Zilebesiran (ALN-AGT)

An Investigational RNAi Therapeutic in Development for the Treatment of Hypertension

Overview
- Zilebesiran (pronounced “zile-BEE-siran”) is an investigational, subcutaneously administered RNA interference (RNAi) therapeutic targeting liver-expressed angiotensinogen (AGT) in development for the treatment of hypertension.\(^1,2\)
- AGT is the most upstream precursor in the renin-angiotensin-aldosterone system (RAAS), a cascade which has a demonstrated role in blood pressure regulation and whose inhibition has well-established antihypertensive effects.\(^3\) Inhibiting the synthesis of AGT in the liver (the primary source of AGT) could potentially lead to durable reductions in AGT protein and ultimately, in the vasoconstrictor angiotensin (Ang) II.\(^3,4\)

Unmet Need in Hypertension
- Hypertension, or high blood pressure, is the leading cause of cardiovascular disease worldwide, and a major risk for premature mortality.\(^5\)
  - Early effects of hypertension can include subtle target organ damage such as left-ventricular hypertrophy and cognitive dysfunction.\(^6\)
  - Over time, uncontrolled hypertension can lead to heart failure, atrial fibrillation, valvular heart disease, peripheral arterial disease and aortic syndromes, chronic kidney disease and end stage renal disease, dementia, and Alzheimer’s disease.\(^7,8,9\)
- Despite well-established management strategies such as lifestyle modifications and several classes of available antihypertensive treatments, fewer than 20 percent of people with hypertension have it under control.\(^10,11\)

Clinical Development Overview
- In an ongoing Phase 1 study evaluating the safety, tolerability and preliminary pharmacokinetic and pharmacodynamic activity of zilebesiran in adults with hypertension:\(^2\)
  - Zilebesiran was generally well tolerated through Week 12, with no serious treatment-related adverse events (AEs) or AEs leading to study withdrawals, supporting continued development of this investigational therapeutic. The most common AE was injection site reactions in 5 patients (8.9%) receiving zilebesiran, all of which were mild and transient.\(^2\)
  - Single doses of zilebesiran at 100 mg or higher resulted in:\(^2\)
    - Serum AGT reductions of more than 90 percent through 12 weeks, with concomitant reductions in blood pressure.
    - Mean reductions in 24-hour systolic blood pressure (SBP) of >10 mm Hg were observed at Week 8.
- At 800 mg, mean reductions in 24-hour SBP of 17 mm Hg were observed at Week 8 and sustained through Week 12.²
- The serum AGT and blood pressure reductions sustained through Week 12 support the potential for once quarterly or biannual dosing.²
- The safety and efficacy of zilebesiran are being evaluated in global Phase 2 studies:¹,¹²

![KARDIA](image)

- KARDIA-1 (NCT04936035) and KARDIA-2 (NCT05103332) are randomized, double-blind, placebo-controlled, multicenter studies of adults with mild-to-moderate hypertension. KARDIA-1 will enroll approximately 375 patients, and KARDIA-2 will enroll an estimated 800 patients.¹,¹²
- KARDIA-1 will evaluate the efficacy and safety of zilebesiran as a monotherapy, and KARDIA-2 will evaluate the efficacy and safety of zilebesiran when used in combination with conventional antihypertensive medications.¹,¹²
  - The primary endpoint of both studies is the change from baseline in SBP, assessed by ambulatory blood pressure monitoring after three months of treatment.¹
  - Key secondary and exploratory endpoints will evaluate additional measures of blood pressure reduction over time, clinical outcomes, and safety.¹

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⁸ Thorin, E. Hypertension. 2015;65:36-38.