Safety, pharmacokinetics, and antiviral activity of single ascending doses of ALG-125755, a GaINAc-conjugated small interfering RNA in subjects with chronic hepatitis B

A. Jucov1, E. Gane2, M. Fitzgerald3, K. Lee1, S. Wang2, L. Ammar4, C. Burnett4, A. Hacetcanan4, K. Gupta5, D. Clarke5, M. Venkatraman5, L. Beigelman5, L. Blatt5, T. Lin6, S. Chandak7, M. McClure, J. Fry

1. ARENSIA Exploratory Medicine, Republican Clinical Hospital, Chisinau, Moldova
2. Nicola Tei State University of Medicine and Pharmacy, Moldova
3. University of Auckland, New Zealand
4. Aligos Therapeutics, Inc., South San Francisco, CA
5. Aligos Belgium BV, Leuven, BE

Introduction

Long-term treatment with current standard of care for chronic hepatitis B (CHB), nucleos(t)ide analogues (NA) or pegylated interferon, 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 GaINAc-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.

Aim

To evaluate the safety, pharmacokinetics (PK) and antiviral activity of ALG-125755, an siRNA designed to reduce HBsAg in CHB subjects.

Methods

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 preliminary safety, PK and antiviral data from Part 2, which is comprised of linear PK in HVs. In Part 2, single doses of up to 200 mg ALG-125755 were well tolerated with linear PK in HVs.

The study is ongoing and still blinded. Reported here are available preliminary safety, PK and antiviral data from Part 2, which is comprised of data through Day 90 after receiving a single dose of ALG-125755 in Cohorts 1 and 2.

For each single ascending dose (SAD) cohort in Part 2:
- 8 virologically suppressed (VS) HBeAg negative CHB subjects were randomized to ALG-125755 or placebo in a 3:1 ratio
- Safety assessments (adverse events (AEs), vital signs, physical examination, ECG, and laboratories), viral markers, and plasma and urine PK were collected throughout study conduct
- Key inclusion criteria: HBsAg ≥50 IU/mL, HBeAg <10U/mL; HBV DNA <20 IU/mL; ALT ≤1.2x ULN

Pharmacokinetic Analysis

- Plasma concentrations of ALG-125755 and the active metabolite ALG-126144 (AS(N-1)3’ ALG-125755) were quantified using a validated hybridization based-anion-exchange high performance liquid chromatography (AEX-HPLC) method coupled to a fluorescence detector.
- Preliminary safety, PK and antiviral data from Part 2, which is comprised of data through Day 90 after receiving a single dose of ALG-125755 in Cohorts 1 and 2.

Results

Pharmacokinetics

- Plasma exposures increased on a dose proportional manner with low-moderate inter-subject variability
- ALG-125755 was quickly absorbed (tmax ~ 2–3 hr), highly distributed (V/F > 400 L) and had low plasma CL (CL/F < 30 L/hr)
- Metabolite to parent ratio was ~10 %

Safety

After single SC doses of up to 120 mg:
- There were no serious adverse events (SAEs) or dose limiting toxicities
- All treatment emergent AEs (TEAEs) were mild (Grade 1) or moderate (Grade 2) in severity
- No evidence of dose response for any TEAE
- No clinically concerning laboratory, ECG, vital sign or physical examination findings were reported

Dose Levels Evaluated

Across Cohorts 1-2, the following SC doses were evaluated: 50 and 120 mg

Baseline Characteristics

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

Table 1. Part 2 Baseline Characteristics and Demographics

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>50</td>
<td>120</td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age, years (mean,[SD])</td>
<td>57.6 (2.3)</td>
<td>54.3 (4.0)</td>
</tr>
<tr>
<td>% Male</td>
<td>37.5</td>
<td>87.5</td>
</tr>
<tr>
<td>BMI, kg/m² (mean,[SD])</td>
<td>30.4 (1.3)</td>
<td>27.0 (1.8)</td>
</tr>
<tr>
<td>HBsAg, mean log₂ IU/mL (range)</td>
<td>3.55 (2.11-4.14)</td>
<td>3.53 (2.85-4.41)</td>
</tr>
<tr>
<td>ALT, U/L (mean,[SD])</td>
<td>22.8 (3.8)</td>
<td>30.4 (4.8)</td>
</tr>
</tbody>
</table>

Table 2. PK Parameters

<table>
<thead>
<tr>
<th>Dose</th>
<th>Analyte</th>
<th>C₀ (hr)</th>
<th>CₚK (ng/mL)</th>
<th>AUC₀₋∞ (ng.hr/mL)</th>
<th>AUC₀₋∞ (ng.hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>ALG-125755</td>
<td>2.01 (5.4, 4.0)</td>
<td>143 (49.2)</td>
<td>1660 (28.1)</td>
<td>233 (38.3)</td>
</tr>
<tr>
<td>120 mg</td>
<td>ALG-125755</td>
<td>3.53 (10.0, 4.0)</td>
<td>588 (98.9)</td>
<td>5530 (45.6)</td>
<td>810 (42.1)</td>
</tr>
<tr>
<td>50 mg</td>
<td>ALG-126144</td>
<td>3.03 (5.2, 4.8)</td>
<td>478 (77.6)</td>
<td>2300 (10.0)</td>
<td></td>
</tr>
<tr>
<td>120 mg</td>
<td>ALG-126144</td>
<td>3.03 (5.2, 4.8)</td>
<td>478 (77.6)</td>
<td>2300 (10.0)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- Single ascending SC doses of ALG-125755 up to 120 mg were well tolerated in VS HBeAg negative CHB subjects
- Dose proportional PK with low-moderate variability was observed

Acknowledgements

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Disclosures