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

Abstract #1216

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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.[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.

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, 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-anion-exchange 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.

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Dose (mg)	20	60	100	200
N	8	8	8	8
Age, years (mean (SE))	33.8 (3.5)	30.9 (3.3)	31.4 (3.6)	32.3 (3.7)
% Male	100	100	87.5	87.5
BMI, kg/m^2 (mean (SE))	24.6 (1.5)	22.7 (0.8)	25.9 (1.4)	23.8 (1.2)

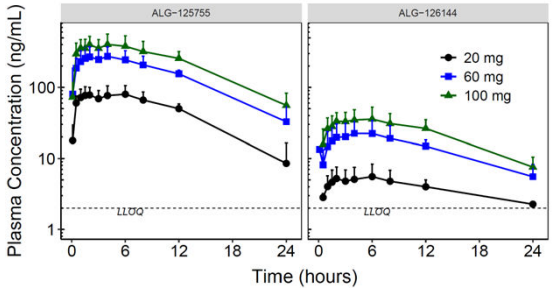
SE = Standard Error

Results

Pharmacokinetics

- Following SC administration, ALG-125755 was rapidly absorbed (t_{max} ~3-6 hrs) and had a short terminal plasma half life (<10 hrs)
- Plasma ALG-125755 exposure increased proportionally to dose with low PK variability (CV< 33%)
- Low metabolite to plasma ratio (<10%)

Figure 1. Mean (SD) Plasma Concentration-Time Profiles of ALG-125755 and ALG-126144 Following Single Doses



Cohort	Analyte	C_{max} (ng/mL)	AUC_{0-24} (ng.hr/mL)	AUC_{0-inf} (ng.hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
1 (20 mg) N=6	ALG-125755	80 (34.9)	1060 (20.8)	1200 (19)	4 (1.5,6)	6.9 (6.1)
	ALG-126144	5.28 (51)	71.2 (32.5)	143 (NA)	6 (4,12)	16 (NA)
2 (60 mg) N=6	ALG-125755	276 (36.3)	3470 (19.8)	3770 (14.7)	3 (1.5,6)	5.5 (1.7)
	ALG-126144	21.3 (53.9)	285 (21.3)	368 (17.2)	4 (3,6)	10 (4.2)
3 (100 mg) N=6	ALG-125755	421 (40.7)	5390 (24.7)	6150 (18.5)	4 (2,12)	5.9 (2.0)
	ALG-126144	36.7 (42.8)	519 (30.3)	648 (17.5)	6 (2,8)	7.7 (3.4)

Geometric mean (geometric CV)), except for t_{max}: median(min,max), and $t_{1/2}$: mean (SD); NA = Not Available

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), dyspepsia (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 2 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. Doses of 40-100 mg are projected to achieve steady state liver ALG-125755 concentrations necessary for antiviral activity in CHB patients. In Part 2, single 50 mg doses of ALG-125755 are being evaluated in patients with CHB.

References

1 Lok A et al. Hepatology Communications 2019;3(1):8-19.
2 Fitzgerald M et al. ILC 2022; SAT386.

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