AASLD The Liver Meeting® Nov. 10-14, 2023

SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF MULTIPLE ASCENDING ORAL DOSES OF ALG-055009, A THYROID HORMONE RECEPTOR BETA AGONIST, IN HYPERLIPIDAEMIC SUBJECTS AND RELATIVE BIOAVAILABILITY/FOOD EFFECT OF A SOLID FORMULATION IN HEALTHY VOLUNTEERS

ALIGOS THERAPEUTICS

CHARFI Hakim [1]; PINQUIER Jean-Louis [1]; LE Kha [2]; WANG Stanley [2]; WESTLAND Christopher [2]; KAN-ENG Ifong [2]; GUPTA Kusum [2]; MOHAMMED Naqvi [2]; VENKATRAMAN Meenakshi [2]; BLATT Lawrence M. [2]; BEIGELMAN Leonid N. [2]; CHANDA Sushmita [2]; LIN Tse-I [2]; McCLURE Matthew [2]

1 – *Biotrial, France.* 2.– *Aligos Therapeutics, Inc, United States.*

Abstract #41459
Poster #2900-A

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 metabolic dysfunction-associated steatohepatitis (MASH) by decreasing hepatic fat content and improving liver histology, as evidenced by recent Phase 3 data for the THR-β agonist resmetirom.[3]
- ALG-055009 is a THR-β agonist that in preclinical models had:
  - High selectivity for THR-β over THR-α
  - Nanomolar potency (EC_{50} = 50 nM) in cell-based assays that is 5-50x more potent than other THR-β drugs in development[4]
  - High efficacy (i.e., reductions in total cholesterol and/or low-density lipoprotein cholesterol (LDL-C)) 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 3-part, first-in-human study (NCT05090111).

- Across Parts 1 and 2 (double-blind, randomized, placebo-controlled), single (≤4 mg) and multiple (0.3, 0.5, 0.6 and 1.0 mg x 14 days) ascending oral doses of ALG-055009 (in a polyethylene glycol-containing solution formulation) were evaluated in HV and subjects with mild hyperlipidemia, respectively, and these data were previously reported.[7,8] An additional Part 2 cohort at the 0.75 mg dose level has since been evaluated. In each Part 2 cohort, 10 subjects were randomized to receive 14 once daily oral doses of ALG-055009 (N=8) or placebo (N=2) in a fasted state.
- Part 3 (open label) assessed in HV the relative bioavailability of a softgel capsule vs. solution formulation of ALG-055009 and food effect (softgel capsule). 8 subjects received single 0.6 mg ALG-055009 doses in a fixed sequence: solution (fasted), softgel capsule (fasted) and softgel capsule (fed), with a ≥10-day washout between doses.
- For all parts, subjects were followed for 2 weeks after last dose
- Key Inclusion Criteria:
  - LDL-C >110 mg/dL (Part 2)
  - 18-55 years, body mass index (BMI) 18-32.0 kg/m^2 (Part 3)
- 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 and Part 3.

RESULTS

BASELINE CHARACTERISTICS

In Part 2, the baseline characteristics were generally similar across cohorts (Table 1).

In Part 3, 75% of the subjects were male, with mean (SD) age of 39.1 (8.3) years and mean (SD) BMI of 24.7 kg/m^2 (2.9).

Table 1: Part 2 Demographics and Baseline Characteristics

ALG-055009 Dose	PBO	0.3 mg	0.5 mg	0.6 mg	0.75 mg	1 mg
N	10	8	8	8	8	8
Age, years, mean (SD)	43.2 (14.5)	39.1 (11.6)	49.4 (10.9)	41.4 (11.6)	37.4 (11.8)	33.4 (13.6)
Male, N (%)	10 (100%)	7 (87.5%)	6 (75%)	8 (100%)	8 (100%)	8 (100%)
Non-Hispanic, N (%)	10 (100%)	8 (100%)	8 (100%)	8 (100%)	7 (87.5%)	7 (87.5%)
BMI, kg/m^2, mean (SD)	25.9 (3.3)	28.1 (2.2)	28.4 (3.8)	27.1 (3.1)	25.3 (4.1)	24.7 (3.9)
LDL, mg/dL, mean (SD)	145 (36.0)	142 (28.4)	151 (28.2)	142 (16.6)	132 (20.0)	126 (13.7)

PBO = Placebo. SD= Standard Deviation.

SAFETY

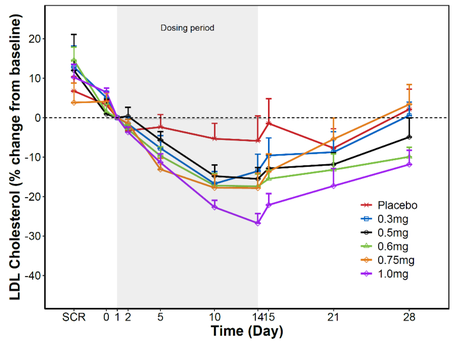
Administration of ≤1.0 mg ALG-055009 for 14 days in subjects with mild hyperlipidemia and a single 0.6 mg ALG-055009 dose (fasted or fed) in HV was well tolerated

- 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
- In Part 2, the most common TEAEs (≥2 subjects) were:
  - Insomnia (N=2; 0.3 mg)
  - Headache (N=5; N=2 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=3; N=1 PBO, N=1 0.6 mg; N=1 1.0 mg)
- In Part 3, TEAEs occurring in ≥2 subjects included: nasopharyngitis (N=3) and diarrhea (N=2)
- 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

- In Part 2, generally dose-related declines in LDL-C were observed, with the highest reductions at the 1.0 mg dose level (Fig 1). Similar dose-related declines were observed with triglycerides & Apo-Lipoprotein B.

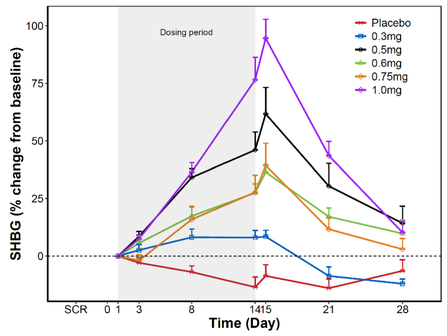
Fig 1: Mean (± SEM) % Change from Baseline in LDL-C



PHARMACODYNAMICS: SHBG

- In Part 2, SHBG increased in a generally dose-related manner, confirming liver target engagement, with the highest percent change from baseline (~95%) occurring at the 1.0 mg dose level (Fig 2)

Fig 2: Mean (± SEM) % change from Baseline in SHBG



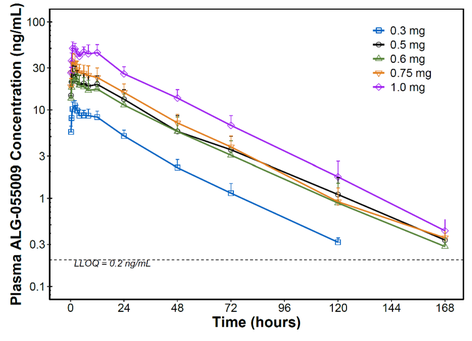
PHARMACODYNAMICS: Thyroid Hormones

- Transient, dose-dependent thyroid hormone level reductions were observed. Mean hormone levels remained within or near the normal range for doses ≤0.75mg. At all dose levels, hormone levels returned to baseline within 2 weeks of stopping study drug and there was no evidence of thyroid dysfunction; specifically, no changes to cardiovascular parameters (e.g., heart rate, blood pressure) were observed.

PHARMACOKINETICS

- In Part 2, plasma ALG-055009 exposures increased in a dose proportional manner with low variability (geometric CV <30%) and a terminal $t_{1/2}$ of ~20 hours (Fig 3, Table 2)
- Steady state concentrations were achieved by Day 5 with an accumulation ratio of ~2-fold, consistent with single dose PK

Fig 3: Mean (SD) Plasma ALG-055009 Concentrations at Steady State (Day 14) Following Multiple Doses in Subjects with Hyperlipidemia



PHARMACOKINETICS

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

ALG-055009 Dose	0.3 mg	0.5 mg	0.6 mg	0.75 mg	1 mg
N	8	8	8	8	8
C_{min} (ng/mL)	5.03 (16.4)	12.8 (26.8)	10.8 (35.5)	15.4 (27.2)	25.3 (21.3)
AUC_{0-24} (ng.hr/mL)	183 (16.0)	423 (25.0)	380 (27.2)	533 (26.5)	922 (20.8)
T_{max} (hr)	2 (1,2)	2 (1,2)	2 (1,2)	2 (1,2)	2 (1,12)
C_{max} (ng/mL)	11.3 (13.7)	24.9 (26.1)	23.1 (23.2)	33.9 (28.7)	51.3 (15.7)

AUC_{0-24}, C_{min} and C_{max}: geometric mean (geometric CV%); T_{max}: median (min, max)

- In Part 3, geometric mean ratios for all parameters (C_{max}, AUC_t, AUC_{inf}) were 86% for softgel capsule vs. solution formulations, and 97%, 106%, and 106%, respectively, for softgel capsule exposures in fed vs. fasting conditions. All 90% confidence intervals were within the 80-125% bioequivalent range.

CONCLUSIONS

- Multiple oral doses of ALG-055009 (0.3 – 1.0 mg solution) x 14 days demonstrated a favorable safety, PK and PD profile in subjects with hyperlipidemia, supporting further evaluation in longer term studies
- The softgel capsule formulation (to be used in Phase 2a) delivers 86% of the exposures observed with the solution formulation and has no associated food effect
- Startup of a double-blind, randomized, Phase 2a study evaluating up to 4 dose levels of ALG-055009 vs. placebo for 12 weeks in MASH patients with liver fibrosis (F1-F3) has been initiated with topline data expected in Q4 2024.

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 Genevieve Harrington and Megan Fitzgerald for their assistance.

REFERENCES

1. Sinha RA et al. Nat Rev Endocrinol. 2018; 14 (5): 259-269
2. Pramfalk C. et al. Biochim & Biophys Acta 2011; 1812: 929-937
3. Harrison S. et al. EASL 2023. Abstract #GS-001.
4. Gupta K. et al. AASLD 2020 Publication Number 1656
5. Deval J. et al. AASLD 2019 Abstract #2149
6. Gupta K. et al. AASLD 2021. Abstract #1932
7. Charfi H. et al. EASL 2022 Abstract #SAT-145
8. Charfi H. et al. APASL 2023 Abstract #1213

DISCLOSURES

Charfi H.: none. **Pinquier J-L.**: Sqy Therapeutic, Torskal, Ceres Brain, Oncodesign, Jellynov, Servier. **Le K, Wang S., Westland C., Kan-Eng I., Gupta K., Mohammmed N., Venkatraman M., Blatt L.M., Beigelman L.N., Lin TL., Chanda S., McClure M.**: Aligos employees

CONTACT INFORMATION

Stanley Wang (swang@aligos.com)