Dose-Related Reductions in Blood Pressure with a RNA Interference (RNAi) Therapeutic Targeting Angiotensinogen in Hypertensive Patients: Interim Results from a First-In-Human Phase 1 Study of ALN-AGT01

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Hypertension remains the leading cause of death and disability-adjusted life-years worldwide\textsuperscript{1–4}...

...but treatment of hypertension remains suboptimal despite availability of effective antihypertensives\textsuperscript{1–4}

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

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

\textsuperscript{1} McClellan et al., \textit{Circulation} 2019; \textsuperscript{2} Chang TE et al., \textit{Hypertension}, 2019; \textsuperscript{3} Carey RM et al., \textit{Hypertension}, 2018; \textsuperscript{4} Elliott WJ, \textit{J Clin Hypertens}, 2016

BMI, body mass index; LDL, low-density lipoprotein; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid
**ALN-AGT01 Therapeutic Hypothesis**

**Liver-specific AGT Knockdown**

- **AGT**
- **Renin**
- Des(Ang1)AGT
- Angiotensin peptides

**Potential Mechanistic Advantages**

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

AGT, angiotensin; BP, blood pressure; q3M, every 3 months; siRNA, small interfering ribonucleic acid
- A total of 60 patients with hypertension completed treatment as of 16-September-2020
- Patients received either placebo (n=4 per cohort) or ALN-AGT01 (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 mmHg 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

Primary Endpoint
- Safety and tolerability

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

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

Additional cohorts planned to evaluate the use of ALN-AGT01:
- Controlled salt intake: tolerability in salt depletion, recovery of BP with high salt
- Obese patients: PK/PD and effect of ALN-AGT01 on BP and body composition
- Addition of ARB in background of ALN-AGT01: safety and tolerability

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

ABPM, ambulatory blood pressure monitoring; ARB, angiotensin II receptor blocker; DBP, diastolic blood pressure; PD, pharmacodynamics; PK, pharmacokinetics; SBP, systolic blood pressure; SC, subcutaneous
### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=20)</th>
<th>10 mg (N=8)</th>
<th>25 mg (N=8)</th>
<th>50 mg (N=8)</th>
<th>100 mg (N=8)</th>
<th>200 mg (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years; median (range)</strong></td>
<td>52 (36-64)</td>
<td>53 (37-60)</td>
<td>56 (47-63)</td>
<td>41 (35-64)</td>
<td>56 (35-65)</td>
<td>56 (43-64)</td>
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<tr>
<td><strong>Gender</strong></td>
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<td>Male</td>
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<td>4</td>
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<td>4</td>
<td>6</td>
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<tr>
<td>Other</td>
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<td>0</td>
<td>1</td>
<td>0</td>
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</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>24h ABPM SBP median (range)</td>
<td>141 (126,153)</td>
<td>139 (130, 147)</td>
<td>140 (132, 157)</td>
<td>135 (113, 144)</td>
<td>136 (131, 152)</td>
<td>139 (129, 154)</td>
</tr>
<tr>
<td>24h ABPM DBP median (range)</td>
<td>87 (72-102)</td>
<td>83 (76, 93)</td>
<td>91 (75, 103)</td>
<td>84 (74, 91)</td>
<td>86 (80, 90)</td>
<td>83 (75, 95)</td>
</tr>
</tbody>
</table>
**PRIMARY ENDPOINT: SAFETY & TOLERABILITY**

**ALN-AGT01 Was Generally Well-Tolerated Supporting Continued Development**

<table>
<thead>
<tr>
<th>Patients Reporting an Adverse Event (AE), N (%)</th>
<th>Placebo (N=20)</th>
<th>10 mg (N=8)</th>
<th>25 mg (N=8)</th>
<th>50 mg (N=8)</th>
<th>100 mg (N=8)</th>
<th>200 mg (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 Adverse Event</td>
<td>17</td>
<td>5</td>
<td>7</td>
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<tr>
<td>At least 1 Serious Adverse Event</td>
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<tr>
<td>At least 1 Severe Adverse Event</td>
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<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

- 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-AGT01, based upon a biopsy that was performed in the screening period and reported as positive after dosing
- No patient has required intervention for low blood pressure
- No clinically significant elevations in serum ALT, serum creatinine, or serum potassium
- 5 patients with injection site reactions, all mild and transient

AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event
Durable Reduction of Serum AGT >90% Sustained for 3 Months After Higher Single Doses of ALN-AGT01

- Mean reduction in serum AGT at 8 weeks was 95 +/- 2% after 200 mg dose
- Maximum AGT reductions of 98% observed in individual patients after 200 mg dose

No. of patients:
- Placebo: 20
- 10 mg: 8, 8, 8, 8, 8, 8, 8, 8
- 25 mg: 8, 8, 8, 8, 8, 8, 8, 8
- 50 mg: 8, 8, 8, 8, 8, 8, 8, 7
- 100 mg: 8, 8, 8, 8, 8, 8, 8, 7
- 200 mg: 8, 8, 8, 8, 7, 7, 7, 8

SEM, standard error of the mean
EXPLORATORY ENDPOINTS: DOSE-DEPENDENT REDUCTIONS IN SBP AND DBP

24h SBP Reduction >10 mm Hg at 8 Weeks After Higher Single Doses of ALN-AGT01

- Mean reductions in BP at 8 weeks were 11 +/- 2 mm Hg for systolic and 8 +/- 1 mm Hg for diastolic after 200 mg dose
- Maximum reductions of 19 mm Hg for systolic BP and 12 mm Hg for diastolic BP observed in individual patients after 200 mg dose
CONCLUSION

• Single subcutaneous doses of investigational ALN-AGT01 were generally well-tolerated in patients with mild to moderate hypertension supporting continued development, with no treatment-related serious adverse events

• ALN-AGT01 led to a dose-dependent and durable reduction of serum AGT

• Serum AGT reductions >90% after higher single doses of ALN-AGT01 sustained for 3 months, supporting potential for infrequent dosing interval

• BP reductions mirror AGT knockdown, with >10 mm Hg reduction in 24h SBP observed at 8 weeks after single doses of 100 mg or higher

• This ongoing single ascending dose study will characterize maximum effect of ALN-AGT01 and potential durability of effect in lowering AGT beyond 3 months

Thank you to the patients, their families, investigators, study staff, and collaborators for their continued participation in the ALN-AGT01 Phase 1 study