AASLD The Liver Meeting® Nov. 4-8, 2022

SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF MULTIPLE ASCENDING ORAL DOSES OF ALG-055009, A THYROID HORMONE RECEPTOR BETA AGONIST, IN HYPERLIPIDAEMIC SUBJECTS

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ALIGOS THERAPEUTICS

Abstract #2354

INTRODUCTION

- Thyroid hormone receptor-beta (THR-β) is the primary THR expressed in liver and plays an important role in lipid metabolism[1,2]
- Therapeutics targeting THR-β represent a promising approach to treating patients with fatty liver by decreasing hepatic fat content and improving liver histology[3]
- ALG-055009 is a THR-β agonist that in preclinical models had:
  - High selectivity for THR-β and nanomolar potency[4]
  - High efficacy in diet-induced obese rat and mouse models[4,5]
  - A favorable pharmacokinetic (PK) profile with low plasma clearance, metabolic stability, high oral bioavailability and a long plasma half-life[5,6]

AIM

- To evaluate the safety, PK, and pharmacodynamics (PD) of ALG-055009 in healthy volunteers (HV) and in subjects with mild hyperlipidemia

MATERIALS AND METHODS

ALG-055009-301 is a multi-part, double blind, randomized, placebo controlled first-in-human study (NCT05090111).

- Part 1 evaluated single ascending oral doses of ALG-055009 up to 4 mg in HV, the data from which were previously reported[7]
- Part 2 evaluated multiple ascending doses in four cohorts of subjects with mild hyperlipidemia
  - Each cohort was comprised of 10 subjects randomized to receive 14 once daily oral doses of ALG-055009 (N=8) or placebo (N=2) in a fasted state while receiving a standardized diet. Subjects were followed for 2 weeks after the last dose.
  - Key Inclusion Criteria:
    - Low Density Lipoprotein (LDL) >110 mg/dL
  - Key Exclusion Criteria:
    - TSH (thyrotropin) and Free Thyroxine (T4) > ULN
- Throughout the study, safety assessments, treatment emergent adverse events [TEAEs], vital signs, electrocardiogram [ECG] and laboratories, PK, and PD markers (including Sex Hormone Binding Globulin [SHBG] and lipids) were collected
- Plasma concentrations of ALG-055009 were quantified by validated liquid chromatography–tandem mass spectrometry
- Here we report data from all Part 2 cohorts

RESULTS

BASELINE CHARACTERISTICS

The baseline characteristics were generally similar across cohorts

Table 1: Demographics and Baseline Characteristics

ALG-055009 Dose	PBO	0.3 mg	0.5 mg	0.6 mg	1 mg
N	N=8	N=8	N=8	N=8	N=8
Age (years), mean (SEM)	41.3 (5.5)	39.1 (4.1)	49.4 (3.9)	41.4 (4.1)	33.4 (4.8)
Male, N (%)	8 (100%)	7 (87.5%)	6 (75%)	8 (100%)	8 (100%)
Non-Hispanic, N (%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	7 (87.5%)
BMI, kg/m^2, mean (SEM)	25.6 (1.3)	28.1 (0.8)	28.4 (1.3)	27.6 (1.1)	24.7 (1.4)
LDL, mg/dL, mean (SEM)	147.9 (13.9)	141.7 (10.1)	150.5 (10.0)	142.0 (5.9)	125.8 (4.8)

PBO = Placebo. SEM= Standard Error of the Mean.

RESULTS

SAFETY

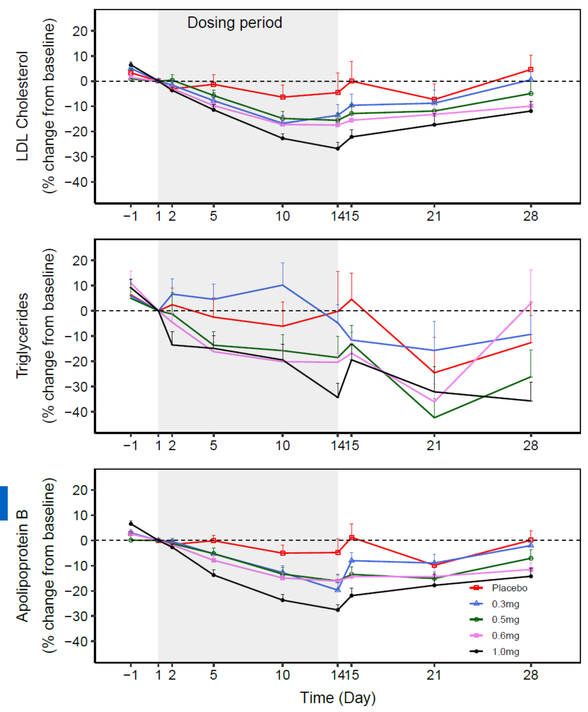
Administration of ≤1 mg ALG-055009 for 14 days was well tolerated

- There were no serious adverse events, dose-limiting toxicities, or TEAEs leading to premature discontinuation
- All TEAEs were mild (Grade 1) or moderate (Grade 2) in severity
- The most common TEAEs (≥2 subjects) were:
  - Insomnia (N=2; 0.3 mg);
  - Headache (N=4; N=1 PBO, N=1 0.5 mg, N=2 0.6 mg)
  - Abdominal distension (N=4; N=1 PBO; N=1 0.5 mg; N=2 0.6 mg)
  - Diarrhea (N=2; N=1 0.6 mg N=1, 1 mg)
- No evidence of clinical hypo- or hyperthyroidism was observed
- No clinically concerning laboratory, ECG, vital sign or physical examination findings were reported

PHARMACODYNAMICS: Anti-Lipid-Effects

- A generally dose related decline in LDL-c, triglycerides and Apo-Lipoprotein B was observed. Maximum decline occurred at Day 14 (Fig 1)

Fig 1: Mean (± SEM) % change from Baseline in Lipids

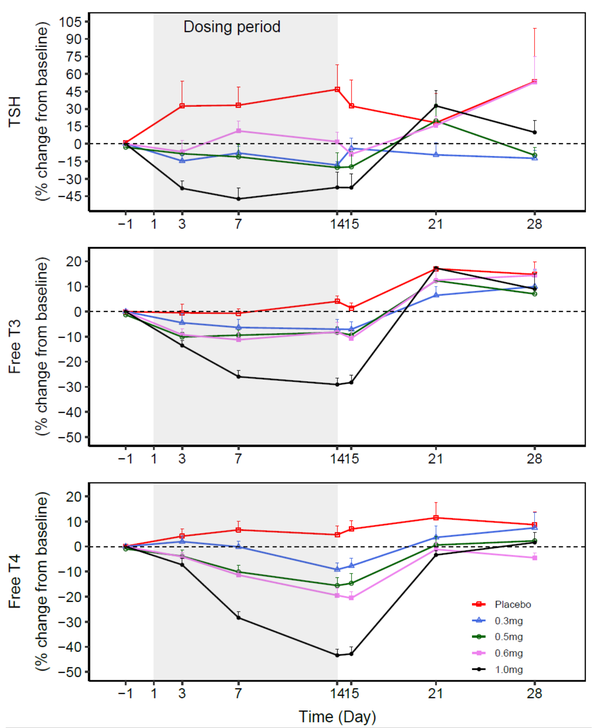


- An inconsistent or no dose response effect was observed for Cholesterol, HDL-c, non-HDL-c, Apolipo-A1 and Lipoprotein-A

PHARMACODYNAMICS: Thyroid Hormones

- Thyroid hormones levels transiently declined in a generally dose responsive manner, then returned to (near) baseline within 2 weeks (Fig 2)
  - ALG-055009 doses ≤0.6 mg: maximum mean declines were ~10-20%, with mean values of all thyroid hormones remaining in the normal range
  - ALG-055009 1 mg dose level: maximum mean declines in TSH, Total/FreeT4, Total T3 and Free T3 were 47%, 43%, 33% and 29%, respectively. The mean values of TSH and free T3 remained within the normal range throughout dosing, while mean values of Total/Free T4 and Total T3 were outside of the normal range between Day 7-15

Fig 2: Mean (±SEM) % Change From Baseline in Thyroid Hormones



PHARMACODYNAMICS: SHBG

- SHBG increased in a generally dose related manner, confirming liver target engagement
- Maximum % change was observed at Day 15 and was: ~8% (0.3 mg), ~62% (0.5 mg), ~36% (0.6 mg) and ~95% (1 mg)

PHARMACOKINETICS

- Plasma ALG-055009 exposures increased in a dose proportional manner with low variability (geometric CV < 30%) (Fig 3)
- Steady state concentrations were achieved by Day 5 with an accumulation ratio of ~2- fold, consistent with single dose PK (Fig 3, Table 2)

Fig 3: Mean (+SD) Plasma ALG-055009 Concentrations at Steady State (Day 14)

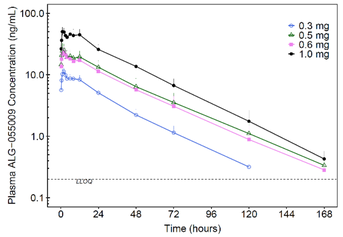


Table 2 : Plasma ALG-055009 PK Parameters at Steady State (Day 14)

ALG-055009 Dose (mg)	N	C_{min} (ng/mL)	AUC_{0-24} (ng.hr/mL)	T_{max} (hr)	C_{max} (ng/mL)
0.3	8	5.03 (16.4)	183(16.0)	2(1,2)	11.3(13.7)
0.5	8	12.8 (26.8)	423(25.0)	2(1,2)	24.9(26.1)
0.6	8	10.8 (35.5)	380(27.2)	2(1,2)	23.1(23.2)
1	8	25.3 (21.3)	922(20.8)	2(1,12)	51.3(15.7)

AUC, C_{min} and C_{max}: geometric mean (geometric CV%); T_{max}: median (min, max)

CONCLUSIONS

- Multiple ascending oral doses of ALG-055009 up to 1 mg x 14 days were well tolerated in subjects with hyperlipidemia
- ALG-055009 showed favorable PK with dose-proportional increases in exposure and low variability following repeat doses
- Favorable safety and anti-lipid effects were observed at doses ≤0.6 mg. These data support further evaluation in longer studies

ACKNOWLEDGMENTS

The authors wish to thank the subjects for participating in this clinical study. The Sponsor is grateful to the staff at Biotrial. The authors also wish to thank Aligos internal team members Chris Burnett and Genevieve Harrington for their assistance

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DISCLOSURES

Charfi H.: none. **Pinquier J-L.**: Davolterra, Cureteq, Sqy Therapeutic, Torskal, Ceres Brain, Abivax, Oncodesign, Jellynov, Theranexus. **Massetto B., Le K, Westland C., Kan-Eng I., Gupta K., Lai F., Venkatraman M., Blatt L.M., Beigelman L.N., Chanda S., McClure M., Fry J.**: Aligos employees

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