Zilebesiran (ALN-AGT)

An Investigational RNAi Therapeutic in Development for the Treatment of Hypertension[1]

Overview

- Zilebesiran (pronounced "zile-BEE-siran") is an investigational, subcutaneously administered RNA interference (RNAi) therapeutic targeting hepatic synthesis of angiotensinogen (AGT) in development for the treatment of hypertension in high unmet need populations.[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] Zilebesiran's ability to specifically inhibit liver production of angiotensinogen has been shown to reduce circulating levels of angiotensin II. Zilebesiran works upstream by targeting AGT which may yield durable RAAS inhibition.
- Zilebesiran utilizes Alnylam's Enhanced Stabilization Chemistry Plus (ESC+) GalNAc-conjugate technology, which may support the potential for sustained reduction of blood pressure with twice-yearly or quarterly subcutaneous administration.
- Zilebesiran is being studied as monotherapy and in combination with standard of care antihypertensive medication to assess its efficacy and safety, including potential impact on tonic blood pressure control, including long-term, 24-hour blood pressure control, nighttime blood pressure and morning-surge regulation, and long-term blood pressure variability.

Unmet Need in Hypertension

- Hypertension, or high blood pressure, is a leading cause of cardiovascular disease worldwide and carries a substantial risk of morbidity and mortality.[4]
    - Early effects of hypertension can include subtle target organ damage such as left-ventricular hypertrophy and cognitive dysfunction.[5]
    - 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.[6,7,8]
- Despite well-established management strategies such as lifestyle modifications and several classes of available antihypertensive treatments, up to 80% of people with hypertension remain uncontrolled.[9,10]

Clinical Development Overview

- A Phase 1 study evaluating the safety, tolerability and preliminary pharmacokinetic and pharmacodynamic activity of zilebesiran was conducted in adults with mild-to-moderate hypertension:[2,11]
    - In Part A, patients were randomized 2:1 to receive single ascending subcutaneous doses of zilebesiran (10, 25, 50, 100, 200, 400 or 800 mg) or placebo.
    - Part B of the study assessed the effects of zilebesiran (800 mg) on blood pressure under low- and high-salt diet conditions.
    - Part D of the study assessed the safety and pharmacology of two sequential doses of zilebesiran (800 mg) in patients with Class II or III obesity.
    - Part E assessed the effects of zilebesiran (800 mg) coadministration with irbesartan (an angiotensin II receptor blocker).
    - The primary endpoint of the study was the frequency of adverse events (AEs), and secondary and exploratory endpoints included change from baseline in serum AGT, pharmacokinetics and change from baseline in blood pressure.

Continued on back page

- In the study,
  - Zilebesiran demonstrated an acceptable safety profile supporting its continued clinical development.[2,11]
    - AEs were reported for 58 patients receiving zilebesiran (72%) and 28 receiving placebo (88%).[2]
    - The most frequent treatment-related AEs were mild, transient injection site reactions reported in 5 patients (6%).[2]
    - No events of hypotension, hyperkalemia or worsening renal function requiring intervention were observed.[2,11]
  - In Part A, versus placebo, zilebesiran was associated with dose-dependent reductions in serum AGT that were sustained for up to six months.[2]
    - Single doses of zilebesiran (≥200 mg) resulted in reductions in systolic (>10 mmHg) and diastolic (>5 mmHg) blood pressure by Week 8, which were consistent throughout the diurnal cycle and sustained to six months.[2]
    - At the 800 mg dose, zilebesiran treatment resulted in mean systolic and diastolic reductions of 22.5 ± 5.1 mmHg and 10.8 ± 2.7 mmHg at Month 6, respectively.[2]
  - In Parts B and E of the study, blood pressure changes following zilebesiran treatment could be attenuated through high dietary salt intake and were augmented by irbesartan coadministration.[2]
  - In Part D of the study, administration of two sequential doses of zilebesiran (800 mg) (12 weeks apart) in patients with Class II/III obesity was associated with durable reductions in serum AGT levels and sustained reductions in blood pressure persisting to 24 weeks. These data suggest that pharmacodynamics, efficacy and safety of zilebesiran may be similar across a wide BMI range.[11]
    - AEs were reported for 6 patients receiving zilebesiran (75%) and 4 patients receiving irbesartan (100%); the majority were mild or moderate.[11]

KARDIA

- KARDIA-1 (NCT04936035) and KARDIA-2 (NCT05103332) are randomized, double-blind, placebo-controlled, multicenter studies of adults with mild-to-moderate hypertension.[1,12,13] KARDIA-1 enrolled a total of 394 patients, and KARDIA-2 enrolled 672 patients.[1,12,13]
  - KARDIA-1 is evaluating the efficacy and safety of zilebesiran as a monotherapy, and KARDIA-2 is evaluating the efficacy and safety of zilebesiran when used in combination with one of three standard classes of antihypertensive medications.[1,12,13]
  - The primary endpoint of both studies is the change from baseline in systolic blood pressure (SBP), assessed by 24-hour ambulatory blood pressure monitoring (ABPM) after three months of treatment.[1,12,13]
  - Secondary and exploratory endpoints will evaluate additional measures of blood pressure reduction over time.[1,12,13]
- KARDIA-3 (NCT06272487) is a Phase 2 randomized, double-blind, placebo-controlled, two-cohort study of adults with uncontrolled hypertension at high CV risk. KARDIA-3 is expected to enroll 390 patients.[14,15]
  - KARDIA-3 is evaluating the efficacy and safety of zilebesiran in combination with two to four antihypertensive medications.[14]
  - The primary endpoint is the change from baseline in mean seated office SBP after three months of treatment.[14]
  - Secondary endpoints include additional measures of blood pressure reduction at three and six months and change in daytime average and night-time average blood pressure.[14]
  - Approximately 270 patients in Cohort A will be randomized 1:1:1 to receive 300 or 600 mg zilebesiran or placebo.[15]
  - Up to 120 patients in Cohort B will be randomized 1:1:1:1 to receive 150, 300, or 600 mg zilebesiran or placebo.[15]

For more information on KARDIA-1 (NCT04936035), KARDIA-2 (NCT05103332) or KARDIA-3 (NCT06272487), please visit www.clinicaltrials.gov or contact media@alnylam.com.

The safety and efficacy of zilebesiran have not been evaluated by the U.S. Food and Drug Administration, European Medicines Agency or any other health authority. Zilebesiran is being co-developed and co-commercialized by Alnylam and Roche.

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