Research

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RNA Interference With Zilebesiran for Mild to Moderate Hypertension
The KARDIA-1 Randomized Clinical Trial

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Despite the availability of a broad range of effective pharmacologic therapies, hypertension remains the leading risk factor worldwide for cardiovascular mortality and progression of kidney disease. Global estimates suggest that up to 80% of patients with hypertension do not meet guideline-recommended blood pressure (BP) targets.

- Furthermore, even patients who appear to have wellcontrolled hypertension during periodic office visits may experience significant between-visit variability, which is associated with residual risk for cardiovascular events.
- Although a broad range of patient and clinician factors contribute to inadequate BP control, inconsistent adherence to complex, multidrug oral treatment regimens that require daily dosing may be an important driver

Zilebesiran is an investigational RNA interference therapeutic targeting hepatic synthesis of angiotensinogen, the predominant precursor for angiotensin peptides and a key regulator of systemic BP. In a phase 1 study of patients withmild to moderate hypertension, treatment with single subcutaneous doses of zilebesiran was associated with dose-dependent reductions in serum angiotensinogen and 24-hour ambulatory BP that were sustained for 24 weeks. The randomized KARDIA-1 phase 2 study was conducted to evaluate the antihypertensive efficacy and safety of 4 different quarterly and biannual zilebesiran dosing regimens compared with placebo in patients with mild to moderate hypertension.

Methods

KARDIA-1 (NCT04936035) was a phase 2, randomized, doubleblind, placebo-controlled, dose-ranging study conducted at 78 sites in Canada, Ukraine, the UK, and the US between July 2021 and June 2023 .

Eligible patients included adults aged 18 to 75 years with hypertension who were either untreated or treated with a stable regimen of up to 2 antihypertensive therapies and had a daytime mean ambulatory systolic BP (SBP) between 135 mm Hg and 160 mm Hg following washout of background antihypertensive medication.

Those with secondary hypertension, orthostatic hypotension, a serum potassium concentration greater than 5 mEq/L (5 mmol/L), or estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m2 or lower (based on the Modification of Diet in Renal Disease formula18) were excluded.

Patients with type 1 diabetes, poorly controlled type 2 diabetes (glycated hemoglobin A1c [HbA1c] >9.0% [75 mmol/mol]), or laboratory evidence of diabetes during screening (HbA1c ≥7.0%) without known diagnosis were also excluded.

Following a washout period of at least 2 weeks, or 4 weeks for long-acting antihypertensives eligible patients were randomized in a double-blind fashion and in equal proportions using interactive response technology to receive 1 of 4 dosing regimens of subcutaneous zilebesiran (150 mg once every 6 months, 300 mg once every 6 months, 300 mg once every 3 months, or 600 mg once every 6 months) or subcutaneous placebo once every 3 months.

Patients randomized to receive zilebesiran once every 6 months received subcutaneous placebo at month 3 to maintain blinding. Randomization was stratified by race (Black vs other) and by baseline 24-hour mean ambulatory SBP (<145 or ≥145 mm Hg).

No additional antihypertensive treatment was permitted before month 3, but oral antihypertensive medications could subsequently be reinitiated at the discretion of the investigator.

Any additional antihypertensive medications were discontinued at month 5 to permit assessment of the isolated effect of zilebesiran vs placebo at month 6.

At month 6, patients in the placebo group were rerandomized to 1 of the 4 zilebesiran groups for an extension phase of the study.

This report presents results from the 6-month placebo-controlled treatment period.

End Points and Assessments

The primary end point was change from baseline to month 3 in 24-hour mean ambulatory SBP for each zilebesiran dose group vs placebo. Key secondary end points were change from baseline to month 3 in office SBP, change from baseline to month 6 in 24-hour mean ambulatory SBP, change from baseline to month 6 in office SBP, and the percentage of patients meeting the following response criteria at month 6: 24-hour mean ambulatory SBP of less than 130 mm Hg and/or reduction of 20 mm Hg or more from baseline without additional hypertensivemedication intervention (binary end point).

Other secondary end points included changes from baseline in 24-hour mean ambulatory diastolic BP (DBP), office DBP, serum angiotensinogen levels, daytime BP (6:00 AM to 9:59 PM, from ambulatory BP monitoring), and nighttime BP (10:00 PM to 5:59 AM) through 6 months. For the efficacy analyses of end points assessed atmonth 3, the zilebesiran 300mg groups (once every 3 months and once every 6 months) were combined because both had received the same zilebesiran dose.

Measurements were conducted initially during screening (following a 2- or 4-week antihypertensive therapy washout period) and again at months 1, 3, and 6.

The pharmacodynamic end point was change in serum angiotensinogen levels from baseline to month 6. Serum angiotensinogen levels were assessed at a central laboratory using validated enzyme-linked immunosorbent assays. The safety end point was frequency of adverse events (AEs) throughmonth 6.

Analyses were also conducted to assess the consistency of treatment effect in various prespecified subgroups defined by the following baselinecharacteristics: *age* (<65 or ≥65 years), *sex*, *race* (Black or other), *baseline 24-hour mean ambulatory SBP*(<145 or ≥145 mm Hg), and e*GFR* (<60 or ≥60 mL/min/1.73 m2).

Race and ethnicity were self-reported by patients and were included because it is known that race and ethnicity impact prevalence/severity of hypertension and response to renin–angiotensin–aldosterone system inhibition.

Assuming an SD of 20 mm Hg for the primary end point and a 15% rate of loss to follow-up, a sample size of 375 (75 patients per treatment group) was calculated to provide at least 84% power todetect a reduction of 10mmHg in ambulatory SBP from baseline tomonth 3 among zilebesiran doses and placebo. The power calculation was based on the Dunnett test.

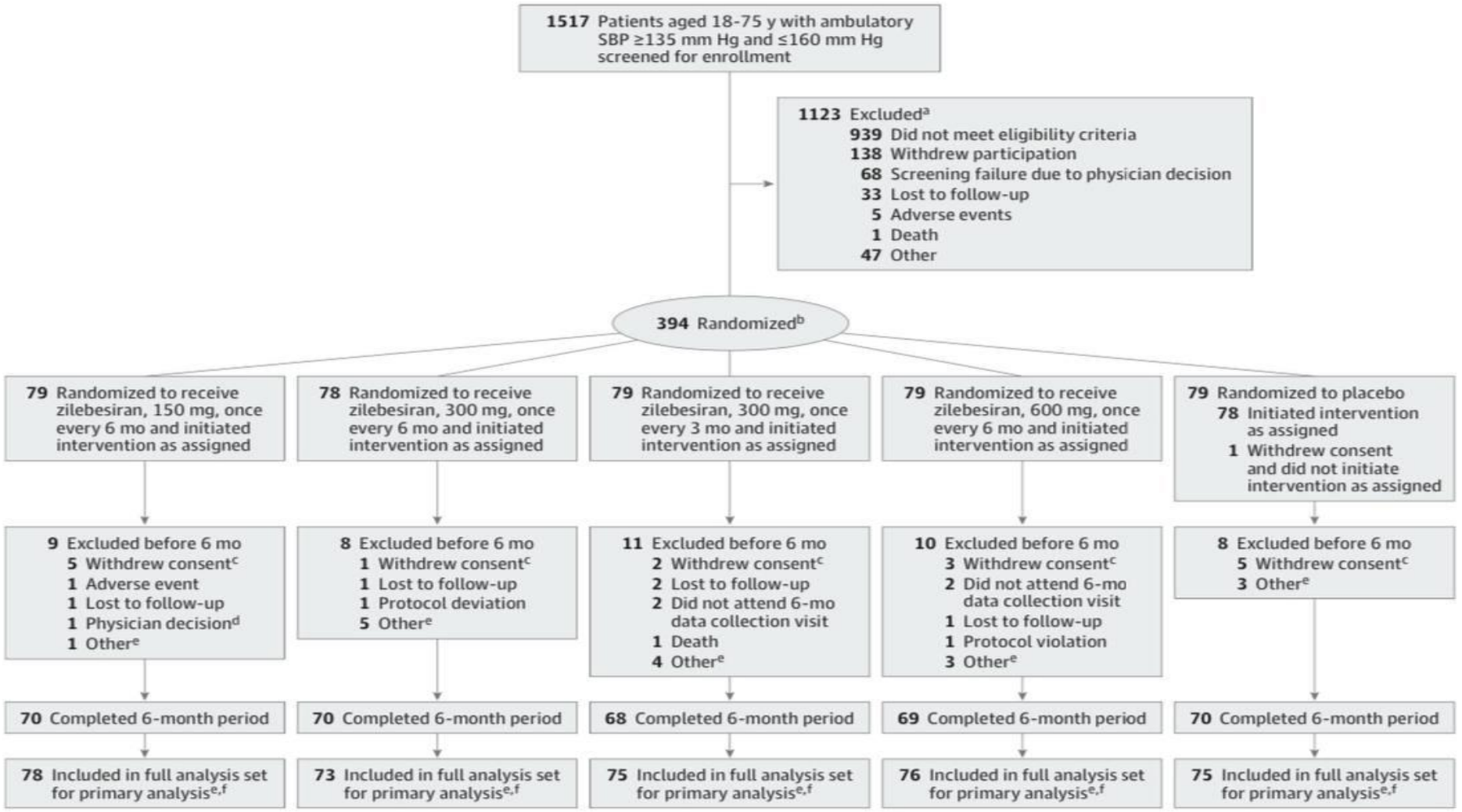
The full analysis set included all patients who received at least 1 dose of the study drug (excluding 16 patients randomized in Ukraine before the onset of war in February 2022).

For analysis of the binary SBP response end point, a logistic regression model adjusted for treatment, race (Black vs other), and baseline 24-hour mean ambulatory SBP was used with summary of treatment comparisons as odds ratios. Frequency of AEs, percent change from baseline in serum angiotensinogen levels by visit, and changes in body weight were summarized by treatment group using descriptive statistics.

Results

Of 1517 patients initially screened for enrollment, 394 were randomized (79 to receive placebo; 79 to receive zilebesiran,150 mg, once every 6 mo; 78 to receive zilebesiran, 300 mg,every 6 mo; 79 to receive zilebesiran, 300 mg, every 3 mo; and 79 to receive zilebesiran, 600 mg, every 6 mo). All but 1 patient (n = 393) received at least 1 dose of the study drug.

Figure 1. Flow of Participants in the KARDIA-1 Trial of Subcutaneous Zilebesiran for Hypertension



[a] A patient could have multiple reasons for screen failure and was counted for each reason separately.

[b] Randomization was stratified by race (Black or other) and baseline mean 24-hour systolic blood pressure (<145 or ≥145 mm Hg).

[c] Patients withdrew consent because of work-related reasons (n = 4), distance to the site (n = 3), no disclosed reason (n = 2), principal care clinician's advice (n = 2), time constraints (n = 1), the study not being worth their time (n = 1), personal reasons (n = 1), unwillingness to adhere to ambulatory blood pressure monitoring requirements (n = 1), and adverse events (n = 1).

[d] Patient was incarcerated during study.

[e] Patients enrolled at sites in Ukraine (n = 16) were excluded after randomization because war prevented continued data collection.

[f] Primary analysis was carried out in the full analysis set, which included all randomized patients who received any amount of study drug.

Owing to challenges with data collection related to the ongoing war, data from 16 patients randomized in Ukraine were excluded from the analyses. Accordingly, the full analysis set included 377 patients (302 assigned to receive zilebesiran and 75 assigned to receive placebo), of whom 347 patients (92.0%) completed the 6-month placebo-controlled treatment period.

Table 1. Patient Baseline Characteristics Among the Full Analysis Set[a]

Characteristic	Zilebesiran 150 mg every 6 mo (n = 78)	Zilebesiran 300 mg every 6 mo (n = 73)	Zilebesiran 300 mg every 3 mo (n = 75)	Zilebesiran 600 mg every 6 mo (n = 76)	Placebo (n = 75)
Age, mean (SD), y	55.5 (10.6)	56.4 (10.3)	57.7 (10.6)	57.4 (10.2)	56.8 (11.2)
Women, No. (%)	39 (50)	29 (40)	30 (40)	31 (41)	38 (51)
Men, No. (%)	39 (50)	44 (60)	45 (60)	45 (59)	37 (49)
Race, No. (%)[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, No. (%)[b]					
Hispanic or Latino	19 (24)	16 (22)	10 (13)	20 (26)	9 (12)
Not Hispanic or Latino	59 (76)	57 (78)	65 (87)	56 (74)	66 (88)
Body mass index ≥30, No. (%)	46 (59)	46 (63)	40 (53)	45 (59)	37 (49)
Type 2 diabetes, No. (%)[c]	14 (18)	11 (15)	17 (23)	16 (21)	10 (13)
Receiving ≥1 hypertensive agent before study enrollment, No. (%)[d]	43 (55)	55 (75)	57 (76)	63 (83)	55 (73)
24-h ambulatory blood pressure, mean (SD), mm Hg					
Systolic	140.6 (8.5)	142.5 (8.8)	141.6 (7.7)	143.1 (9.0)	141.1 (7.9)
Diastolic	81.7 (8.3)	82.3 (8.7)	82.0 (8.6)	81.4 (8.3)	81.7 (7.8)
Mean office BP, mm Hg (SD)					
Systolic	142.0 (10.9)	143.0 (11.3)	140.0 (11.0)	140.8 (10.6)	143.1 (13.3)
Diastolic	87.4 (9.6)	88.8 (8.8)	85.3 (9.1)	85.6 (8.8)	87.9 (10.5)
eGFR, mean (SD), mL/min/1.73 m^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/1.73 m^2, No. (%)	68 (87)	70 (96)	69 (92)	68 (90)	64 (85)
Serum angiotensinogen 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)

Of the analyzed population, 167 patients (44.3%) were women and 93 (24.7%) were Black.

Mean (SD) age at baseline was 56.8 (10.6) years and, at baseline, 24-hour mean ambulatory SBP was 142 (8) mm DBP was 82 (8) mm Hg.

Primary end point data were available for 68 patients in the group assigned to receive zilebesiran, 150 mg, every 6 months; 137 patients receiving zilebesiran, 300 mg, every 6 months or every 3 months; 65 patients receiving zilebesiran, 600 mg, every 6 months; and 60 patients receiving placebo.

LSM changes from baseline to month 3 in 24-hour mean ambulatory SBP were −7.3mm Hg (95% CI, −10.3 to −4.4) for zilebesiran, 150mg, every 6 months; −10.0 mm Hg (95% CI, −12.0 to −7.9) for zilebesiran, 300 mg, every 3 months or every 6 months; −8.9 mm Hg (95% CI, −11.9 to −6.0) for zilebesiran, 600 mg, every 6 months; and 6.8 mm Hg (95% CI, 3.6-9.9) for placebo. LSM differences in the change from baseline to month 3 in 24-hour mean ambulatory SBP between zilebesiran and placebo were−14.1 mm Hg (95% CI, −19.2 to −9.0) for zilebesiran, 150 mg, every 6 months; −16.7 mm Hg (95% CI, −21.2 to −12.3) for zilebesiran, 300 mg, every 3 months or every 6 months; and−15.7 mm Hg (95% CI, −20.8 to −10.6) for zilebesiran, 600 mg, every 6 months ($P < .001$ for all comparisons).

Table 2. Change From Baseline to Month 3 or 6 in 24-Hour Mean Ambulatory and Office Systolic Blood Pressure (SBP) Among the Full Analysis Set[a]

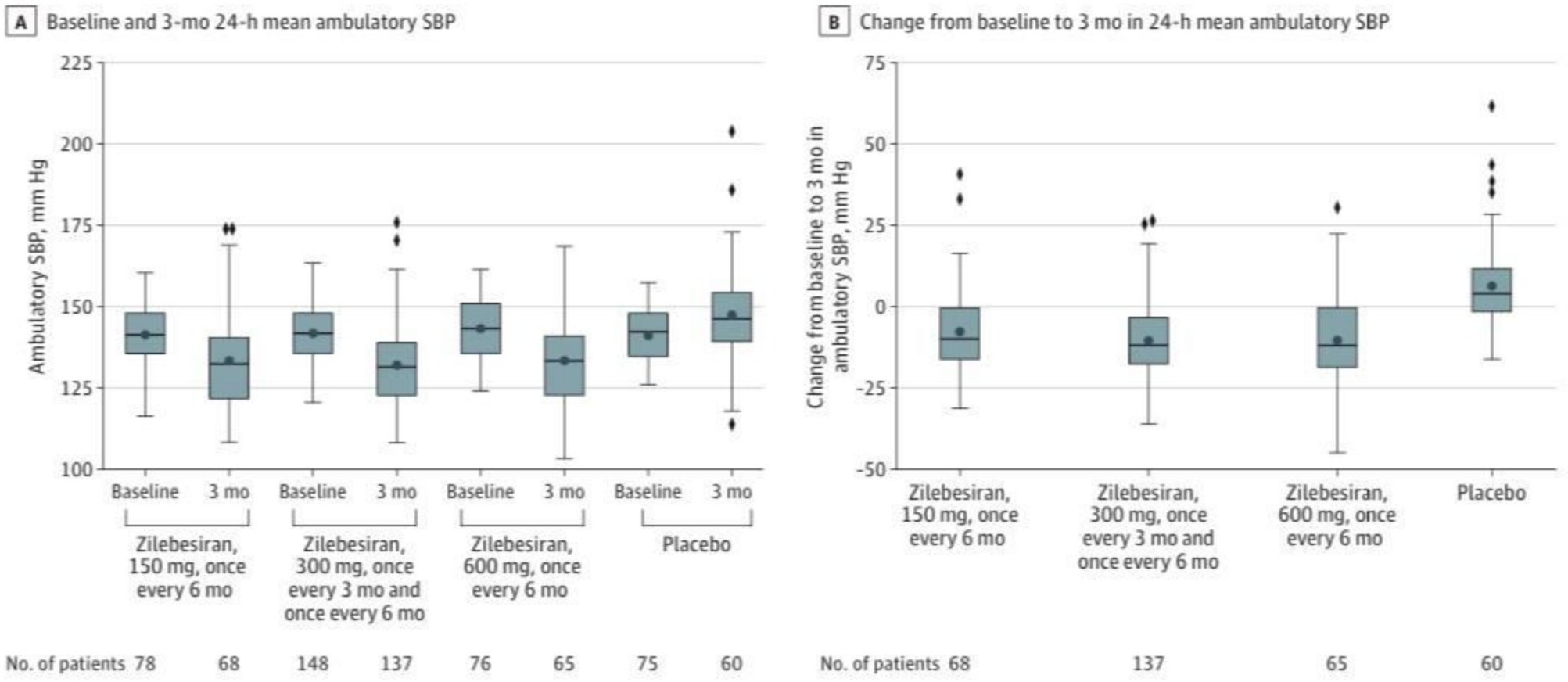
Outcome	Zilebesiran					Placebo (n = 75)
	150 mg every 6 mo (n = 78)	300 mg every 6 mo (n = 73)	300 mg every 3 mo (n = 75)	300 mg every 3 mo or every 6 mo (n = 148)	600 mg every 6 mo (n = 76)	
Ambulatory SBP at baseline, patients with data, mean (SD), mm Hg	140.6 (8.5)	142.5 (8.8)	141.6 (7.7)	142.0 (8.3)	143.1 (9.0)	141.1 (7.9)
Office SBP at baseline, mean (SD), mm Hg	142.0 (10.9)	143.0 (11.3)	140.0 (11.0) [n = 74]	141.5 (11.2) [n = 147]	140.8 (10.6)	143.1 (13.3)
Primary end point						
Ambulatory SBP at month 3, mean (SD), mm Hg	133.2 (14.7) [n = 68]			131.8 (12.8) [n = 137]	133.1 (14.9) [n = 65]	147.3 (15.2) [n = 60]
LSM change from baseline (95% CI), mm Hg	−7.3 (−10.3 to −4.4)			−10.0 (−12.0 to −7.9)	−8.9 (−11.9 to −6.0)	6.8 (3.6 to 9.9)
LSM difference vs placebo (95% CI), mm Hg[b]	−14.1 (−19.2 to −9.0)			−16.7 (−21.2 to −12.3)	−15.7 (−20.8 to −10.6)	
P value[b]	<.001			<.001	<.001	
Secondary end point						
Office SBP at month 3, mean (SD), mm Hg	131.8 (13.6) [n = 68]			129.1 (13.8) [n = 134]	131.3 (15.9) [n = 64]	141.4 (12.6) [n = 60]
LSM change from baseline (95% CI), mm Hg	−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)
LSM difference vs placebo (95% CI), mm Hg[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	<.001			<.001	<.001	
Ambulatory SBP at month 6, mean (SD), mm Hg	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), mm Hg	−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)
LSM difference vs placebo (95% CI), mm Hg[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	<.001	<.001	<.001		<.001	
Office SBP at month 6, mean (SD), mm Hg	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), mm Hg	−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)
LSM difference vs placebo (95% CI), mm Hg[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	.003	<.001	<.001		<.001	

Abbreviations: LSM, least-squares mean; SBP, systolic blood pressure.

[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. *P* values and 95% CIs for the primary end point are adjusted based on the Dunnett test.

Figure 2. Ambulatory Systolic Blood Pressure (SBP) Among the Full Analysis Set[a]



[a] 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 1.5 × the IQR (whiskers), and more extreme values (diamonds). For the efficacy analyses of end points assessed at month 3, the zilebesiran 300 mg and 600 mg groups were combined because both had received the same zilebesiran dose.

At month 3, LSM change from baseline in office SBP was −9.7 mm Hg (95% CI, −12.6 to −6.8) for zilebesiran, 150 mg, every 6 months; −12.1 mm Hg (95% CI, −14.2 to −10.0) for zilebesiran, 300 mg, every 3 months or every 6 months; −9.2 mm Hg (95% CI, −12.2 to −6.2) for zilebesiran, 600 mg, every 6 months; and −0.1 mm Hg (95% CI, −3.2 to 3.0) for placebo (Figure 2B). Differences between zilebesiran and placebo were −9.6 mm Hg (95% CI, −13.8 to −5.3) for zilebesiran, 150 mg, every 6 months; −12.0 mm Hg (95% CI, −15.7 to −8.3) for zilebesiran, 300 mg, every 3 months or every 6 months; and −9.1 mm Hg (95% CI, −13.4 to −4.8) for zilebesiran, 600 mg, every 6 months ($P < .001$ for all comparisons). Similar changes from baseline and differences vs placebo were observed at month 6 for 24-hourmean ambulatory and office SBP.

Table 3. Summary of Adverse Events (AEs)[a]

Adverse event	Patients, No. (%)					
	Zilebesiran					
	150 mg every 6 mo (n = 78)	300 mg every 6 mo (n = 73)	300 mg every 3 mo (n = 75)	600 mg every 6 mo (n = 76)	Zilebesiran total (n = 302)	Placebo (n = 75)
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 (0)	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)
Injection site reaction	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

[a] AEs are defined per Medical Dictionary for Regulatory Activities (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] Serious AEs (SAEs) are any untoward medical occurrence that, at any dose, results in death; is life-threatening (an event that places the patient at immediate risk of death from the event as it occurred but does not include an event that had it occurred in a more severe form might have caused death); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above.

[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.

The change from baseline to month 3 and month 6 in serum angiotensinogen was greater in patients who received any dose of zilebesiran than placebo, with a decrease of more than 90% from baseline persisting to month 6 after single 300-mg or 600-mg doses of zilebesiran.

At month 3 and month 6, reductions from baseline SBP were largely consistent for each hour of the 24-hour diurnal cycle in zilebesiran-treated patients and were greater in magnitude than placebo regardless of zilebesiran dose.

Serious AEs were reported in 5 patients (6.7%) in the placebo group and 11 patients (3.6%) in the zilebesiran groups, including 1 death due to cardiopulmonary arrest 5 days after treatment with zilebesiran, 300 mg, none of which were considered by the investigators to be related to the study drug (Table 3).

Drug-related AEs were all mild to moderate in severity; those reported in more than 5% of patients in the zilebesiran group were injection site reaction in 19 patients (6.3%) and hyperkalemia in 16 patients (5.3%).

More patients in the group that received zilebesiran every 3 months experienced injection site reactions than those who received zilebesiran every 6 months; all events were mild or moderate in severity and transient, and the most common injection site reaction symptoms were pain and erythema.

Four patients had drug-related AEs leading to an investigator decision to discontinue further study drug dosing during the double-blind period (orthostatic hypotension [n = 2], BP elevation [n = 1], and injection site reaction [n = 1]). Clinically relevant AEs of acute kidney failure were reported in 4 patients (1.3%) receiving zilebesiran vs 0 receiving placebo, hepatic AEs were reported in 9 patients (3.0%) receiving zilebesiran vs 1 (1.3%) receiving placebo, hypotension was reported in 13 (4.3%) receiving zilebesiran vs 1 (1.3%) receiving placebo, and hyperkalemia was reported in 19 (6.3%) patients receiving zilebesiran vs 2 (2.7%) receiving placebo.

Hypotension AEs were mild or moderate in severity, nonserious, and transient in nature, with a single event in the zilebesiran, 300 mg, every 3 months group requiring treatment with normal saline.

Hyperkalemia AEs were mild and none were associated with acute kidney injury or led to study drug discontinuation.

One event of acute kidney injury was reported by the investigator in a patient in the zilebesiran, 300 mg, every 3 months group at the month 6 visit

At month 6, mean (SD) change in body weight was −0.04 (2.87) kg among patients receiving zilebesiran, 150 mg, every 6 months; 0.57 (3.20) kg among patients receiving zilebesiran, 300 mg, every 6 months; −0.03 (3.40) kg among those receiving zilebesiran, 300 mg, every 3 months; and 0.48 (4.83) kg among those receiving zilebesiran, 600mg, every 6months;and 0.35 (3.07) kg among those receiving placebo. On laboratory evaluation, 17 patients (5.6%) assigned to receiving zilebesiran had a serum potassium level greater than 5.5 mmol/L on at least 1 occasion over the 6-month treatment period compared with none assigned to receive placebo.
Of these 17 patients, 2 (0.7%) had a serum potassium level greater than 6 mmol/L, which resolved on repeated measurement.
Levels of greater than 5.5 mmol/L were confirmed on repeated measurement in 2 additional patients (0.7%) out of 17.
Three patients assigned to receive zilebesiran received treatment for hyperkalemia with potassium binders during the study, although no hyperkalemia events led to study drug discontinuation during the 6-month treatment period

Discussion

In this randomized, dose-ranging study of patients with mild to moderate hypertension, treatment with single subcutaneous doses of zilebesiran was associated with significant reductions in 24-hour mean ambulatory SBP at month 3 compared with placebo.

This targeted approach to reduce hepatic angiotensinogen levels through RNA interference is novel for the treatment of hypertension; the longterm safety profile of zilebesiran, either alone or in combination with other antihypertensive agents, requires further study.

The study benefited from the use of continuous 24-hour ambulatory BP monitoring, which is considered the criterion standard of BP assessment.

BP reductions associated with a single dose of zilebesiran persisted tomonth 6, particularly at 300-mg and 600-mg doses, consistent with pharmacodynamic data demonstrating angiotensinogen reduction.

Although mild to moderate drug-related AEs, including injection site reactions and hyperkalemia, were more commonly reported in those receiving zilebesiran than placebo, most were mild and transient and did not require treatment or discontinuation of subsequent drug dosing, and no hyperkalemia AEs were classified as serious.

These data regarding the efficacy, safety, and pharmacodynamic effects of zilebesiran amplify and extend the preliminary findings from the phase 1 study of zilebesiran by confirming effective reduction of serum angiotensinogen associated with lowering of BP over the full 24-hour interval and persisting 6 months after treatment with zilebesiran.

Although dose-related reductions in serum angiotensinogen levels were observed, with some variability in duration of effect by dose and dosing interval, the observation that maximal SBP reduction occurred with doses of 300 mg or higher suggests that angiotensinogen reduction of greater than 90% may be sufficient for optimal and sustained lowering of BP.

Consistent clinical and pharmacodynamic effects of 300mg every 3 months, 300 mg every 6 months, and 600 mg every 6 months doses indicate that these regimens achieve effective BP reduction, although this needs to be confirmed in future studies and over longer duration of follow-up.

A potential concern with durable reduction of angiotensinogen with zilebesiran is the risk of refractory hypotension, either as a direct adverse effect of treatment or as a consequence of impaired renin–angiotensin system activation during hemodynamic stress from unanticipated volume depletion, bleeding, infection, or cardiac injury.

In this regard, it is reassuring that there were no serious or severe related AEs of hypotension or orthostasis observed during zilebesiran treatment in this study.

In instances in which blood pressure needs to be restored while receiving zilebesiran, it is likely that standard intervention will be sufficient.

More research will be needed to establish the long-term efficacy and safety of zilebesiran.

Drug-related AEs will be further evaluated in longer-term safety follow-up, and whether the safety profile of zilebesiran is modified during combination treatment with other therapies will be addressed in the ongoing KARDIA-2 study (NCT05103332), which will investigate the efficacy of zilebesiran as add-on therapy in patients with hypertension that is inadequately controlled with olmesartan, amlodipine, or indapamide.

Conclusions

In this study of patients with mild to moderate hypertension,treatment with single doses of subcutaneous zilebesiran was associated with clinically meaningful reductions in SBP, compared with placebo, sustained to 6 months. These data support further investigation of zilebesiran as a therapeutic strategy for patients with hypertension.


Thank you