=75)	300 mg q6m or q3m (n=148)	600 mg q6m (n=76)	
Office SBP at month 3, mean (SD), mmHg	131.8 (13.6) [n=68]	–	–	129.1 (13.8) [n=134]	131.1 (15.9) [n=64]	141.4 (12.6) [n=60]
LSM change from baseline (95% CI), mmHg	-9.7 (-12.6 to -6.8)	–	–	-12.1 (-14.2 to -10.0) [n=133]	-9.2 (-12.1 to -6.2)	-0.1 (-3.2 to 3.0)
LSMD vs placebo (95% CI), mmHg[b]	-9.6 (-13.8 to -5.3)	–	–	-12.0 (-15.7 to -8.3) [n=133]	-9.1 (-13.4 to -4.8)	–
P-value	<0.001	–	–	<0.001	<0.001	–
Ambulatory SBP at month 6, mean (SD), mmHg	134.4 (15.0) [n=62]	132.2 (13.8) [n=68]	131.6 (12.2) [n=60]	–	131.7 (16.8) [n=63]	144.6 (15.0) [n=54]
LSM change from baseline (95% CI), mmHg	-6.5 (-9.7 to -3.3)	-9.9 (-13.0 to -6.8)	-9.5 (-12.8 to -6.3)	–	-9.6 (-12.8 to -6.4)	4.6 (1.2 to 8.0)

LSMD vs placebo (95% CI) , mmHg[b]	-11.1 (-15.8 to -6.4)	-14.5 (-19.1 to -9.9)	-14.1 (-18.9 to -9.4)	–	-14.2 (-18.9 to -9.5)	–
P-value	<0.001	<0.001	<0.001	–	<0.001	–
Office SBP at month 6, mean (SD), mmHg	133.7 (13.6) [n=65]	131.2 (16.1) [n=68]	127.4 (14.5) [n=58]	–	128.9 (15.6) [n=62]	140.6 (12.4) [n=57]
LSM change from baseline (95% CI), mmHg	-8.2 (-11.5 to -4.8)	-11.1 (-14.4 to -7.8)	-12.8 (-16.3 to -9.2) [n=57]	–	-10.8 (-14.2 to -7.4)	-0.6 (-4.2 to 2.9)
LSMD vs placebo (95% CI), mmHg[b]	-7.5 (-12.4 to -2.7)	-10.5 (-15.3 to -5.7)	-12.1 (-17.2 to -7.1) [n=57]	–	-10.2 (-15.1 to -5.3)	–
P-value	0.003	<0.001	<0.001	–	<0.001	–

Abbreviations: CI = confidence interval; LSM = least-squares mean; LSMD = least-squares mean difference; q3m = every 3 months; q6m = every 6 months; SBP = systolic blood pressure; SD = standard deviation.

[a]All randomized patients who received any amount of study drug, analyzed according to randomized treatment.

[b]Mixed model for repeated measures adjusted for race and corresponding baseline SBP.

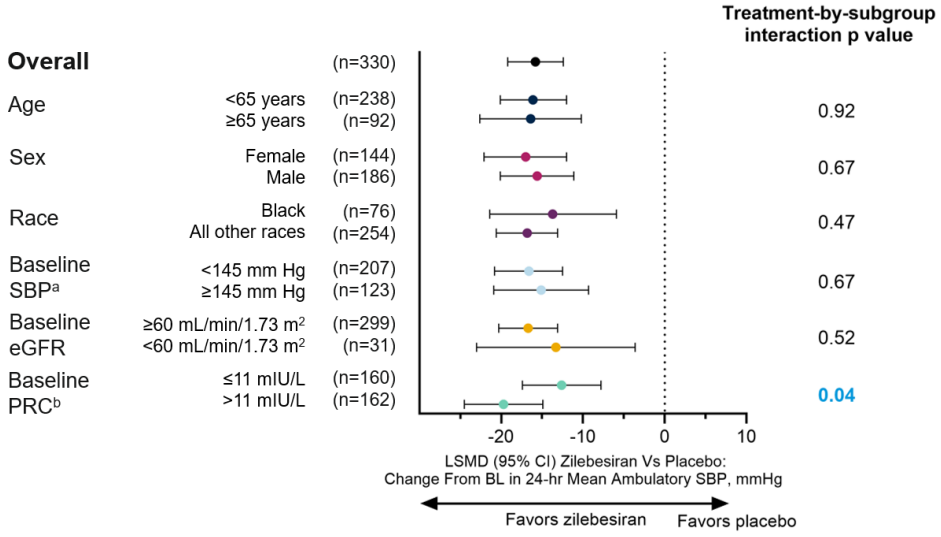
At months 3 and 6, reductions from baseline SBP were consistent for each hour of the 24-hour diurnal cycle in zilebesiran-treated patients and were greater in magnitude than placebo across all zilebesiran regimens studied.[1]

Subgroup Analyses of SBP

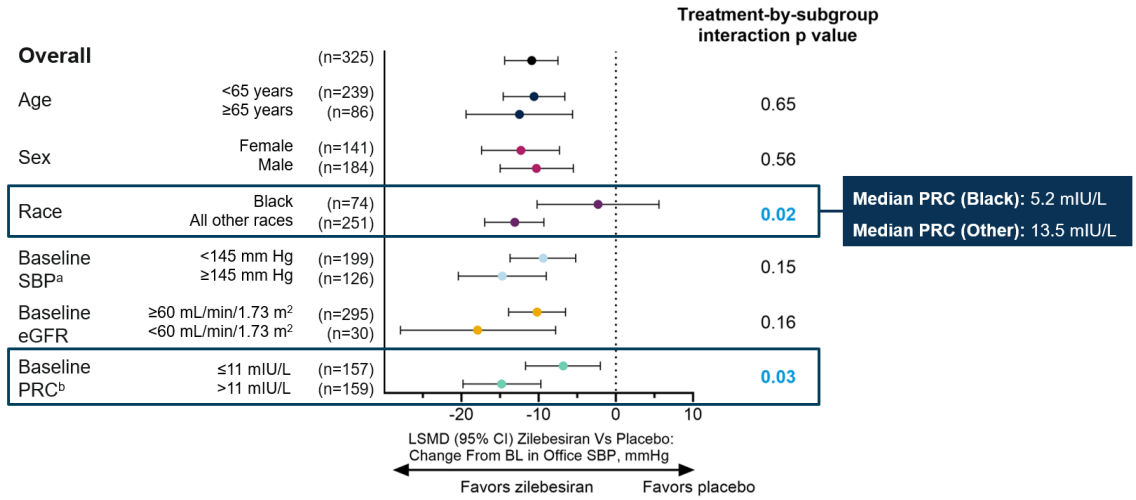
At month 3, the ambulatory SBP reductions were generally consistent across subgroups (**Figure 2**).[4] A variation in SBP reduction was observed in the race subgroup, in which Black patients experienced lower SBP reduction compared to patients of all other races. A post hoc analysis of the subgroup defined by baseline PRC identified that this racial variation was largely attributed to the low baseline PRC in Black patients (median of 5.2 mIU/L) compared to the PRC level (median of 13.5 mIU/L) in patients of all other races. Patients with higher baseline PRC had greater mean reductions across both 24-hour mean ambulatory SBP and office SBP measures (**Table 3**).[4]

Figure 2. LSMD (95% CI) for Zilebesiran (All Doses Combined) vs Placebo.[4]

A. Change from Baseline to Month 3 in 24-Hour Mean Ambulatory SBP



B. Change from Baseline to Month 3 in Mean Office SBP



Abbreviations: ABPM = ambulatory blood pressure monitoring; BL = baseline; CI = confidence interval; eGFR = estimated glomerular filtration rate; hr = hours; LSMD = least-squares mean difference; PRC = plasma renin concentration; SBP = systolic blood pressure.

[a]24-hour mean SBP assessed by ABPM.

[b]Baseline PRC above or below median (11mIU/L).

From Saxena et al.[4]

Table 3. LSM Change from Baseline to Month 3 in SBP by PRC and Race Subgroups.[4,a]

Race	Baseline PRC Above or Below Median (11 mIU/L)	Zilebesiran (all doses combined)	
		24-hour Mean Ambulatory SBP (SE)	Office SBP (SE)
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)

Abbreviations: LSM = least-squares mean; PRC = plasma renin concentration; SBP = systolic blood pressure; SE = standard error.
[a]Placebo data not presented owing to small sample size.

Diastolic Blood Pressure

The changes from baseline in 24-hour mean ambulatory DBP and office DBP at months 3 and 6 were consistent with the observed changes in SBP and are summarized in **Table 4.**[1,3]

Table 4. Change from Baseline to Month 3 or 6 in 24-Hour Mean Ambulatory and Office DBP (Full Analysis Set).[3,a]

Outcome	Zilebesiran					Placebo (n=75)
	150 mg q6m (n=78)	300 mg q6m (n=73)	300 mg q3m (n=75)	300 mg q6m or q3m (n=148)	600 mg q6m (n=76)	
Ambulatory DBP at month 3, mean (SD), mmHg	76.7 (10.6) [n=68]	–	–	76.1 (9.3) [n=137]	75.4 (8.2) [=65]	84.8 (9.3) [n=60]
LSM change from baseline (95% CI), mmHg	-4.5 (-6.1 to -2.9)	–	–	-5.7 (-6.8 to -4.5)	-5.8 (-7.4 to -4.1)	3.5 (1.8 to 5.2)
LSMD vs placebo (95% CI), mmHg	-8.0 (-10.3 to -5.6)	–	–	-9.2 (-11.2 to -7.1)	-9.2 (-11.6 to -6.8)	–
Office DBP at month 3, mean (SD), mmHg	81.6 (10.0) [n=68]	–	–	79.8 (9.5) [n=134]	80.0 (9.6) [n=64]	86.8 (8.5) [n=60]
LSM change from baseline (95% CI), mmHg	-5.3 (-7.2 to -3.4)	–	–	-7.0 (-8.4 to -5.7) [n=133]	-5.4 (-7.3 to -3.5)	-0.6 (-2.6 to 1.3)
LSMD vs placebo (95% CI), mmHg	-4.7 (-7.4 to -2.0)	–	–	-6.4 (-8.8 to -4.0) [n=133]	-4.7 (-7.5 to -2.0)	–
Ambulatory DBP at month 6, mean (SD), mmHg	76.8 (11.5) [n=62]	75.9 (8.9) [n=68]	75.6 (9.4) [n=60]	–	74.2 (9.5) [n=63]	83.1 (10.9) [n=54]
LSM change from baseline (95% CI), mmHg	-4.8 (-6.6 to -3.0)	-6.1 (-7.9 to -4.4)	-6.3 (-8.1 to -4.5)	–	-6.3 (-8.0 to -4.5)	2.2 (0.3 to 4.1)

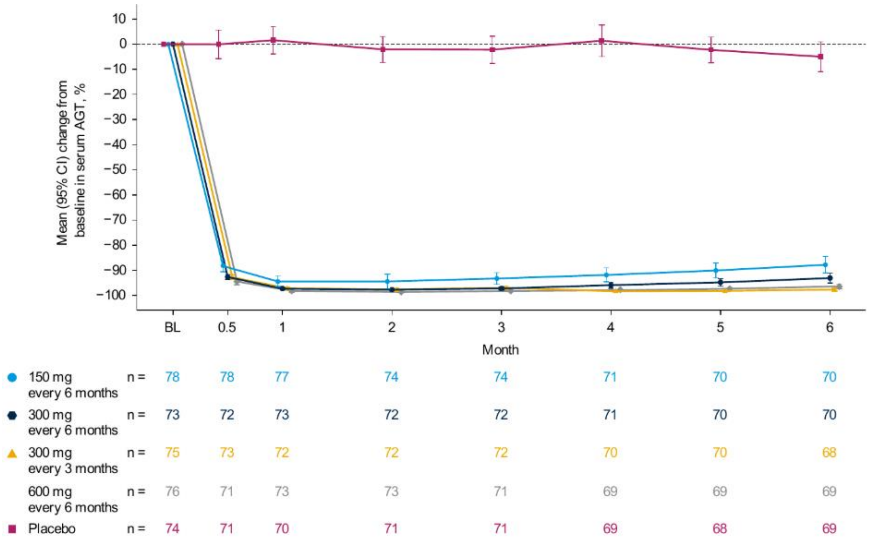
LSMD vs placebo (95% CI), mmHg	-7.0 (-9.6 to -4.3)	-8.3 (-10.9 to -5.7)	-8.5 (-11.1 to -5.8)	–	-8.4 (-11.0 to -5.8)	–
Office DBP at month 6, mean (SD), mmHg	83.2 (11.0) [n=65]	81.3 (11.3) [n=68]	77.6 (10.1) [n=58]	–	79.8 (12.1) [n=62]	86.1 (11.1) [n=57]
LSM change from baseline (95% CI), mmHg	-4.1 (-6.3 to -1.8)	-6.8 (-9.0 to -4.6)	-8.2 (-10.5 to -5.8) [n=57]	–	-5.0 (-7.3 to -2.8)	-1.2 (-3.6 to 1.2)
LSMD vs placebo (95% CI), mmHg	-2.9 (-6.1 to 0.4)	-5.6 (-8.8 to -2.4)	-7.0 (-10.3 to -3.6) [n=57]	–	-3.8 (-7.1 to -0.6)	–

Abbreviations: CI = confidence interval; DBP = diastolic blood pressure; LSM = least-squares mean; LSMD = least-squares mean difference; q3m = every 3 months; q6m = every 6 months; SD = standard deviation.
[a]All randomized patients who received any amount of study drug, analyzed according to randomized treatment.

Serum Angiotensinogen

The change from baseline to months 3 and 6 in serum AGT was greater in patients receiving any dose of zilebesiran compared with those who received placebo (**Figure 3**). After single 300 mg or 600 mg doses of zilebesiran, a decrease greater than 90% in serum AGT was observed and persisted to month 6.[1,3]

Figure 3. Mean Percent Change from Baseline in Serum AGT.[3,a]



Abbreviations: AGT = angiotensinogen; BL = baseline; CI = confidence interval
[a]Data points are staggered for visualization.
From Bakris et al.[3]

EXPLORATORY ENDPOINT

Patients Requiring Rescue Antihypertensives

During the 6-month double-blind treatment period, a higher percentage of patients in the placebo arm required rescue antihypertensives (52.0%) compared to patients in the zilebesiran arms (20.5%–32.1%).

In all study arms, the most frequently prescribed classes of rescue antihypertensives were calcium channel blockers and diuretics.[1]

SAFETY RESULTS

Drug-related AEs reported in >5% of patients treated with zilebesiran included ISRs (n=19/302, 6.3%) and hyperkalemia (n=16/302, 5.3%); all of these events were mild to moderate in severity and transient in nature (**Table 5**). Serious AEs were reported in 5 patients (6.7%) in the placebo group and 11 patients (3.6%) in the zilebesiran groups, none of which were considered related to the study drug. There were 3 patients with drug-related AEs leading to dose interruption and 4 patients with drug-related AEs leading to discontinuation (orthostatic hypotension [n=2], BP elevation [n=1], and injection site reaction [n=1]).[1]

Among the treatment-emergent AEs of clinical interest, 1 event of AKI was reported in the zilebesiran 300 mg every 3 months arm, which was considered unrelated to zilebesiran. There were no serious hepatic AEs, and the majority of LFT elevations were transient and resolved while receiving treatment. Hypotension AEs were mild or moderate in severity and transient in nature, with one event in zilebesiran 300 mg every 3 months group requiring treatment with normal saline. Hyperkalemia AEs were mild and did not lead to acute kidney injury or study drug discontinuation.[1]

Table 5. Summary of AEs During the 6-Month Double-Blind Treatment Period.[1,a]

AE, n (%)	Zilebesiran				Zilebesiran Total (N=302)	Placebo (n=75)
	150 mg q6m (n=78)	300 mg q6m (n=73)	300 mg q3m (n=75)	600 mg q6m (n=76)		
At least 1 AE	45 (58)	44 (60)	46 (61)	49 (64)	184 (61)	38 (51)
Related to study drug[b]	12 (15)	12 (16)	14 (19)	13 (17)	51 (17)	6 (8)
At least 1 SAE[c]	0	1 (1)	4 (5)	6 (8)	11 (4)	5 (7)
Related to study drug[b]	0	0	0	0	0	0
At least 1 study drug-related AE leading to study drug interruption[b,d]	1 (1)	0	1 (1)	1 (1)	3 (1)	0
At least 1 study drug-related AE leading to study drug discontinuation[b,e]	1 (1)	1 (1)	1 (1)	1 (1)	4 (1)	0
Death	0	0	1 (1)	0	1 (<1)	0
Study drug-related AEs occurring in at least 5% of patients[b]						
Hyperkalemia	4 (5)	3 (4)	4 (5)	5 (7)	16 (5)	1 (1)
ISR	3 (4)	4 (5)	8 (11)	4 (5)	19 (6)	0
Additional treatment-emergent AE of clinical interest (any relatedness)						
Potential hypotension[f]	6 (8)	6 (8)	5 (7)	7 (9)	24 (8)	5 (7)
Hyperkalemia[g]	5 (6)	4 (5)	5 (7)	5 (7)	19 (6)	2 (3)
Hypotension[h]	3 (4)	3 (4)	3 (4)	4 (5)	13 (4)	1 (1)
Hepatic AE[i]	2 (3)	2 (3)	4 (5)	1 (1)	9 (3)	1 (1)
Acute kidney failure[j]	1 (1)	1 (1)	1 (1)	1 (1)	4 (1)	0

Abbreviations: AE = adverse event; AKI = acute kidney injury; BP = blood pressure; ISR = injection site reaction; MedDRA = Medical Dictionary for Regulatory Activities; q3M = every 3 months; q6M = every 6 months; SAE = serious adverse event; SMQ = Standardized MedDRA Query.

[a]AEs are defined per MedDRA terminology.

[b]Related to study drug indicates a reasonable possibility that the event may have been caused by the study drug as evaluated by the investigator.
[c] Included AEs that were life-threatening, required hospitalization, prolonged existing hospitalization, or resulted in disability, birth defect, or death.
[d]Study drug interruption refers to a pause of further study drug dosing (including placebo dosing) with potential to resume.
[e]Study drug discontinuation is the stopping of further study drug dosing (including placebo dosing) without potential to resume.
[f]Include decreased blood pressure, hypotension, orthostatic hypotension, dizziness, syncope, and orthostasis.
[g]Include hyperkalemia, increased serum potassium, and abnormal serum potassium.
[h]Include additional terms of decreased blood pressure, hypotension, and orthostatic hypotension.
[i]Include AEs mapped to the standardized MedDRA query drug-related hepatic disorders, both narrow and broad terms. Terms include but are not limited to alanine aminotransferase increased; aspartate aminotransferase increased; serum alkaline phosphatase increased; serum bilirubin increased; gamma-glutamyltransferase increased; liver function test abnormal; liver function test increased; and transaminases increased.
[j]Acute kidney failure includes events of increased serum creatinine, increased blood urea, decreased glomerular filtration rate, and acute kidney injury.

ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring; AE = adverse event; AGT = angiotensinogen; AKI = acute kidney injury; BL = baseline; BMI = body mass index; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; ISR = injection site reaction; LSM = least-squares mean; LSMD = least-squares mean difference; MedDRA = Medical Dictionary for Regulatory Activities; mo = month; no = number; PRC = plasma renin concentration; q3m = every 3 months; q6m = every 6 months; RNAi = RNA interference; SAE = serious adverse event; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; SMQ = Standardized MedDRA Query.

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