Safety, Tolerability and Pharmacokinetics of Single Ascending Doses of ALG-020572, a GalNAc-Conjugated Antisense Oligonucleotide, in Healthy Subjects

GANE E[1], YUEN MF[2], SCHWABE C[3], WU M[4], LE K[4], RITO J[4], GUPTA K[4], WESTLAND C[4], LAI F[4], VENKATRAMAN M[4], FITGERALD M[4], LIN TI.[4], BLATT L[4], BEIGELMAN L[4], CHANDA S[4], McCLURE M[4], FRY J[4], and AGARWAL K[5]

[1]Faculty of Medicine, University of Auckland; [2]The University of Hong Kong; [3]New Zealand Clinical Research; [4]Aligos Therapeutics, Inc.; [5]Institute of Liver Studies, King's College Hospital

INTRODUCTION

- Antisense oligonucleotides (ASOs) have been shown to substantially reduce HBsAg levels in chronic hepatitis B (CHB) patients.[1]
- Covalent conjugation with N-acetylgalactosamine (GalNAc) has been shown to enhance the delivery of ASOs to hepatocytes.
- Compared to unconjugated ASOs, GalNAc-conjugated HBV 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, a GalNAc-conjugated 18-mer PS Gapmer ASO demonstrated potent HBsAg lowering activity in vivo[4] and was well tolerated in nonclinical safety studies.

AIM

To evaluate the safety and pharmacokinetics (PK) of single doses of ALG-020572 in healthy volunteers (HVs)

METHODS

ALG-020572-401 is a two-part, multi-center, double-blind, randomized, placebo-controlled phase 1 study (NCT05001022):

- In Part 1, cohorts containing 8 HVs, including at least 4 Asians, were randomized to receive a single ascending subcutaneous (SC) dose of ALG-020572 or placebo in a 3:1 ratio.
- 50 mg as the starting dose in Part 1 provides a safety margin of ≥19-fold based on the human-equivalent dose (HED) and ≥700-fold based on the projected human exposure compared with the nonclinical no observed adverse effect level (NOAEL).
- In Part 2, cohorts containing 8 CHB subjects were randomized 3:1 to receive multiple ascending SC doses of ALG-020572 or placebo.
- Assessments include adverse events (AEs), 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.

Continuous data are presented as mean (standard deviation [SD] or standard error of the mean [SEM]). Categorical data are presented as percentage.

Reported here are preliminary safety and PK data from Part 1.

RESULTS

DOSE LEVELS EVALUATED

In Part 1, subjects were assigned to receive single SC doses of ALG-020572: 50 mg (Cohort 1), 150 mg (Cohort 2), 300 mg (Cohort 3) and 480 mg (Cohort 4) or matching placebo.

BASELINE CHARACTERISTICS

The baseline characteristics were similar across dose levels and are typical for a HV population

Characteristics	ALG-020572				Placebo N=8
	50 mg N=6	150 mg N=6	300 mg N=6	480 mg N=6	
Mean age, years (SEM)	25.8 (1.6)	29.3 (2.6)	28.7 (2.1)	32.3 (6.4)	33.5 (3.8)
N, % Male	6, 100%	6, 100%	6, 100%	6, 100%	6, 75%
N, % Asian	3, 50%	3, 50%	4, 67%	4, 66.7%	2, 25%
Mean BMI, kg/m^2 (SEM)	22.8 (1)	25.4 (1.2)	25.3 (1)	23.8 (0.8)	24.0 (1)

SAFETY

ALG-020572 was well tolerated in HVs after single subcutaneous doses of up to 480 mg:

- No serious adverse events were reported
- There was no apparent relationship between dose and any treatment emergent adverse events (TEAEs) reported
- Summary of TEAEs

TEAEs	ALG-020572				Placebo N=8
	50 mg N=6	150 mg N=6	300 mg N=6	480 mg N=6	
Any TEAE	5	16	10	13	13
TEAE ≥ Grade 2*	0	1	1	2	0
Most common (≥ 2 subjects) TEAEs					
Injection Site Erythema	0	3	2	1	0
Injection Site Pain	3	3	2	3	1
Injection Site Swelling	0	1	0	1	0
Injection Site Bruising	0	2	1	2	1
Diarrhea	0	1	0	1	0
Headache	0	1	1	1	3
Rash	0	2	0	0	1
Vascular access site complication	1	0	2	1	0
COVID-19	0	0	0	1	1

** 4 Grade 2 TEAEs (one each): injection site pain (150 mg), injection site erythema (300 mg), unrelated upper limb fracture (480 mg) and unrelated vascular access site complication (480 mg)*

- Laboratory abnormalities
  - The majority were Grade ≤ 1 in severity
  - There were no clinically concerning lab abnormalities that were Grade ≥2 or >1 Grade change from baseline
  - Two asymptomatic post-treatment ALT increases occurred, which were reviewed by the Study Review Committee (SRC)
    - One Grade 1 ALT (peak 95 U/L) and Grade 2 AST (peak 137 U/L) elevation on Day 30 in Cohort 2 (150 mg) was associated with Grade 4 creatinine kinase (CK) elevation (peak 7,936 U/L), which was attributed to strenuous activity. ALT/AST/CK normalized by Day 46. There was no change in liver synthetic function.
    - One Grade 1 ALT (peak 110 U/L) and AST (peak 61 U/L) elevation was observed in Cohort 3 (300 mg) at Day 15, which resolved within 2 weeks spontaneously. There was no change in liver synthetic function.
- No concerning ECG, vital sign, or physical examination findings were observed
- No clinically significant differences were observed in the safety profile for Asian compared to non-Asian subjects

PHARMACOKINETICS

- Plasma exposures increased in a more than dose proportional manner between 50 and 480 mg
- Low-to-moderate PK variability (CV: ~30% for AUC, 30-64% for C_{max})
- Quick absorption (t_{max} ~ 3hrs), high volume of distribution (V/F > 150 L) and relatively high plasma CL (CL/F >6 L/hr)
- Low urinary excretion (<6% total administered dose)
- Adjusting for body weight, there were no significant differences in PK were observed between Asian and Non-Asian subjects

Dose (mg)	BW (kg)	Cmax (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng.hr/mL)	AUC_{0-168} (ng.hr/mL)	AUC_{INF_obs} (ng.hr/mL)	CLss_F (L/hr)	Vz_F (L)
50 (N=6)	68.4 (9.9)	198 (64.3)	2.5 (1,6)	1480 (33)	1490 (32.5)	1490 (32.6)	33.8 (28.3)	151 (50)
150 (N=6)	79.8 (10.3)	789 (27.7)	1.75 (1,3)	6620 (16.8)	6760 (17)	6760 (17)	22.7 (19)	204 (38.9)
300 (N=6)	77.4 (17.2)	2950 (44.3)	3 (2,8)	28,800 (32.7)	29,500 (32.6)	29,600 (33)	10.4 (25.8)	539 (78.5)
480 (N=6)	73 (14.7)	9060 (37.6)	3 (3,6)	74,200 (28.9)	75,000 (28.6)	75,300 (28.8)	6.47 (31.6)	390 (85.5)

Values are geometric mean (CV%), except for BW [mean(CV)] and tmax [median (min,max)]

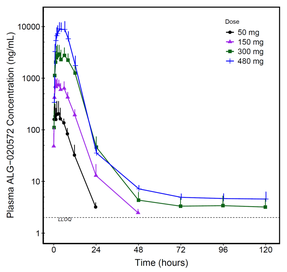

Figure 1: Mean (+SD) Plasma Concentration-Time Profiles of ALG-020572 following single SC dosing 50-480mg in HVs

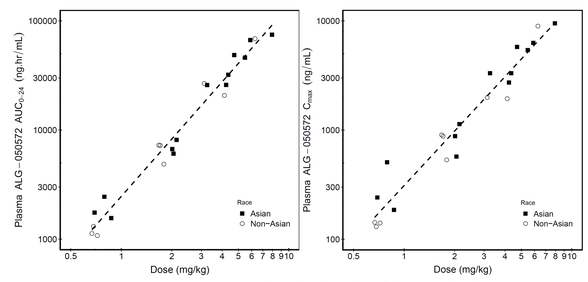

Figure 2: ALG-020572 PK Parameters vs Body Weight Adjusted Dose following single SC dosing 50-480mg in Asian vs non-Asian HVs

CONCLUSIONS

- ALG-020572 demonstrated an acceptable safety and PK profile in HVs receiving single SC doses from 50 mg to 480 mg. Exposures increased in a more than dose proportional manner with moderate variability and no differences across ethnicities.
- Multiple doses of ALG-020572 (Part 2) were evaluated subsequently in CHB subjects per SRC recommendations. Unfortunately, this study has been discontinued prematurely due to multiple cases of severe ALT flares being reported.

ACKNOWLEDGEMENTS

The authors wish to thank the subjects for participating in this clinical study. We are also grateful to the staff at New Zealand Clinical Research and Novotech for assisting in the conduct of this study. The authors also wish to thank Chris Burnett for his assistance in the conduct of the study.

REFERENCES

[1] Yuen MF et al. 10.1038/s41591-021-01513-4; [4] Yuen MF et al. 10.1016/S0168-8278(20)30648-6; [5] Yuen MF et al. AASLD 2019; [6] Gupta K et al. AASLD 2020

CONTACT INFORMATION

Min Wu – mwu@aligos.com