Dose-Related and Prolonged Reductions in Blood Pressure with a RNAi Therapeutic Targeting Angiotensinogen in Hypertensive Patients: Interim Results from a Phase 1 Study with Zilebesiran (ALN-AGT01)

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Investigators and Contributors

Zilebesiran Phase 1 Study

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Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the ALN-AGT Phase 1 study
Background

Hypertension remains the leading cause of death and disability-adjusted life-years worldwide\(^1\text{–}^4\)…

Approx. half of all patients with hypertension are not controlled to guideline-recommended targets

\[ \text{High blood pressure} \]
\[ \text{Overweight-obesity (high BMI)} \]
\[ \text{Physical inactivity} \]
\[ \text{Smoking} \]
\[ \text{High LDL cholesterol} \]
\[ \text{High blood glucose} \]
\[ \text{High dietary sodium (salt)} \]
\[ \text{Low dietary omega-3 fatty acids (seafood)} \]
\[ \text{High dietary trans fatty acids} \]
\[ \text{Low intake of fruits and vegetables} \]
\[ \text{Low PUFA (in place of SFA)} \]
\[ \text{Alcohol Use} \]

\[ \text{Deaths in Thousands} \]

\[ -100 \quad 0 \quad 100 \quad 200 \quad 300 \quad 400 \quad 500 \]

\[ \text{~400,000} \]

deaths/year\(^1\)

…but treatment of hypertension remains suboptimal despite availability of effective antihypertensives\(^1\text{–}^4\)

>50% of patients are nonadherent or suboptimally adherent to antihypertensive treatment

Figure permission pending

BMI, body mass index; LDL, low-density lipoprotein; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid

AGT is the First Substrate in the RAAS Cascade

The Renin-Angiotensin-Aldosterone System (RAAS) cascade has a demonstrated role in blood pressure regulation\(^1\),\(^2\)

- Traditional RAAS-targeted anti-hypertensive pharmacotherapy targets include...
  - Renin inhibition
  - Inhibition of angiotensin converting enzyme (ACE)
  - Inhibition of angiotensin II (ANG II) receptor binding

Angiotensinogen (AGT) is the most upstream precursor of the RAAS cascade, and is predominantly produced in the liver\(^2\)

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Angiotensinogen (AGT) is a Genetically Validated Target

AGT is First Gene Linked to Primary Hypertension\(^1\); Multiple Lines of Evidence Support Causal Association\(^2,3\)

Three Independent Lines of Evidence Replicated in Independent Samples from Salt Lake City and Paris

- Linkage of AGT locus with primary hypertension in hypertensive sibling pairs
- Association of specific AGT variants with primary hypertension in case-control studies
- Association of same variants with elevated plasma AGT levels

Role of AGT in Genetics of Blood Pressure Regulation Confirmed in Large GWAS Study of 342,415 Individuals

- AGT locus highly significantly associated with:
  - Systolic BP (P value = 9.65 \(\times\) 10\(^{-13}\)) and
  - Diastolic BP (P value = 9.53 \(\times\) 10\(^{-15}\))

AGT, angiotensinogen; BP, blood pressure; GWAS, genome-wide association study
Zilebesiran Therapeutic Hypothesis

An Investigational RNAi Therapeutic

Liver-specific AGT Knockdown

- Liver-specific silencing of AGT
- Prolonged duration of action
  - Consistent and durable BP response
  - Potential for infrequent dose administration

AGT, angiotensinogen; BP, blood pressure; GalNAc, N-acetylgalactosamine; siRNA, small interfering ribonucleic acid
Zilebesiran First-in-Human Single Ascending Dose Study

- A total of 84 patients with hypertension completed treatment as of 25-February-2021
- Patients received either placebo (n=4 per cohort) or ALN-AGT (n=8 per cohort)
- Study conducted in outpatient setting with usual activity and dietary sodium intake

**Patient Population (N=12 / dose cohort)**
- Adults 18 to 65 years of age
- SBP >130 and ≤165 mm Hg without antihypertensive meds
- 24h ABPM SBP ≥130 mm Hg
- BMI ≥18 and ≤35 kg/m²
- Exclude secondary hypertension
- Treatment naïve or had prior antihypertensives washed out before enrollment

**2:1 RANDOMIZATION**

- Placebo SC x 1
- ALN-AGT 10 mg SC x 1
- ALN-AGT 25 mg SC x 1
- ALN-AGT 50 mg SC x 1
- ALN-AGT 100 mg SC x 1
- ALN-AGT 200 mg SC x 1
- ALN-AGT 400 mg SC x 1
- ALN-AGT 800 mg SC x 1

**Primary Endpoint**
- Safety and tolerability

**Secondary Endpoints**
- Change from baseline in serum AGT
- Plasma & Urine PK

**Exploratory Endpoint**
- Change from baseline in SBP/DBP by 24hr ABPM

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*Patients previously taking medication for hypertension must be without antihypertensives for ≥2 weeks prior to screening

ClinicalTrials.gov Identifier: NCT03934307

ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BMI, body mass index; DBP, diastolic blood pressure; PD, pharmacodynamics; PK, pharmacokinetics; SBP, systolic blood pressure; SC, subcutaneous
**Baseline Demographics and Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=28)</th>
<th>ALN-AGT Dose Cohort</th>
<th>All ALN-AGT (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years; median (range)</strong></td>
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<td>52 (36, 64)</td>
<td>53 (37, 60)</td>
<td>56 (35, 64)</td>
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<td>41 (35, 64)</td>
<td>56 (35, 65)</td>
<td>56 (43, 64)</td>
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<td>56 (44, 64)</td>
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<td>61 (45, 62)</td>
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<tr>
<td><strong>Gender</strong></td>
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<td>Male</td>
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<td>7</td>
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<tr>
<td>Female</td>
<td>12</td>
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<td><strong>Race</strong></td>
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<tr>
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<tr>
<td>Other</td>
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<tr>
<td><strong>Blood Pressure</strong></td>
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<tr>
<td>24h ABPM SBP median (range)</td>
<td>142 (126, 153)</td>
<td>139 (130, 147)</td>
<td>140 (132, 157)</td>
</tr>
<tr>
<td>24h ABPM DBP median (range)</td>
<td>88 (72, 103)</td>
<td>84 (76, 93)</td>
<td>91 (75, 103)</td>
</tr>
</tbody>
</table>

ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; SBP, systolic blood pressure
Primary Endpoint: Safety & Tolerability

ALN-AGT Was Generally Well-Tolerated Supporting Continued Development

- Most AEs mild or moderate in severity and resolved without intervention
- No deaths or AEs leading to study withdrawal
- No treatment-related Serious AEs (SAEs)
  - Severe and serious AE of prostate cancer reported in 1 patient who received 200 mg ALN-AGT, based upon a biopsy that was performed in the screening period and reported as positive after dosing
- 5 patients who received zilebesiran had injection site reactions, all mild and transient
- No patient has required intervention for low blood pressure
- No clinically significant elevations in serum ALT, serum creatinine, or serum potassium

<table>
<thead>
<tr>
<th></th>
<th>All ALN-AGT (N=56)</th>
<th>Placebo (N=28)</th>
<th>ALN-AGT Dose Cohort</th>
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<tbody>
<tr>
<td>Adverse Event</td>
<td>42</td>
<td>24</td>
<td>10 mg (N=8)</td>
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<td>800 mg (N=8)</td>
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<td>Serious Adverse Event</td>
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<td>800 mg (N=8)</td>
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<td>Severe Adverse Event</td>
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<td>10 mg (N=8)</td>
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Safety data presented as of 25 February 2021

AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event
Secondary Endpoint: Dose-Dependent AGT Lowering

Durable Reduction of Serum AGT >90% Sustained for 12 weeks After Single Doses of ALN-AGT ≥ 100 mg

- Serum AGT reduced 96-98% at Week 12 in all patients given single dose of 800 mg

Data presented as of 25 February 2021

AGT, angiotensinogen; SEM, standard error of the mean
Exploratory Endpoint: Dose-Dependent Reductions in BP

24h SBP Reduction >10 mm Hg at 8 Weeks After Single Doses of ALN-AGT ≥100 mg
24h SBP Reduction >15 mm Hg at 8 Weeks After Single Doses of ALN-AGT 800 mg

• Mean 24h blood pressure reduction of 17 mm Hg / 9 mm Hg at Week 12 in patients given single dose of 800 mg
Exploratory Endpoint: 24-Hour Blood Pressure Profile

Blood Pressure Profiles 6 Weeks After Single Dose of Zilebesiran (800mg) or Placebo

- BP Reduction at All Timepoints During the 24-Hour Period

All Week 6 ABPM data as of 28-May-2021 pooled from patients treated with placebo (N = 28) vs. zilebesiran 800 mg (N = 32) in Phase 1
Ongoing Additional Phase 1 Study Cohorts

• Cohort designed to assess zilebesiran tolerability during extracellular fluid volume reduction caused by salt depletion

• Irbesartan-coadministration cohort designed to assess combinability with conventional RAAS blockade

• Multidose cohort designed to assess potential effects of zilebesiran in obese patients
Phase 2 Clinical Development Plan

**Monotherapy Phase 2 Study (N ~375)**
- IND filing expected year-end 2022
- Evaluate efficacy and safety of zilebesiran as a monotherapy in patients with mild-to-moderate hypertension
- Exploring both quarterly and biannual dosing regimens
- Study initiated June 2021

**Add-On Phase 2 Study**
- Phase 2 combination therapy study of zilebesiran
- Targeting study initiation in late 2021
Zilebesiran Phase 2 Study
Randomized, Double-blind, Placebo-Controlled Study in Patients with Mild-to-Moderate Hypertension

N ~ 375
Patient Population

Key Inclusion Criteria:
• 18 - 75 years of age
• Daytime SBP ≥135 & ≤160 mm Hg
• Treatment naive or prior antihypertensives washed out before enrollment

Key Exclusion Criteria:
• Secondary HTN
• eGFR <30 ml/min/1.73m²

N ~ 375
Patient Population

4-Week Washout

Zilebesiran
150 mg SC q6M

Zilebesiran
300 mg SC q6M

Zilebesiran
300 mg SC q3M

Zilebesiran
600 mg SC q6M

Placebo*
SC q3M

1:1:1:1 RANDOMIZATION

Primary Endpoint
• Change in SBP from baseline to Month 3 assessed by ABPM

Secondary Endpoints Include
(through Month 6)
• Change in SBP and DBP by ABPM
• Time-adjusted change in SBP and DBP by office BP

Exploratory Endpoints Include
(through Month 12)
• Change in 24h average, daytime average, and nighttime average SBP and DBP
• Time-adjusted change in SBP and DBP assessed by office BP, home BP monitoring, and ABPM

ClinicalTrials.gov Identifier: NCT04936035

Study Initiated
June 2021

* Placebo randomized across four zilebesiran treatment arms after 6 months on study

SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension; q3M: every 3 months (quarterly); q6M: every 6 months (semiannual); ABPM: ambulatory blood pressure measurement
Conclusion

- Single subcutaneous doses of zilebesiran were generally well tolerated in patients with mild to moderate hypertension in an interim analysis of an ongoing Phase 1 study, supporting continued development.

- Patients receiving zilebesiran had dose-dependent and durable reduction of serum AGT.

- Serum AGT reductions >90% sustained to 3 months after single doses of zilebesiran ≥100 mg.

- Patients receiving zilebesiran had >10 mm Hg reduction in 24h SBP at 8 weeks after single doses of 100 mg or higher and >15 mm Hg reduction in 24h SBP after single doses of 800 mg.

- Phase 1 data indicate potential for quarterly or biannual dosing; both regimens to be evaluated in Phase 2 studies.

- KARDIA-1 and KARDIA-2 Phase 2 studies currently being initiated.