Zilebesiran: KARDIA-3 Study

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 has 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 blood pressure 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 study, KARDIA-3, is an ongoing study to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients with hypertension and established CV disease or at high CV risk.[2]

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STUDY DESIGN

The KARDIA-3 (NCT06272487) study is an ongoing* 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 high CV risk and hypertension that is not adequately controlled with at least 2 standard-of-care antihypertensives. Patients eligible for the study include those with[2]:

- 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 in mean seated office SBP from baseline to Month 3.[2]

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

- 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 March 11, 2024.

ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring; AGT = angiotensinogen; CV = cardiovascular; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; GalNAc = N-acetyl galactosamine; mRNA = messenger RNA; RNAi = RNA interference; SBP = systolic blood pressure.

Updated 11 March 2024

REFERENCES

1. Bakris GL, Saxena M, Gupta A, et al. RNA Interference With Zilebesiran for Mild to Moderate Hypertension: The KARDIA-1 Randomized Clinical Trial. *JAMA*. 2024;331(9):740-749. doi:10.1001/jama.2024.0728
2. Alnylam Pharmaceuticals: Zilebesiran as Add-on Therapy in Patients With High Cardiovascular Risk and Hypertension Not Adequately Controlled by Standard of Care Antihypertensive Medications (KARDIA-3). Available from: https://www.clinicaltrials.gov/study/NCT06272487. Accessed March 4, 2024.