

## Zilebesiran: Phase 2 Studies

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The safety and efficacy of zilebesiran are currently being investigated in clinical studies and have not been evaluated by the US Food and Drug Administration or any health authority.

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### SUMMARY

- Zilebesiran is an investigational subcutaneously administered RNAi therapeutic that targets the synthesis of hepatic AGT, leading to a reduction in blood pressure, and is currently being studied for the treatment of hypertension in adults.<sup>1</sup> Zilebesiran utilizes GalNAc conjugation, which enables subcutaneous dosing for liver-specific silencing of AGT mRNA.<sup>2</sup>
- KARDIA-1 was a phase 2 study designed to evaluate the efficacy and safety of zilebesiran as a monotherapy in patients with mild-to-moderate hypertension.<sup>1</sup>
- 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.<sup>3</sup>
- KARDIA-3 was a phase 2 study designed to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients with uncontrolled hypertension and established CV disease or high CV risk, with or without advanced CKD.<sup>4,5</sup>

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### KARDIA-1

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 as monotherapy in patients aged 18 to 75 years with mild-to-moderate hypertension (N=394).<sup>1</sup>

Study participants were randomized 1:1:1:1 to receive subcutaneous injections of placebo Q3M or zilebesiran 150 mg Q6M, 300 mg Q6M, 300 mg Q3M, or 600 mg Q6M for the first 6 months of the 12-month double-blind treatment period. Patients randomized to placebo were re-randomized at Month 6 to 1 of the 4 initial dosing regimens for an extension phase of the study.<sup>1,6</sup>

Key study inclusion criteria were<sup>1</sup>:

- Untreated or treated hypertension with a stable regimen of up to 2 antihypertensive medications
- Daytime mean SBP  $\geq 135$  mmHg and  $\leq 160$  mmHg (evaluated through ABPM) following washout of background antihypertensive medication

Key study exclusion criteria were<sup>1</sup>:

- Secondary hypertension
- Orthostatic hypertension
- Serum potassium >5 mEq/L (5 mmol/L)
- eGFR ≤30 mL/min/1.73m<sup>2</sup>
- Type 1 diabetes, poorly controlled type 2 diabetics (HbA<sub>1c</sub> >9.0%), or laboratory evidence of diabetes during screening (HbA<sub>1c</sub> ≥7.0%) without known diagnosis

The primary endpoint of the study was to evaluate the change from baseline in 24-hour mean ambulatory SBP at Month 3.<sup>1</sup>

Key secondary endpoints included<sup>1</sup>:

- Change from baseline in 24-hour mean ambulatory SBP at Month 6
- Change from baseline in mean sitting office SBP at Month 3
- Change from baseline in mean sitting office SBP at Month 6
- Proportion of patients with 24-hour mean ambulatory SBP <130 mmHg and/or reduction of ≥20 mmHg without additional antihypertensive medications at Month 6

## KARDIA-2

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.<sup>3</sup>

The study included an open-label run-in period of at least 4 weeks and a 6-month double-blind treatment period. Following discontinuation of antihypertensive therapies, eligible patients with a screening eGFR <45 mL/min/1.73 m<sup>2</sup> or UACR ≥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 double-blind period.<sup>3</sup>

Key study inclusion criteria were<sup>3</sup>:

- 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 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

Key study exclusion criteria were<sup>3</sup>:

- Secondary hypertension
- Orthostatic hypertension
- Serum potassium >5 mmol/L
- eGFR <30 mL/min/1.73m<sup>2</sup>
- Symptomatic heart failure
- Type 1 diabetes, poorly controlled type 2 diabetes, or newly diagnosed diabetes

The primary endpoint of the study was to evaluate the change from baseline in 24-hour mean ambulatory SBP at Month 3.<sup>3</sup>

Key secondary endpoints assessed hierarchically in the following order included<sup>3</sup>:

- Between-group difference in change from baseline in office SBP at Month 3
- Time-adjusted change from baseline in 24-hour mean ambulatory SBP at Month 6
- Time-adjusted change from baseline in office SBP at Month 6
- Proportion of patients with 24-hour mean ambulatory SBP <130 mmHg and/or a reduction from baseline  $\geq$ 20 mmHg without rescue antihypertensive medication at Month 6

### KARDIA-3

The KARDIA-3 (NCT06272487) study was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging multicenter study to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients with established CV disease or high CV risk with or without CKD, and with hypertension that is not adequately controlled with 2 to 4 standard-of-care antihypertensives.<sup>4,5</sup>

Study participants were assigned to 1 of 2 cohorts (Cohort A or Cohort B). In Cohort A, participants with an eGFR  $\geq$ 45 mL/min/1.73 m<sup>2</sup> were randomized (1:1:1) to receive placebo (n=88) or a single subcutaneous injection of zilebesiran 300 (n=91) or 600 mg (n=91). In Cohort B, participants with an eGFR 30 to <45 mL/min/1.73 m<sup>2</sup> were randomized (1:1:1:1) to receive placebo (n=26) or a single subcutaneous injection of zilebesiran 150 (n=25), 300 (n=26), or 600 mg (n=26). A key aim of the KARDIA-3 study was to inform the design of a phase 3 CV outcomes study in this population.<sup>4,5</sup>

Key study inclusion criteria were<sup>4,5</sup>:

- Adult patients with established CV disease or high CV risk (ASCVD score >15%)
- Uncontrolled hypertension (defined as seated automated mean office SBP 140–170 mmHg at screening and 24-hour mean ambulatory SBP 130–170 mmHg before randomization)
- Already prescribed 2 to 4 classes of antihypertensive medications (including a diuretic or CCB)
- Cohort B: eGFR between 30-45 mL/min/1.73m<sup>2</sup>

Key study exclusion criteria were<sup>7</sup>:

- Secondary hypertension
- Orthostatic hypertension
- Proteinuria >3 g/day or UACR >2 g/g
- Serum potassium >4.8 mEq/L

The primary endpoint of the study was to evaluate the change from baseline in mean seated office SBP at Month 3.<sup>4</sup>

Key secondary endpoints included<sup>4</sup>:

- Change from baseline in mean seated office SBP at Month 6
- Change from baseline in 24-hour mean ambulatory SBP at Months 3 and 6
- Change from baseline in mean daytime and nighttime ambulatory SBP at Month 6

Key exploratory endpoints include<sup>4</sup>:

- Hourly mean daytime and nighttime ambulatory SBP at Month 6

Safety was assessed by the frequency of AEs through Month 6. Cohorts A and B were analyzed separately. Cohort B was not powered to evaluate efficacy and was designed to assess the safety of zilebesiran in patients with an eGFR of 30 to <45 mL/min/1.73 m<sup>2</sup>.<sup>5</sup>

## ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring; AE = adverse event; AGT = angiotensinogen; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CCB = calcium channel blocker; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; GalNAc = N-acetyl galactosamine; HbA<sub>1c</sub> = hemoglobin A1c; mRNA = messenger RNA; Q3M = every 3 months; Q6M = every 6 months; RNAi = RNA interference; SBP = systolic blood pressure; SC = subcutaneous; UACR = urine albumin-to-creatinine ratio.

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