Safety and Tolerability of ALN-AGT, an RNA Interference Therapeutic Targeting Hepatic Angiotensinogen Synthesis, in Hypertensive Patients during Sodium Depletion or Irbesartan Coadministration

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Zilebesiran (ALN-AGT) is under investigation for the treatment of hypertension.
Disclosures

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Abbott: Research grant, consulting fees
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Bayer: Research grant
Biofourmis: Consulting fees
Boston Scientific: Consulting fees
Boehringer Ingelheim: Consulting fees
Cytokinetics: Consulting fee
DalCor Pharmaceuticals: Consulting fees
Lexicon Pharmaceuticals: Consulting fees
Lupin Pharma: Consulting fees
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Regeneron Pharmaceuticals: Consulting fees
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Verily: Consulting fees

Jorg Taubel
Alnylam Pharmaceuticals: Investigator

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Employees of Alnylam Pharmaceuticals
*Now an employee of Beam Therapeutics

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Hypertension

- Hypertension is a leading cause of mortality and morbidity worldwide\(^1-^5\)
- Despite effective antihypertensives, hypertension is uncontrolled in ~50% of patients and >50% of patients are non- or suboptimally adherent\(^1-^5\)
- The RAAS has a demonstrated role in BP regulation\(^6,^7\)
  - AGT is the most upstream precursor of the RAAS\(^7\)

Zilebesiran

- Zilebesiran (ALN-AGT), a SC administered RNAi therapeutic targeting hepatic AGT synthesis is under investigation for the treatment of hypertension
- Previous presentations demonstrated that zilebesiran reduced BP and was generally well tolerated in a Phase 1, single ascending dose study of patients with hypertension\(^8\)
  - Dose-dependent reductions in serum AGT were observed

Objective

- To assess the safety and tolerability of zilebesiran during sodium deprivation or irbesartan coadministration in a Phase 1 study

AGT, angiotensinogen; BP, blood pressure; RAAS, renin-angiotensin-aldosterone system; RNAi, ribonucleic acid interference; SC, subcutaneous

Assessing Tolerability of Zilebesiran During Sodium Deprivation

- Randomized, double-blind, placebo-controlled study
- Two-week dietary sub-protocol with varying sodium consumption, to test for potential salt-sensitive BP responses

### Patient Population (N=12)
- Adults 18-65 years of age
- SBP >130 and ≤165 mmHg without antihypertensive medications
- 24-hour SBP ≥130 mmHg
- BMI ≥18 and ≤35 kg/m²
- Secondary hypertension excluded
- Treatment naïve or had prior antihypertensives washed out for >2 weeks before screening

### Primary Endpoint
- Safety and tolerability

### Key Secondary Endpoint
- Change from baseline in serum AGT

### Key Exploratory Endpoint
- Change in SBP/DBP under low vs high sodium intake assessed by 24-hour ABPM

**2:1 RANDOMIZATION**

**Low salt diet**

**High salt diet**

**Zilebesiran 800 mg SC x 1**

**OR**

**Placebo SC x 1**

**Low salt diet**

**High salt diet**

### Baseline Demographics and Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=4)</th>
<th>Zilebesiran (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; median (range)</td>
<td>52 (35–62)</td>
<td>60 (49–64)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>3 (75)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Blood Pressure (24-hour ABPM, mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP median (range)</td>
<td>147 (133–151)</td>
<td>138 (129–150)</td>
</tr>
<tr>
<td>DBP median (range)</td>
<td>98 (87–103)</td>
<td>88 (77–93)</td>
</tr>
</tbody>
</table>

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\(^a\)Low salt diet (0.23 g sodium per day) pre-dose (Day -22 to Day -15) and post-dose (Day 43 to Day 50). High salt diet (5.75 g sodium per day) pre-dose (Day -15 to Day -8) and post-dose (Day 50 to Day 57) ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SC, subcutaneous.
Safety and Tolerability in Low/High Salt Diet

Zilebesiran Was Generally Well Tolerated With No Drug-Related SAEs

- All AEs mild in severity and resolved without intervention
- No deaths or SAEs were reported
- No AEs leading to study withdrawal
- No AEs of injection site reaction or hypotension
- No patient required intervention for low blood pressure, including during the sodium deprivation period
- No clinically significant elevations in ALT, serum creatinine or serum potassium in zilebesiran group were reported
- One patient receiving placebo had transient ALT elevation >3x ULN attributed to alcohol consumption

<table>
<thead>
<tr>
<th>Summary of Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients with at Least One Event, n</td>
</tr>
<tr>
<td>Adverse Event</td>
</tr>
<tr>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>Severe Adverse Event</td>
</tr>
</tbody>
</table>

AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event; ULN, upper limit of normal.

Data transfer date: May 28, 2021 (all patients completed low- and high-salt diets before data transfer). Safety reported from start of study drug to day 85.
Changes in 24-Hour BP in Low/High Salt Diet

- Zilebesiran 800 mg resulted in a reduction in serum AGT levels of >90%, sustained between Week 2 and Week 12 (data not shown).

- A reduction in 24-hour SBP/DBP was observed pre-dose for all patients following a low-salt diet; BP increased upon switching to a high-salt diet.

- Post-dose, BP changes were more profound following a low-salt diet for patients receiving zilebesiran vs patients receiving placebo; a high-salt diet modulated the BP lowering effect of zilebesiran.
All patients received single-dose open-label zilebesiran 800 mg SC. On Day 41, patients with 24-hour mean SBP ≥120 mmHg (N=10) proceeded to receive irbesartan from Day 43 to Day 57.

### Baseline Demographics and Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Zilebesiran (N=6)</th>
<th>Zilebesiran + Irbesartan (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; median (range)</td>
<td>56 (44–58)</td>
<td>56 (42–64)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (83)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Race, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Blood Pressure (24-hour ABPM, mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP median (range)</td>
<td>135 (124–141)</td>
<td>146 (135–158)</td>
</tr>
<tr>
<td>DBP median (range)</td>
<td>83 (78–98)</td>
<td>89 (76–99)</td>
</tr>
</tbody>
</table>
Safety and Tolerability With and Without Irbesartan Coadministration

Zilebesiran Was Generally Well Tolerated, With No Drug-Related SAEs

- All AEs were mild in severity
- 1 SAE (mild) of acute anemia in the irbesartan add-on group considered not related to study drug
  - A complication of esophagogastroduodenoscopy with biopsy performed during screening prior to dose of zilebesiran
- No deaths or AEs leading to study withdrawal
- No patient required intervention for low blood pressure
- There were no AEs of concern for hypotensive events during irbesartan coadministration, and no patient required intervention for low blood pressure
- No clinically significant elevations in serum ALT, serum creatinine or serum potassium were reported

<table>
<thead>
<tr>
<th>Number of Patients with at Least One Event, n</th>
<th>Period 1 (Before Day 43)</th>
<th>Period 2 (On or After Day 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zilebesiran only (N=6)</td>
<td>Zilebesiran prior to irbesartan (N=10)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Serious Adverse Event</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Severe Adverse Event</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event
Data transfer date: 28 May 2021. Safety reported from start of study drug to day 85.
BP Further Reduced with Irbesartan Coadministration

- Reductions in serum AGT levels of >90% were achieved and sustained between Week 2 and Week 12 following a single dose of zilebesiran 800 mg alone (data not shown)
  - Coadministration of irbesartan 300 mg PO daily had no additional effect on serum AGT levels
- A single dose of zilebesiran 800 mg SC reduced both systolic and diastolic BP (Day 1–41)
- Daily coadministration of irbesartan for 2 weeks in patients with SBP ≥120 mmHg further reduced systolic and diastolic BP (Day 43–57)

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Zilebesiran only (N=6)</th>
<th>Zilebesiran prior to irbesartan (N=10)</th>
<th>Zilebesiran only (N=6)</th>
<th>Zilebesiran prior to irbesartan (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 (Baseline) to Day 41</td>
<td>-22.0 (2.9)</td>
<td>-7.7 (2.5)</td>
<td>-14.3 (2.3)</td>
<td>-3.3 (1.0)</td>
</tr>
<tr>
<td>Day 43 to Day 57</td>
<td>0.4 (2.9)</td>
<td>-6.4 (3.1)</td>
<td>-0.5 (1.6)</td>
<td>-3.2 (1.9)</td>
</tr>
</tbody>
</table>

AGT, angiotensinogen; BP, blood pressure; DBP, diastolic blood pressure; PO, by mouth; SBP, systolic blood pressure; SC, subcutaneous; SEM, standard error of the mean.
Conclusions

• Single subcutaneous doses of investigational zilebesiran 800 mg were generally well-tolerated in patients with mild to moderate hypertension, with no AE of hypotension or clinically significant laboratory abnormalities reported during the low-salt diet or coadministration with irbesartan.

• A high-salt diet modulated the BP-lowering effect of zilebesiran, providing early evidence that the standard intervention could be effective to treat potential hypotensive adverse events.

• Coadministration of irbesartan with zilebesiran further reduced BP without clinically significant changes in serum creatinine or potassium levels.

• Zilebesiran will be further investigated for the treatment of hypertension in a Phase 2 clinical study in patients with uncontrolled blood pressure despite standard-of-care antihypertensive treatment.

Thank you to the patients, their families, investigators, study staff, and collaborators for their continued participation in the zilebesiran Phase 1 study.