Safety, Tolerability and Pharmacokinetics (PK) of Single Ascending Doses of ALG-125755, a GalNAc-Conjugated Small Interfering RNA (siRNA), in Healthy Volunteers (HV)

Ed Gane¹, Megan Fitzgerald², Kha Le³, Stanley Wang², Lynne Ammar², Kusum Gupta², Christian Schwabe³, Meenakshi Venkatraman², Tse-I Lin⁴, John Fry²

¹University of Auckland, New Zealand; ²Aligos Therapeutics, Inc., United States; ³New Zealand Clinical Research, New Zealand; ⁴Aligos Belgium BV, Belgium

Background

Long-term treatment with current standard of care for chronic hepatitis B (CHB), nucleos(t)ide analogues (NA) or pegylated interferon, suppresses hepatitis B virus (HBV) replication and reduces liver injury in most patients, but rarely results in functional cure, the goal of CHB treatment. Therefore, there is a significant medical need for novel approaches to enhance functional cure rates.

HBV targeted small interfering RNAs (siRNAs) have demonstrated potent antiviral activity i.e., reductions in hepatitis B surface antigen (HBsAg) levels, in CHB patients. ALG-125755 is a N-acetylgalactosamine (GalNAc)-conjugated, S-region targeting siRNA, which has shown favorable safety and potent antiviral activity in nonclinical studies. Specifically, ALG-125755 demonstrated significant and durable HBsAg knockdown in the AAV-HBV mouse model and was well tolerated in both rat and monkey toxicology studies.

Study Design and Objectives

Study ALG-125755-501 (NCT05561530) is a three-part, double-blind, randomized, placebo-controlled phase 1a/1b study. It is evaluating the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics of single subcutaneous (SC) doses of ALG-125755 in healthy volunteers (HV; Part 1) and single (Part 2) and multiple (Part 3) SC doses of ALG-125755 in CHB patients.

The study is ongoing and still blinded. Reported here are preliminary safety results from Part 1 Cohorts 1-4, and PK results from Part 1 Cohorts 1-3.

For each single ascending dose (SAD) cohort in Part 1:
- 8 HVs were randomized to ALG-125755 or placebo in a 3:1 ratio
- Throughout study conduct, safety assessments (adverse events (AEs), vital signs, electrocardiogram (ECG) and laboratories) and plasma/urine PK samples were collected and analyzed.

Pharmacokinetic Analysis

- Plasma and urine concentrations of ALG-125755 and ALG-126144 (n-1 active metabolite of ALG-125755) were quantified from 20 to 100 mg doses for concentrations of ALG-125755 and the active metabolite ALG-126144 (AS(N=1’3’) ALG-125755) using a validated hybridization based-aminonexchange high performance liquid chromatography (AEX-HPLC) method coupled to a fluorescence detector.
- PK parameters were determined by non-compartmental analysis using Phoenix WinNonLin

Results

Dose Levels Evaluated

- Across 4 cohorts, the following single subcutaneous (SC) doses were evaluated: 20, 60, 100 and 200 mg

Baseline Characteristics

The baseline characteristics were generally well balanced across cohorts and typical for a HV population.

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age, years (mean (SE))</td>
<td>33.8 (3.5)</td>
<td>30.9 (3.3)</td>
<td>31.4 (3.6)</td>
</tr>
<tr>
<td>% Male</td>
<td>100</td>
<td>100</td>
<td>87.5</td>
</tr>
<tr>
<td>BMI, kg/m² (mean (SE))</td>
<td>24.6 (1.5)</td>
<td>22.7 (0.8)</td>
<td>25.9 (1.4)</td>
</tr>
</tbody>
</table>

Safety

After single SC doses of up to 200 mg:
- There were no serious adverse events (SAEs) or dose limiting toxicities
- All treatment AEs (TEAE) were mild (Grade 1) in severity
- TEAEs reported in more than one subject include headache (N=4), injection site erythema (N=2), diaphoresis (N=2), and diarrhea (N=2)
- No clinically significant laboratory abnormalities have been reported; all treatment-emergent laboratory abnormalities were Grade 2, except for:
  - One subject in Cohort 1 with a transient Grade 3 LDL cholesterol elevation; subject had Grade 1 LDL cholesterol elevations at baseline
  - One subject in Cohort 2 with exercise-related Grade 4 creatine kinase and Grade 3 aspartate aminotransferase elevations
  - One subject in Cohort 3 with a transient Grade 3 total cholesterol elevation; subject had Grade 2 total cholesterol elevations at baseline
  - One subject in Cohort 4 with a transient Grade 3 LDL cholesterol elevation; subject had Grade 1 LDL cholesterol elevations at baseline
  - There were no clinically significant physical examination, vital sign or ECG abnormalities

Conclusions

Single doses of up to 200 mg of ALG-125755 have been well tolerated in HV. ALG-125755 exposures increased dose proportionally with low PK variability.

References

2 Fitzgerald M et al. ILC 2022; SAT386.

Acknowledgements

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