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Safety and Tolerability of Multiple Doses of ALG-020572, a GalNAc-conjugated Antisense Oligonucleotide, in Chronic Hepatitis B Subjects

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ALIGOS THERAPEUTICS

INTRODUCTION

- Antisense oligonucleotides (ASOs) have been shown to substantially reduce HBsAg levels in chronic hepatitis B (CHB).[1]
- Covalent conjugation with N-acetylgalactosamine (GalNAc) has been shown to enhance the delivery of ASOs to hepatocytes.
- Compared to unconjugated ASOs, GalNAc-conjugated ASOs have demonstrated better tolerability in terms of ALT elevations at the cost of reduced antiviral activity. This could be due to differences in dose and frequency of administration of GalNAc-conjugated ASOs and/or the result of additional immune activation caused by unconjugated ASOs.[2,3]
- ALG-020572 is a GalNAc-conjugated 18-mer phosphorothioated ASO containing novel bridged nucleic acid/DNA with sequence complementary to the HBsAg region of the HBV genome.

AIM

To evaluate the safety, pharmacokinetics (PK), and antiviral activity of multiple doses of ALG-020572 in CHB subjects.

MATERIALS AND METHODS

- Study ALG-020572-401 was a two-part, double-blind, randomized, placebo-controlled Phase 1 study (NCT05001022) to evaluate the safety, tolerability, PK and antiviral activity of ALG-020572.
  - In Part 1, 32 Healthy Volunteers received single ascending subcutaneous (SC) doses of 50-480 mg ALG-020572, which were found to be well tolerated with predictable PK[4]
  - Part 2 was designed to evaluate multiple ascending SC doses of ALG-020572 in virologically suppressed HBeAg negative CHB subjects. In each of the 3 planned cohorts, 8 subjects were to be randomized 3:1 to receive doses of ALG-020572 or placebo on Days 1, 4, 8, 11, 15, 22 and 29
  - A single cohort of 8 (6 active : 2 placebo) subjects received 210 mg of ALG-020572 or placebo before the study was terminated
- Assessments included treatment emergent adverse events (TEAEs), vital signs, physical examination, electrocardiograms (ECG), laboratories, PK, and hepatitis B virus viral markers (Part 2).
- Plasma concentrations of ALG-020572 were quantified using a validated liquid chromatographic hybridization method. Liver concentrations of ALG-020572 (conjugated) and ALG-020579 (unconjugated) were determined by a qualified LC-MS/MS method.
- Reported here are data from the single cohort enrolled in Part 2.

RESULTS

BASELINE CHARACTERISTICS

Baseline characteristics were comparable between subjects receiving ALG-020572 and placebo

Table 1: Baseline Characteristics

Characteristics	Cohort 1	
	ALG-020572 210 mg N=6	Placebo N=2
Age (years), mean (SE)	48.7 (3.5)	47.0 (11.0)
Male, N (%)	6 (100)	2 (100)
White/Asian/Black/Other, N (%)	0(0)/1(17)/3(50)/2(33)	2(100)/0/0/0
BMI (kg/m^2), mean (SE)	25.8 (1.1)	26.3 (0.7)
ALT (U/L), mean (SE)	33.7 (7.2)	28.0 (7.0)
HBsAg (log_{10} IU/mL), mean (SE)	3.2 (0.3)	3.1 (0.2)

BMI = Body Mass Index; SE = Standard Error

SAFETY

- One serious adverse event was reported due to Drug Induced Liver Injury (DILI) requiring hospitalization
- TEAEs leading to discontinuation:
  - 3 subjects experienced alanine aminotransferase (ALT) elevations due to DILI that resulted initially in a pause in dosing. Ultimately, based on emerging data, the entire cohort stopped dosing due to these DILI events
- TEAEs (ALT flares)
  - 4 of the 6 subjects who received 210 mg ALG-020572 experienced significant ALT flares (≥10xULN) after receiving 2-7 doses of ALG-020572.
  - 2 of the 6 subjects also developed liver related symptoms including nausea, vomiting, and fatigue along with elevated total bilirubin values (peak 2xULN), with one subject briefly being hospitalized (SAE).
  - No prolongation of coagulation function was observed.
  - Liver biopsies obtained in 3 of the 4 subjects with significant ALT flares showed varying histologic findings but all were assessed as being suggestive of DILI
  - Based on a review of the totality of available data, these ALT flares were considered by the study review committee to be suggestive of DILI.
  - All subjects recovered with DILI related lab values returning to, or near to, baseline after discontinuation of study drug and no sequelae were observed over the following 4.5 months of follow-up.
- Except as described above, no other concerning safety findings (TEAEs, laboratories, VS, EKG, physical examination) were observed

PHARMACOKINETICS

Plasma PK

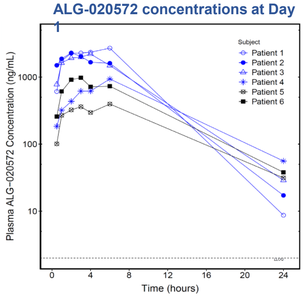
- Plasma ALG-020572 PK parameters at Day 1 in the 4 subjects with significant ALT flares (blue) appeared to be higher than those without these flares (black), but there was no significant overall difference in exposures experienced by CHB subjects compared with healthy volunteers in Part 1

Table 2: Individual plasma ALG-020572 PK parameters at Day 1

Subject #	BW	Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-24} (ng.hr/mL)
#1	62	3.4	2700	20821
#2	75	2.8	2292	16877
#3	82	2.6	2205	16937
#4	74	2.8	937	8889
#5	89	2.4	396	4371
#6	101	2.1	976	8501
Mean	**80**	**2.7**	**1584**	**12733**

BW=body weight

Figure 1: Individual plasma ALG-020572 concentrations at Day 1



Liver Concentration

- Liver biopsy samples were collected 11-13 days after the last dose from 3 of the 4 subjects with significant ALT flares (>10X ULN)
- Liver concentrations of ALG-020579 at time of biopsy were high (2-8-fold above projected liver EC_{90}) but remained 1.7-6.1-fold below the no observed adverse effect (NOAEL) liver concentrations observed in toxicology studies in monkeys. Given the time of biopsy was <1 liver $t_{1/2}$, the concentrations at the time of adverse effect are estimated to have been at or below the monkey NOAEL concentration.
- ALG-020572 was not detected in liver
- Neither increases in ALT nor reductions in HBsAg correlated with liver ALG-020579 concentrations

Table 3: Liver concentration of ALG-020579 following last dosing in available biopsy samples from subjects with ALT flares

Subject #	Number of ALG-020572 210mg SC doses	Liver ALG-020579 in liver (µg/g) 11-13 days after last dose
#1	7 doses	164
#2	6 doses	276
#3	2 doses	588

ANTIVIRAL ACTIVITY

- Treatment with up to seven 210 mg ALG-020572 doses resulted in 0.3-1.63 log_{10} IU/mL HBsAg* reductions, while subjects treated with placebo had no change in HBsAg levels
- No correlation between ALT elevation and HBsAg reduction was observed.

* ElectroChemiLuminescence (ECL) by Roche Cobas 8000 or Chemiluminescent microparticle immunoassay (CMIA) by Abbott Architect was used for HBsAg quantitative

IMMUNE CYTOKINE ANALYSIS

- Immune cytokines were analyzed at predose and 24 hours post dosing on Day 1 in serum and plasma
- Cytokine upregulation or indications of a significant inflammatory response were not observed
- Typical makers of an immune response, like IFN-alpha and IFN-gamma, were not detected

CONCLUSIONS

- Administration of as few as two 210 mg doses of ALG-020572 was associated with some antiviral activity and significant ALT flares, likely due to DILI
- DILI was unexpected given that observed human plasma and liver PK levels were up to 6-fold below the NOAEL and hepatotoxicity was not observed in toxicology studies in monkeys nor in Part 1 of this study
- No correlation was observed between intensity of ALT flares and unconjugated ASO ALG-020579 exposure in liver and/or magnitude of HBsAg reduction
- Development of ALG-020572 has been terminated

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1) Yuen MF et al. 10.1038/s41591-021-01513-4; **2)** Yuen MF et al. 10.1016/S0168-8278(20)30648-6; **3)** Yuen MF et al. AASLD 2019; **4)** Ed Gane et al. EASL 2022

DISCLOSURES

Agarwal K: Abbott, Aligos, Arbutus, Assembly, BMI, BI, Gilead, Janssen, Immunocore, Roche, Sobi, Vir Bio. **Gane E:** AbbVie, Abbott Diagnostics, Aligos, Arbutus, Arrowhead, Assembly, Avalia, Clear B Therapeutics, Dicerna, Enanta, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Roche and Vir Bio. **Danial Forton:** Gilead. **Yuen MF:** AbbVie, Aligos, Antios Therapeutics, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosciences, Bristol-Myers Squibb, Clear B Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Immunocore, Janssen, Merck Sharp and Dohme, Roche, Springbank Pharmaceuticals, Silverback Therapeutics, Sysmex Corporation and Vir Bio. **Wu M, Le K, Rito J, Gupta K, Westland C, Lai F, Venkatraman M, Fitzgerald M, Lin T, Blatt L, Beigelman L, Chanda S, McClure M, Fry J:** Employees of Aligos Therapeutics, Inc.

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