Zilebesiran as Add-On Therapy in Patients with Hypertension Inadequately Controlled with a Standard Antihypertensive Medication: Efficacy and Safety Results from the KARDIA-2 Study

For US HCPs Only

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Conclusions

- **In KARDIA-2, treatment with a single subcutaneous dose of zilebesiran 600 mg reduced serum angiotensinogen (AGT) levels and 24-hour mean ambulatory and office systolic blood pressure (SBP) compared with placebo at Month 3 when added to a diuretic, calcium channel blocker, or maximum-dose angiotensin receptor blocker.**
  - **SBP differences were sustained to Month 6 in the indapamide and amlodipine cohorts, despite the use of rescue antihypertensives.**
- **Most hypotension adverse events (AEs) associated with add-on zilebesiran treatment were mild in severity and there was no clear pattern in the incidence of hepatic AEs among treatment groups. Laboratory values indicated that most instances of hyperkalemia and decline in renal function were transient and resolved without intervention.**
- **These results support the potential for biannual dosing of zilebesiran to achieve additive blood pressure (BP) reductions when combined with standard-of-care antihypertensives.**
- **The Phase 2 KARDIA-3 study is active and enrolling patients with established cardiovascular (CV) disease or high CV risk, with or without advanced chronic kidney disease, and with hypertension uncontrolled by two to four standard-of-care antihypertensives.**

Introduction

Background

- Many patients with hypertension do not meet guideline-recommended BP targets despite the availability of effective therapies.[1–3]
  - Poor adherence to multidrug oral regimens contributes to BP variability and may increase the risk of CV events.[1,4]

Zilebesiran

- Zilebesiran is an investigational RNA interference therapeutic that targets the synthesis of hepatic AGT, the most upstream precursor of the renin–angiotensin system.[5]
- In the Phase 2 KARDIA-1 study, single subcutaneous doses of zilebesiran monotherapy significantly reduced 24-hour mean ambulatory and office SBP from baseline to Months 3 and 6 compared with placebo.[5]

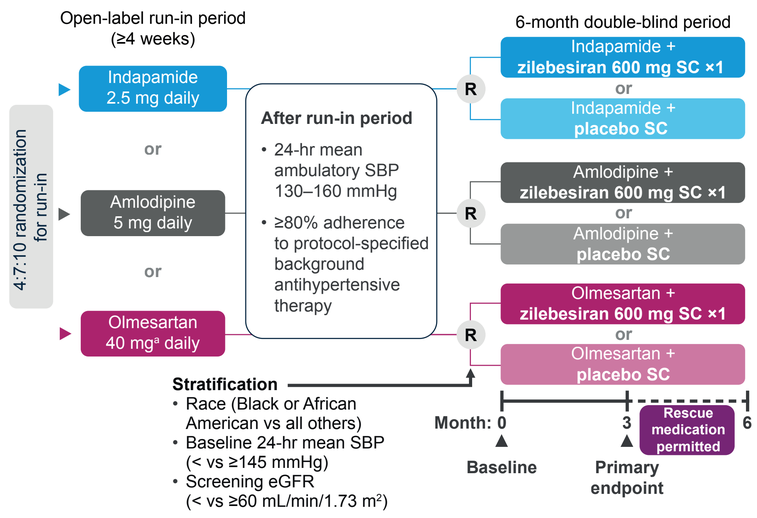
Aim

- KARDIA-2 assessed the efficacy, safety, and pharmacodynamics of zilebesiran when added to a standard-of-care antihypertensive in patients with uncontrolled hypertension.

Methods

- This Phase 2, randomized, double-blind, placebo-controlled study (NCT05103332) enrolled adults with mild-to-moderate hypertension who were untreated (with seated office SBP 155–180 mmHg) or who were receiving stable therapy with one or two antihypertensives (with seated office SBP 145–180 mmHg).
- At entry to the run-in period, previous antihypertensives were discontinued and patients were randomized 4:7:10 to open-label, once-daily, oral background antihypertensive therapy (**Figure 1**).
- After 4 weeks of run-in, patients with a 24-hour mean ambulatory SBP of 130–160 mmHg were randomized double-blind 1:1 to zilebesiran or placebo as add-on to their background antihypertensive therapy.
- Primary endpoint: change from baseline to Month 3 in 24-hour mean ambulatory SBP.
- Select secondary endpoints:
  - change from baseline to Month 6 in serum AGT levels
  - change from baseline to Month 3 in office SBP
  - time-adjusted change from baseline to Month 6 in 24-hour mean ambulatory SBP
  - time-adjusted change from baseline to Month 6 in office SBP.
- Safety endpoint: frequency of AEs.
- Efficacy and safety evaluations included all randomized patients who received any amount of study drug.

Figure 1. KARDIA-2 Study Design



[a]20 mg daily for patients with creatinine clearance ≤60 mL/min at screening enrolled outside of the USA, consistent with local labeling.
eGFR, estimated glomerular filtration rate; hr, hour; R, randomization; SBP, systolic blood pressure; SC, subcutaneous.

Results

Table 1. Patient Baseline Demographics

Baseline Characteristic	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
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/m², %	66.9	62.2	56.3
eGFR <60 mL/min/1.73 m², %	15.7	5.5	11.3
Diabetes, %	21.3	22.3	24.2

Percentages are based on the number of patients who were randomized to and who received zilebesiran or placebo.
BMI, body mass index; eGFR, estimated glomerular filtration rate; hr, hour; SBP, systolic blood pressure; SD, standard deviation.

Table 2. Safety Profile Through Month 6

n (%), unless otherwise specified	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)
ISR AEs	0	4 (6.3)	0	2 (1.7)	1 (0.7)	4 (2.7)
Hypotension/orthostatic hypotension AEs	0	0	4 (3.3)	7 (5.9)	3 (2.1)	7 (4.7)
Hepatic AEs[a]	3 (4.7)	0	1 (0.8)	6 (5.1)	3 (2.1)	5 (3.4)
ALT >3× ULN	0	0[b]	1 (0.8)[b]	3 (2.5)	1 (0.7)[b]	4 (2.7)[b]
AST >3× ULN	1 (1.6)	0[b]	1 (0.8)[b]	2 (1.7)	3 (2.1)[b]	3 (2.0)[b]
Mean change from BL in serum potassium at Month 6, mmol/L (SD)	−0.16 (0.34)[c]	0.12 (0.52)[d]	−0.14 (0.44)[e]	0.09 (0.46)[f]	−0.02 (0.41)[g]	0.06 (0.43)[h]
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/1.73 m²	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)
>2× increase from BL in creatinine µmol/L	0	0	0	0	0	3 (2.0)
Confirmed by repeat measure	0	0	0	0	0	1 (0.7)

AE definitions are based on MedDRA terminology. [a]Hepatic AEs include AEs mapped to the Standardised MedDRA Query for drug-related hepatic disorders (both narrow and broad terms). [b]Assessment missing for 1 patient. [c]n=60. [d]n=57. [e]n=114. [f]n=110. [g]n=134. [h]n=137.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; eGFR, estimated glomerular filtration rate; ISR, injection-site reaction; MedDRA; Medical Dictionary for Regulatory Activities; SD, standard deviation; ULN, upper limit of normal.

Patient Population

- Of the 663 patients randomized to the 6-month double-blind period, 658 patients received placebo or zilebesiran. Background medications were as follows: 127 patients were receiving indapamide, 238 were receiving amlodipine, and 293 were receiving olmesartan.
- Baseline demographics were balanced within each cohort (**Table 1**).
  - The overall mean (standard deviation) age of patients was 58.5 (10.3) years; 57.1% of patients were male and 28.4% were Black or African American.

Pharmacodynamics

- A single dose of zilebesiran reduced serum AGT levels as early as Week 2 with median reductions from baseline of over 95%, which were sustained through Month 6 in all cohorts; median changes in placebo groups were less than 10% at all time points.

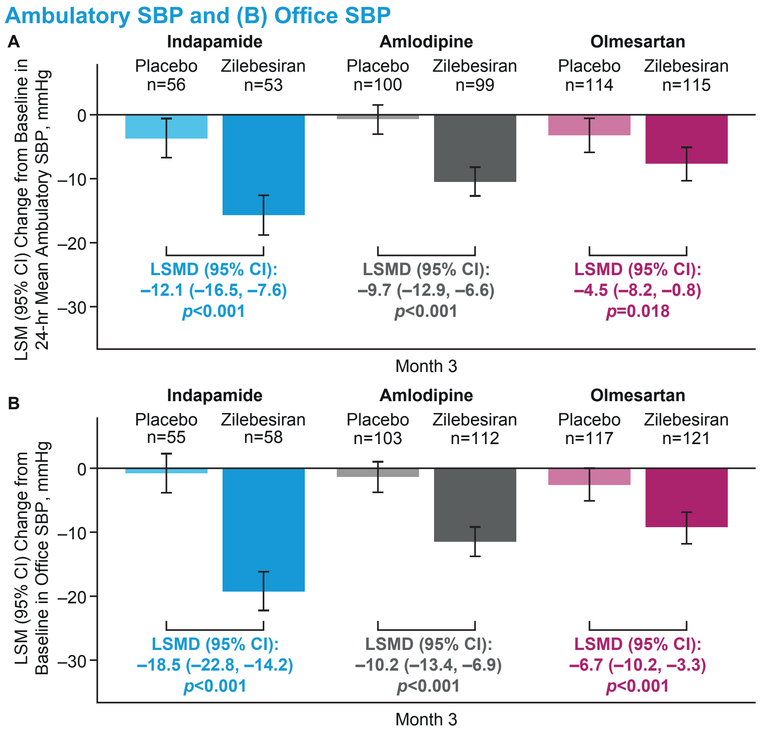
Efficacy

- Zilebesiran significantly reduced 24-hour mean ambulatory SBP (primary endpoint) and office SBP (key secondary endpoint) compared with placebo at Month 3 as add-on therapy to indapamide, amlodipine, or olmesartan ($p<0.05$ for all comparisons; **Figure 2**).
- Although proportionately more patients in the placebo arms than in the zilebesiran arms received rescue antihypertensives during Months 3 to 6, reductions in time-adjusted 24-hour mean ambulatory SBP were significantly greater at Month 6 for zilebesiran than for placebo in the indapamide and amlodipine cohorts ($p<0.001$), while reductions in time-adjusted office SBP were significantly greater for zilebesiran than for placebo in all cohorts ($p<0.001$) (**Figure 3**).

Safety

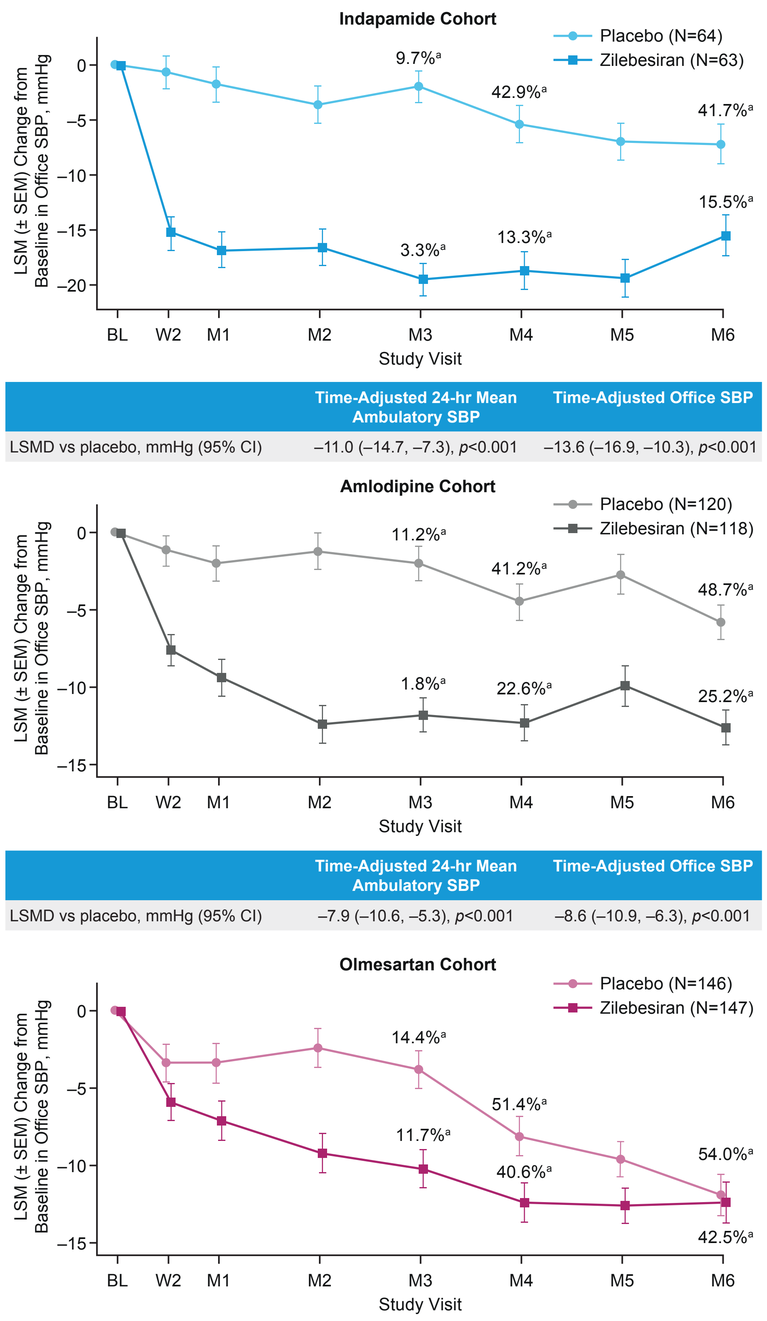
- Zilebesiran had a favorable safety and tolerability profile over the 6-month study period when added to a standard-of-care antihypertensive (**Table 2**).
  - No deaths were reported during the study and no AEs led to study discontinuation.
  - Most hypotension AEs were mild, transient, and resolved without intervention.
  - There was no clear pattern in the incidence of hepatic AEs among treatment groups.
  - Serum potassium and creatinine abnormalities occurred in the first 3 months and most resolved without intervention upon repeat measurement within 1 to 2 weeks.

Figure 2. Change from Baseline to Month 3 in (A) 24-hr Mean Ambulatory SBP and (B) Office SBP



Blood pressure assessed while patients were receiving, or within 2 weeks of stopping, any rescue medication is censored.
CI, confidence interval; hr, hour; LSM, least-squares mean; LSMD, least-squares mean difference; SBP, systolic blood pressure.

Figure 3. Change from Baseline to Month 6 in SBP (All Collected Data)



	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), $p<0.001$

	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), $p<0.001$

	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), $p<0.001$

[a]Proportion of patients receiving rescue antihypertensives.
BL, baseline; CI, confidence interval; hr, hour; LSM, least-squares mean; LSMD, least-squares mean difference; M, month; SBP, systolic blood pressure, SEM, standard error of the mean; W, week.

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DISCLOSURES

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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.

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