Pharmacodynamics of Multiple Ascending Oral Doses of ALG-055009, a THR-β Agonist, in Hyperlipidemic Subjects

P-0368

Hakim Charfi[1], Jean-Louis Pinquier[1], Megan Fitzgerald[2], Stanley Wang[2], Kha Le[2], Ifong Kan-Eng[2], Doug Clark[2], Naqvi Mohammed[2], Meenakshi Venkatraman[2], Lawrence Blatt[2], Tse-I Lin[3], Sushmita Chanda[2], Matthew McClure[2]

[1]Biotrial, France; [2]Aligos Therapeutics, Inc., United States; [3]Aligos Belgium BV, Belgium

Background

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 agonists 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]

Methods

Study Design and Aims

ALG-055009-301 is a completed first-in-human Phase 1 study (NCT05090111) combining evaluation of single-ascending doses (SAD) in healthy volunteers (Part 1), multiple-ascending doses (MAD) in subjects with mild hyperlipidemia (Part 2), and the relative bioavailability/food effect (Part 3) of a softgel formulation in healthy volunteers. The primary aim was to evaluate the safety, PK, and pharmacodynamics (PD) of ALG-055009 in healthy volunteers (HVs) and in subjects with mild hyperlipidemia.

Across Parts 1-3, single (≤4.0 mg) and multiple (≤1.0 mg x 14 days) once daily oral solution doses of ALG-055009 were evaluated in HVs and subjects with mild hyperlipidemia (HL; LDL-C >110 mg/dL), respectively, and these safety data were previously reported.[7,8,9] Reported here are pharmacodynamic data from Part 2.

For each MAD cohort in Part 2:

- 10 HL subjects were randomized to ALG-055009 or placebo in a 4:1 ratio
- Subjects were dosed once daily for 14 days, and followed for 2 weeks after last dose
- 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

Key Inclusion Criteria (Part 2):

- 18-65 years
- Body mass index (BMI) of 18-35.0 kg/m^2
- LDL-C >110 mg/dL

Key Exclusion Criteria:

- TSH (thyrotropin) and Free Thyroxine (T4) > ULN

Pharmacodynamic Analysis

- Levels of SHBG and (fasting) serum lipids, including LDL-C, triglycerides, apolipoprotein-B, very low-density lipoprotein (VLDL), non-high-density lipoprotein (HDL) cholesterol and total cholesterol, were evaluated as key biomarkers for activity of ALG-055009
- Timepoints evaluated for lipid panels: predose Day 1, Day 2, Day 5, Day 10, predose Day 14, Day 14, Day 21, Day 28
- Timepoints evaluated for SHBG: predose Day 1, Day 3, Day 7, predose Day 14, Day 15, Day 21 and Day 28

Results

Part 2: Dose Levels Evaluated

Across 5 cohorts, multiple oral doses (x 14 days) were evaluated: 0.3, 0.5, 0.6, 0.75 and 1.0 mg.

Part 2: Baseline Characteristics

In Part 2, 50 HL subjects (94% male, mean age 41 years, mean BMI 26.5 kg/m^2) were enrolled across 5 cohorts. The baseline characteristics were generally well balanced across cohorts.

ALG-055009 Dose	Placebo	0.3 mg	0.5 mg	0.6 mg	0.75 mg	1.0 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 (75.0)	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 (3.27)	28.1 (2.20)	28.4 (3.80)	27.1 (3.12)	25.3 (4.10)	24.7 (3.86)
LDL, mg/dL, (mean (SD))	145.0 (36.0)	141.7 (28.4)	150.5 (28.2)	142.0 (16.7)	132.2 (20.0)	125.8 (13.7)

SD = Standard Deviation

Safety

Multiple (≤1.0 mg x 14 days) oral solution doses of ALG-055009 were well tolerated with no reported serious adverse events or TEAEs leading to premature study drug discontinuation. TEAEs were mild to moderate, and none were clearly dose related, as previously reported.[9] No clinically significant trends or findings have been observed with respect to any TEAEs, laboratory results, physical examinations, vital signs, or ECGs.

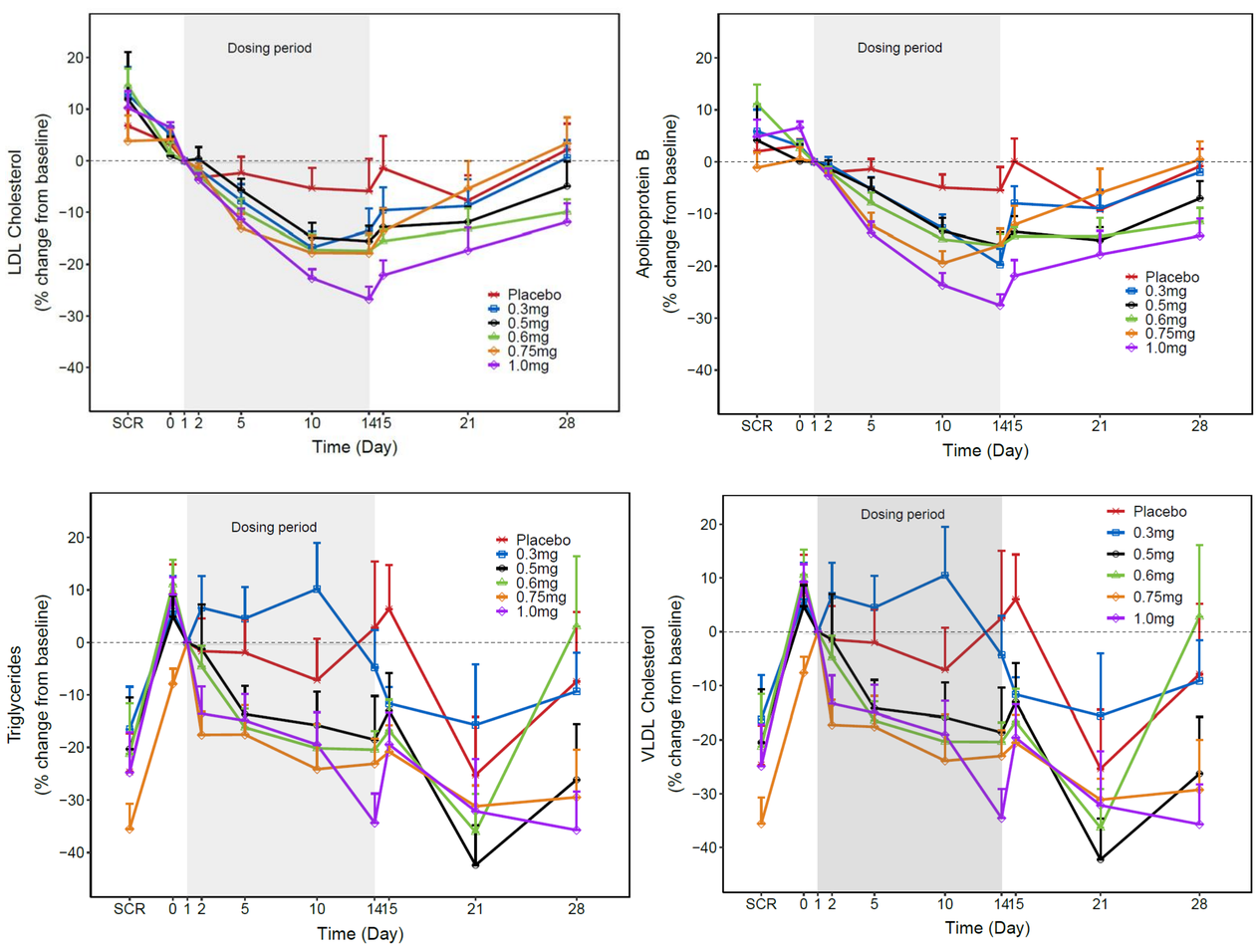
Results

Pharmacodynamics

Lipids

Daily dosing with ALG-055009 for 14 days resulted in generally dose-dependent decreases in LDL-C, apolipoprotein-B, VLDL, and triglycerides throughout the dosing period, followed by a return to baseline by the end of the study at Day 28 (Figure 1). The highest reductions were generally observed at 1.0 mg ALG-055009, with maximum decreases from baseline of 26.8%, 27.6%, 35.7%, and 35.7% in LDL-C, apolipoprotein-B, VLDL and triglycerides, respectively. For other lipids evaluated (e.g., total cholesterol and non-HDL cholesterol), levels were either unaffected or the effect was modest.

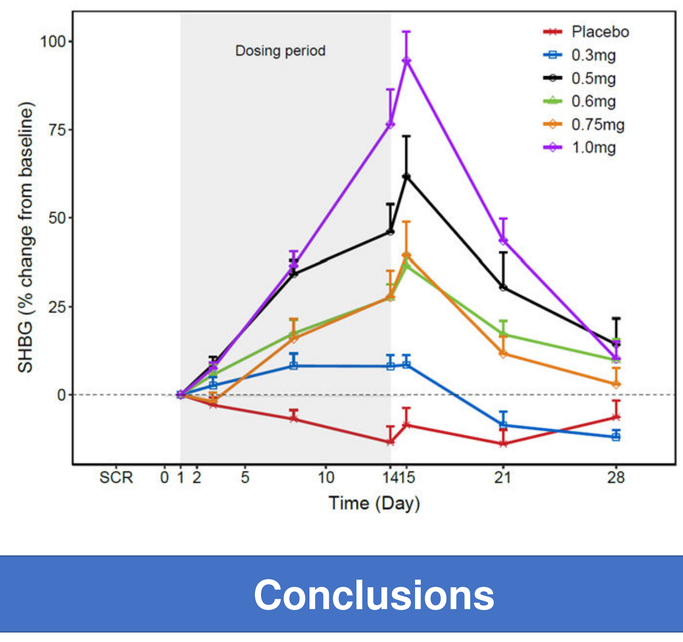
***Figure 1*. Mean (±SD) Percent Change in LDL-C, Apolipoprotein-B, Triglycerides, VLDL Levels from Baseline in Part 2 Subjects**



SHBG

A dose-dependent increase in sex hormone binding globulin (SHBG), a marker of target engagement in the liver, of up to 95% relative to baseline was also observed (Figure 2).

***Figure 2*. Mean (±SD) Percent Change in SHBG Levels from Baseline in Part 2 Subjects**



Conclusions

Favorable, dose-dependent pharmacodynamic effects on atherogenic lipids and SHBG were observed with multiple dosing of ALG-055009 in HL subjects. Importantly, reductions in both LDL-C and apolipoprotein-B were observed along with reductions in liver fat content in a Phase 2 study of the THR-β agonist resmetirom in NASH patients.[10] In accordance with these Phase 2 results, data from the 52-week Phase 3 study of resmetirom has shown significant reductions in both hepatic fat content and LDL-C. [3] Therefore, ALG-055009-induced decreases in LDL-C and apolipoprotein-B may correspond to a reduction in liver fat content in MASH patients in planned studies of longer treatment duration, including the ongoing Phase 2a HERALD study.

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 SA. et al. NEJM. 2024; 390 (6): 497-508.
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
9. Charfi H. et. al. AASLD 2023 Abstract #41459
10. Harrison SA. et al. Lancet. 2019; 394 (10213): 2012-2024.

Acknowledgements

The authors wish to thank the subjects for participating in this clinical study, and the staff at Biotrial for assisting in the conduct of this study.

Contact: Megan Fitzgerald, mfitzgerald@aligos.com