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

SAT-188

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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.[1] 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.[2] 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 safety, tolerability, 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. In Part 1, single doses of up to 200 mg ALG-125755 were well tolerated with linear PK in HVs.[3]

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 <LLOQ; 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.

Results

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

	Cohort 1	Cohort 2
Dose	50	120
N	8	8
Age, years (mean,(SE))	57.6 (2.3)	54.3 (4.0)
% Male	37.5	87.5
BMI, kg/m² (mean (SE))	30.4 (1.3)	27.0 (1.8)
HBsAg, mean log_{10} IU/mL (range)	3.55 (2.11-4.14)	3.53 (2.85-4.41)
ALT, U/L (mean (SE))	22 (3.8)	30 (4.8)

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

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 %

Figure 1. Part 2 Plasma PK

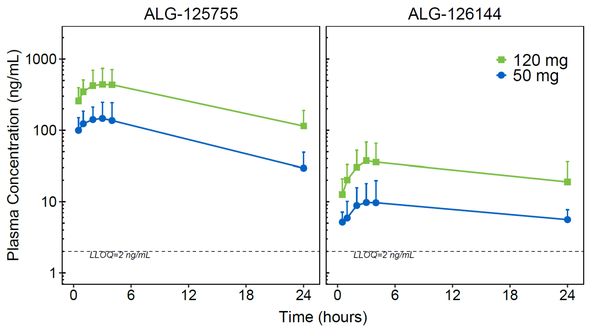


Table 2. PK Parameters

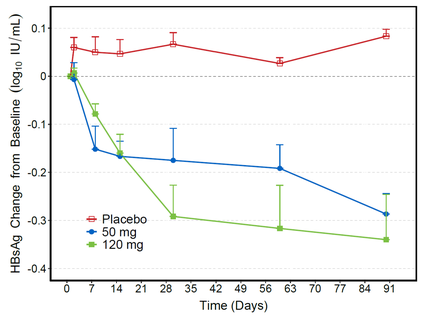
Dose	Analyte	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)
50 mg (N=6)	ALG-125755	2.0(0.5,4.0)	142(49.2)	1660(28.1)	2310(38.3)
	ALG-126144	3.5(3.0,24)	8.84(72.4)	130(25.7)	284(54.0)
120 mg (N=6)	ALG-125755	3.0(1.0,4.0)	388(69.8)	5350(45.6)	8110(42.1)
	ALG-126144	3.0(3.0,24)	30.3(95.7)	487(77.6)	2300(1010)

Geometric means (geometric CV%) except for tmax: median(minimum, maximum)

Antiviral Activity

- Dose dependent decreases in HBsAg were observed over 90 days
- Day 90 Cohort 1 and 2 data demonstrate sustained activity

Figure 2. Change in HBsAg from Baseline over ≥30 Days after a Single Dose



50 mg and 120 mg: n=6 each
Placebo: n=3; one placebo subject was omitted from curve because HBsAg spontaneously declined by 2 log_{10} IU/mL, which is presumed due to spontaneous clearance and thus considered an outlier

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
- Dose dependent reductions in HBsAg were observed over 90 days following a single dose of ALG-125755
- The safety, PK and HBsAg effects support further evaluation with higher doses, which is ongoing (Cohort 3, 320 mg)

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Disclosures

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