Zilebesiran as Add-On Therapy in Patients With Hypertension Who Have Cardiovascular Disease or Are at High Cardiovascular Risk: The ZENITH Trial Design



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Conclusions

- The Phase 3 ZENITH trial will evaluate the impact of zilebesiran 300 mg every 6 months on cardiovascular (CV) events and safety in patients with hypertension (HTN) and CV disease (CVD) or high CV risk.
- Zilebesiran, a long-acting therapy being developed for HTN, targets angiotensinogen (AGT), the most upstream substrate of the renin-angiotensin-aldosterone system (RAAS), to potentially lower CV risk through sustained AGT inhibition and continuous control of blood pressure (BP) with biannual subcutaneous dosing.
- ZENITH is a multicenter trial planned to take place at 1500 sites across 35 countries; enrollment is ongoing.

Introduction

Background

- Uncontrolled HTN is the greatest contributor to CV morbidity and mortality worldwide; however, despite availability of effective therapies, many patients do not achieve and maintain guideline-directed BP targets.^{1,2}
- Continuous control of BP is especially important in patients with high CV risk and chronic kidney disease, owing to a high risk of CV events, organ damage, and adverse events from treatment.^{3,4}

Zilebesiran

- Zilebesiran is an investigational RNA interference therapeutic designed to reduce hepatic production of AGT, the most upstream precursor in the RAAS of BP regulation.⁵
- Zilebesiran exhibited promising efficacy and an acceptable safety profile in the Phase 2 clinical trials (**Figure 1**), with potential for biannual dosing.^{6–9}
- In KARDIA-3, zilebesiran treatment led to clinically meaningful BP reductions in patients with CVD or high CV risk, although statistical significance was not reached.^{8,9}
- Subgroup analyses suggest that those receiving a diuretic had greater BP lowering with zilebesiran, which supports the findings of KARDIA-2.
- No safety concerns were observed, including in patients with moderate-to-severely impaired renal function, or in those receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; there was no evidence of dose-dependent adverse events.
- Phase 2 data support using the zilebesiran 300 mg dose in all patients, irrespective of kidney function.^{6–9}

Figure 1. Overview of Zilebesiran Phase 2 Clinical Trials

KARDIA ?

KARDIA®3

NCT06272487 (N=375)8,9

NCT04936035 (N=394)⁶

Zilebesiran monotherapy (150, 300, 600 mg) in patients with mild-to-moderate HTN

Month 3 office systolic BP zilebesiran 300 mg vs placebo: 12.0 mmHg

Safety:

Acceptable safety profile

KARDIA ?

 $NCT05103332 (N=663)^{7}$

Zilebesiran (600 mg) added to ARB, CCB, or diuretic, in patients with inadequately controlled HTN

Zilebesiran (150, 300, 600 mg) added to

2-4 aHTNs in patients with inadequately

controlled HTN and CVD or high CV risk, ± CKD

Month 3 office systolic BP zilebesiran 600 mg vs placebo: ↓ 6.7–18.5 mmHg (greatest with diuretic)

Safety:

Acceptable safety profile

Month 3 office systolic BP zilebesiran 300 mg vs placebo: ↓ 5.0 mmHg in Cohort A

Safety:

Acceptable safety profile

Efficacy assessed as placebo-adjusted change from baseline to Month 3 in office systolic BP. aHTN, antihypertensive; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HTN, hypertension.

Trial Design

ZENITH (NCT07181109) is a global, randomized, placebo-controlled, double-blind, event-driven Phase 3 trial (Figure 2, Table 1).

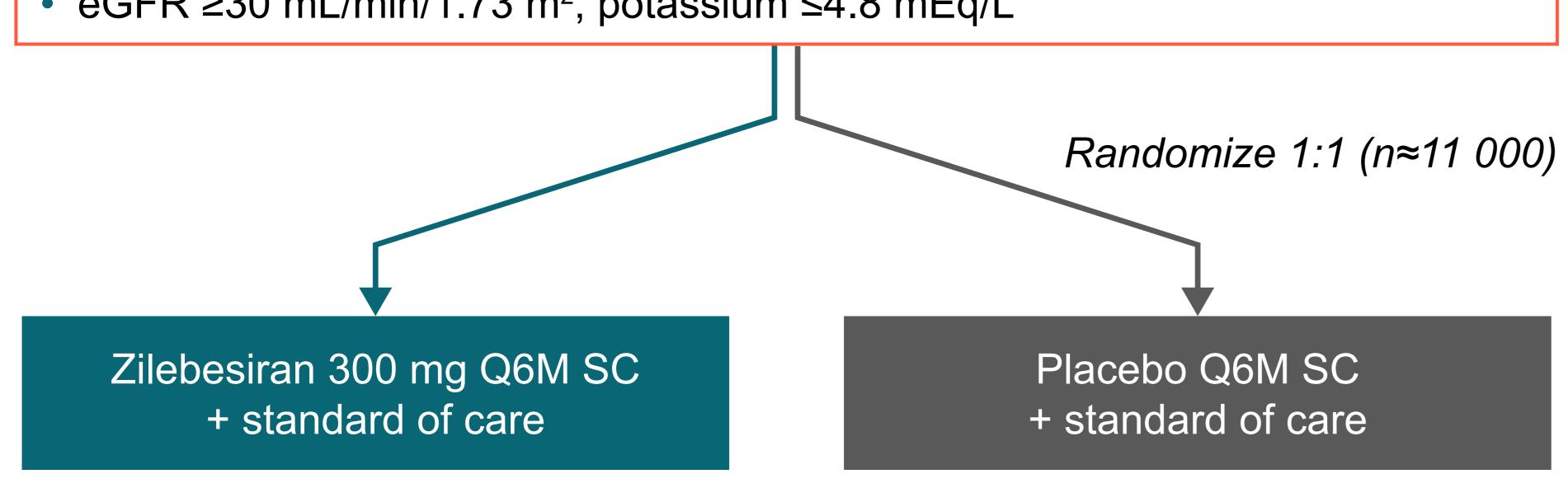
Figure 2. ZENITH Trial Design



Adult patients with uncontrolled HTN and established CVD or at high CV risk Baseline office systolic BP ≥140 mmHg on stable treatment (≥2 aHTNs, one of

Trial Population

which is a diuretic) eGFR ≥30 mL/min/1.73 m², potassium ≤4.8 mEq/L



Minimum follow-up: 2 years



Map shows confirmed trial sites. CVD is defined as coronary, cerebrovascular, or peripheral artery disease. aHTN, antihypertensive; BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HTN, hypertension; Q6M, once every 6 months; SC, subcutaneous.

Table 1. ZENITH Key Trial Endpoints

Endpoint	
Primary	Time to first occurrence of a composite endpoint of CV death, nonfatal MI, nonfatal stroke, or HF event
Secondary	Change from baseline to Month 6 in mean seated office systolic BP
	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 a composite endpoint of CV death, nonfatal MI, nonfatal stroke, or coronary revascularization
	Time to all-cause death

HF events include hospitalization for HF or urgent HF visit. BP, blood pressure; CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

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