# Zilebesiran: ZENITH 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 have not been evaluated by 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 directly lowers hepatic synthesis of AGT, the most upstream precursor of the RAAS, leading to a reduction in blood pressure. Zilebesiran utilizes GalNAc conjugation, which enables subcutaneous dosing for liver-specific silencing of AGT mRNA.[1,2]
- ZENITH (NCT07181109) is a phase 3 CVOT designed to evaluate the efficacy and safety of zilebesiran in addition to standard of care medications in reducing the risk of MACE (CV death, nonfatal MI, nonfatal stroke, or HF events) in adult patients with hypertension not adequately controlled and with either established CV disease or high risk for CV disease.[2,3]


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## STUDY DESIGN

ZENITH (NCT07181109) is a phase 3, global, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of zilebesiran in addition to standard of care medications in reducing MACE in adult patients with hypertension not adequately controlled and with either established CV disease or high risk for CV disease. The study will enroll approximately 11,000 patients. Patients will be randomized 1:1 to receive subcutaneous zilebesiran 300 mg or placebo every 6 months, in addition to standard of care medications.[3]

ZENITH is an event-driven study that will continue until the targeted number of positively adjudicated primary endpoint clinical outcome events has been reached, with a time frame of approximately 5 years. Patients will be followed for a minimum of 2 years. The primary endpoint will assess the time to first occurrence of a compositive endpoint of CV death, nonfatal MI, nonfatal stroke, or HF event (hospitalization for HF or urgent HF visit).[2,3]

Secondary endpoints include[3]:

- Change from baseline in mean seated office SBP at Month 6
- Time to first occurrence of a composite endpoint of CV death, nonfatal MI, or nonfatal stroke
- Composite endpoint of CV death and total (first and subsequent) HF events

- Time to first occurrence of composite endpoint of CV death, nonfatal MI, nonfatal stroke, or coronary revascularization
- Time to all-cause death

Select inclusion criteria include[2,3]:

- Patients ≥ 18 years of age with established CVD (defined as coronary, cerebrovascular, or peripheral artery disease)
- Patients ≥ 55 years of age with high risk for CVD
- Established CVD or high risk for CVD
- Office SBP ≥ 140 mmHg on stable therapy with at least 2 standard of care antihypertensive medications, one of which must be a thiazide, thiazide-like, or loop diuretic

Select exclusion criteria include[2,3]:

- Known history of secondary hypertension
- Symptomatic orthostatic hypotension
- ALT or AST >3x ULN
- Total serum bilirubin >1.5x ULN
- INR >1.5
- Serum potassium >4.8 mEq/L
- eGFR <30 mL/min/1.73m$^2$

## ABBREVIATIONS

AGT = angiotensinogen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CV = cardiovascular; CVD = cardiovascular disease; CVOT = cardiovascular outcomes trial; eGFR = estimated glomerular filtration rate; GalNAc = N-acetylgalactosamine; HF = heart failure; INR = international normalized ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; mRNA = messenger ribonucleic acid; RNAi = ribonucleic acid interference; SBP = systolic blood pressure; ULN = upper limit of the normal.

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## REFERENCES


1. Desai AS, Webb DJ, Taubel J, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. *N Engl J Med*. 2023;389(3):228-238. doi:10.1056/NEJMoa2208391
2. Pagidipati N, Weber M, Saxena M, et al. KARDIA-3: Zilebesiran as add-on therapy in adults with hypertension who have established cardiovascular disease or are at high cardiovascular risk. Presented at: European Society of Cardiology (ESC) Congress; August 29-September 1, 2025; Madrid, Spain.
3. Alnylam Pharmaceuticals. Zilebesiran in patients with hypertension not adequately controlled and with either established cardiovascular disease or high risk for cardiovascular disease (ZENITH). Available from: https://clinicaltrials.gov/study/NCT07181109. Accessed October 01, 2025.