Zilebesiran: Phase 2 Studies

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

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

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- Zilebesiran is an investigational, subcutaneously administered RNAi therapeutic designed to reduce circulating AGT protein, leading to reduction in BP and is currently being studied for the treatment of hypertension in adults. Zilebesiran utilizes GalNAc conjugation, which enables subcutaneous dosing for liver-specific silencing of AGT mRNA.[1]
- The Phase 2 studies KARDIA-1, KARDIA-2, and KARDIA-3 are ongoing studies to evaluate[2–4]:
  - The efficacy and safety of zilebesiran as a monotherapy in patients with hypertension (KARDIA-1)
  - The efficacy and safety of zilebesiran as an add-on therapy in combination with standard of care treatment for hypertension (KARDIA-2)
  - The efficacy and safety of zilebesiran as an add-on therapy in combination with standard of care treatment for patients with high CV risk and hypertension (KARDIA-3)

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KARDIA-1

The KARDIA-1 study (NCT04936035) is an ongoing* Phase 2 randomized, DB, placebo-controlled, dose-ranging multicenter study to evaluate the efficacy and safety of zilebesiran in patients aged 18 to 75 years with mild-to-moderate hypertension. Patients included in the study are those with daytime mean SBP ≥135 mmHg and ≤160 mmHg (evaluated through ABPM) without antihypertensive medication.[2]

The primary objective of the study is to evaluate the change in SBP from baseline to month 3, assessed by ABPM.[2]

The secondary objectives of the study are to assess the[2]:

- Change from baseline to month 3 in office SBP
- Change from baseline through month 6 in 24-hour mean SBP assessed by ABPM
- Change from baseline through month 6 in office SBP
- Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction of ≥20 mmHg without additional antihypertensive medications at month 6 (from baseline through month 6)
- Time-adjusted change from baseline through month 6 in 24-hour mean SBP and DBP, assessed by ABPM
- Change from baseline through month 6 in 24-hour mean DBP

- Change from baseline through month 6 in office SBP and DBP
- Change in serum AGT from baseline through month 6
- Change from baseline through month 6 in daytime and nighttime SBP and DBP by ABPM (including dipping pattern)

Patients will receive either zilebesiran or placebo for the first 6 months of the 12-month DB period. Patients randomized to placebo will be re-randomized at Month 6 to 1 of the 4 initial dosing regimens until the end of the 12-month DB treatment period. Participants randomized to zilebesiran regimens will remain on their originally assigned treatment arm through the remainder of the study.[2]

*The trial is listed as active as of June 26, 2024.

KARDIA-2

The KARDIA-2 study (NCT05103332) is an ongoing* Phase 2 randomized, DB, placebo-controlled, multicenter study to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients aged 18 to 75 years with hypertension that is not adequately controlled by a standard of care antihypertensive medication. Add-on therapy includes standard of care treatment with olmesartan, amlodipine, or indapamide. Patients eligible for the study include those with[3]:

- 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

The primary objective of the study is to evaluate the change in 24-hour mean SBP from baseline to month 3, assessed by ABPM.[3]

The secondary objectives of the study are to assess the[3]:

- Change from baseline at month 3 in office SBP
- Time-adjusted change from baseline through month 6 in office SBP, 24-hour mean SBP, assessed by ABPM
- Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or a reduction from baseline ≥20 mmHg without escape antihypertensive medication at month 6
- Change in 24-hour mean SBP and DBP, assessed by ABPM at baseline and month 6
- Change in office SBP and DBP at baseline and month 6
- Change in daytime and nighttime mean SBP and DBP, assessed by ABPM at baseline and month 6
- Change from baseline in serum AGT from baseline through month 6

Participants will receive either zilebesiran or placebo, as an add-on treatment to the following antihypertensive agents: olmesartan, amlodipine, or indapamide for the 6-month DB period. Participants randomized to placebo will receive zilebesiran once every 6 months during the OLE, and the participants randomized to zilebesiran regimens will remain on zilebesiran through the remainder of the study.[3]

*The trial is listed as active as of June 26, 2024.

KARDIA-3

The KARDIA-3 study (NCT06272487) is an ongoing* Phase 2 randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of zilebesiran as an add-on therapy in

patients with high CV risk and hypertension that is not adequately controlled by standard of care antihypertensive medications. Patients eligible for the study include those with[4]:

- History of CV disease, high CV risk, or eGFR ≥30 to <60 mL/min/1.73m^2
- Mean seated office SBP ≥140 mmHg and ≤170 mmHg
- 24-hour mean SBP ≥130 mmHg and ≤170 mmHg assessed by ABPM
- Must be on stable therapy with 2 to 4 classes of antihypertensive medications

The primary objective of the study is to evaluate the change from baseline at month 3 in mean seated office SBP.[4]

The secondary objectives of the study are to assess the[4]:

- Change from baseline at month 3 in 24-hour mean SBP assessed by ABPM
- Change from baseline at month 6 in mean seated office SBP
- Change from baseline at month 6 in 24-hour mean SBP assessed by ABPM
- Proportion of patients with mean seated office SBP <140 mmHg and/or reduction ≥10 mmHg without intensification of antihypertensive regimen at month 6
- Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥10 mmHg without intensification of antihypertensive regimen at month 6
- Change from baseline at month 3 and month 6 in daytime and nighttime mean SBP and DBP assessed by ABPM
- Change from baseline at month 3 and month 6 in mean seated office DBP
- Change from baseline at month 3 and month 6 in 24-hour mean DBP assessed by ABPM
- Change from baseline over time in serum AGT

*The trial is listed as active as of June 26, 2024.

ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring; AGT = angiotensinogen; BP = blood pressure; CV = cardiovascular; DB = double-blind; DBP = diastolic blood pressure; FDA = Food and Drug Administration; GalNAc = N-acetylgalactosamine; mRNA = messenger ribonucleic acid; OLE = open-label extension; RNAi = RNA interference; SBP = systolic blood pressure.

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3. Alnylam Pharmaceuticals: Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2). Available from: https://www.clinicaltrials.gov/study/NCT05103332. Accessed June 26, 2024.
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