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ALG-055009, a novel thyroid hormone receptor beta agonist, demonstrated significant reductions in atherogenic lipids/lipoproteins, including lipoprotein (a), in patients with presumed metabolic dysfunction-associated steatohepatitis in the Phase 2a HERALD Study

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ALIGOS THERAPEUTICS

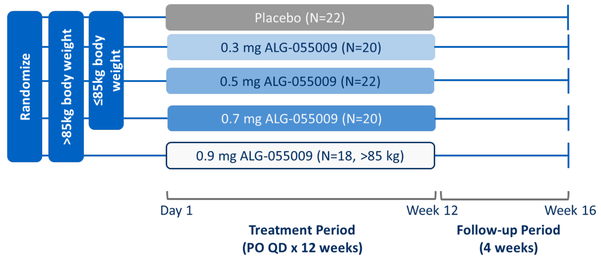
BACKGROUND AND AIMS

Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) are associated with atherogenic dyslipidemia, with cardiovascular disease (CVD) being the leading cause of mortality in this patient population. While statins reduce low density lipoprotein cholesterol (LDL-C), they have no effect on lipoprotein (a) (Lp(a)), an independent risk factor for CVD.[1,2] Thyroid hormones play a critical role in the regulation of lipid metabolism, with thyroid dysfunction being associated with both MASLD/MASH and dyslipidemia. ALG-055009 is a novel next generation thyroid hormone receptor (THR)-beta agonist with beta selectivity and in vitro potency exceeding that of first generation THR-beta drugs. In the randomized, double-blind, placebo-controlled Phase 2a HERALD study (NCT06342947), 12 weeks of once daily ALG-055009 treatment in subjects with presumed MASH and F1-F3 fibrosis was well-tolerated and met the primary endpoint, demonstrating significant reductions (up to 46% placebo-adjusted median relative reductions) in liver fat.[3] An analysis of the effects of ALG-055009 compared to placebo on lipid/lipoprotein levels, including Lp(a), a key secondary endpoint, is reported here.

METHODS

- In the Phase 2a HERALD study, 102 subjects (~20 subjects/arm) were randomized to receive 0.3, 0.5, 0.7 or 0.9 mg ALG-055009 or placebo, orally once daily for 12 weeks (Figure 1). Only subjects with body weight >85 kg were enrolled in the 0.9 mg arm, with no weight restrictions for other arms.
- Blood samples were collected at baseline, Week 6, Week 12 and post-treatment Week 4 to evaluate change from baseline in levels of the following lipid/lipoproteins: total cholesterol, high density lipoprotein cholesterol, LDL-C, non-HDL-C, triglycerides (TG), apolipoprotein B (apoB), apolipoprotein A1, apolipoprotein CIII (apoCIII), Lp(a), and very low-density lipoprotein cholesterol (VLDL).

Figure 1. HERALD Study Design



BASELINE CHARACTERISTICS

Baseline characteristics were generally balanced across treatment arms (Table 1).

Table 1. Baseline Characteristics

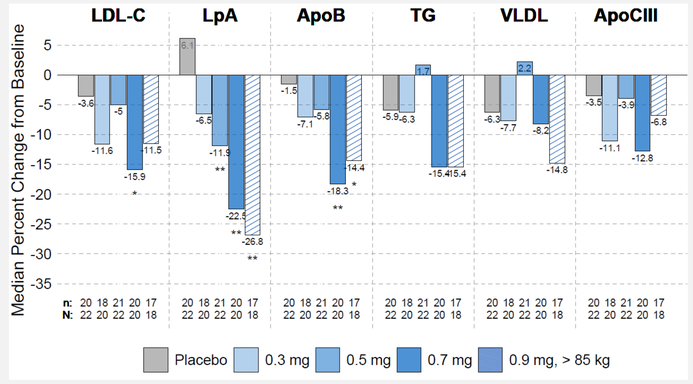
	Placebo (N=22)	ALG-055009 0.3 mg (N=20)	ALG-055009 0.5 mg (N=22)	ALG-055009 0.7 mg (N=20)	ALG-055009 0.9 mg* (N=18, >85 kg)
Age, mean (years)	48.5	53.3	49.5	51.4	48.1
Female, n (%)	21 (95.5)	12 (60.0)	8 (36.4)	14 (70.0)	8 (44.4)
BMI, mean (kg/m²)	42.1	37.8	39.0	37.4	40.2
Type 2 Diabetes, n (%)	11 (50.0)	9 (45.0)	10 (45.5)	10 (50.0)	7 (38.9)
Dyslipidemia, n (%)	13 (59.1)	11 (55.0)	10 (45.5)	11 (55.5)	10 (55.6)
GLP-1 Agonists, n (%)**	4 (18.2)	3 (15.0)	5 (22.7)	5 (25.0)	1 (5.6)
Statins, n (%)**	4 (18.2)	11 (55.0)	7 (31.8)	8 (40.0)	6 (33.3)
LDL-C, mean (mg/dL)	113.8	99.9	105.6	97.1	97.3
Lp(a), mean (nmol/L)	40.7	22.8	27.1	30.0	34.3
ApoB, mean (mg/dL)	102.0	98.1	94.9	96.3	91.6
TG, mean (mg/dL)	152.6	179.4	153.5	164.7	164.9
VLDL, mean (mg/dL)	30.5	35.9	30.7	31.2	32.9
ApoCIII, mean (mg/dL)	10.0	11.2	9.7	10.7	10.1

BMI = body mass index; GLP-1 = glucagon-like peptide-1
*Only subjects weighing >85 kg were enrolled in the 0.9 mg dose group; no body weight restrictions for other dose groups
**Subjects on GLP-1 agonists and statins required to have stable use (≥12 weeks prior to randomization); majority with stable GLP-1 use were on them for >1 year

RESULTS

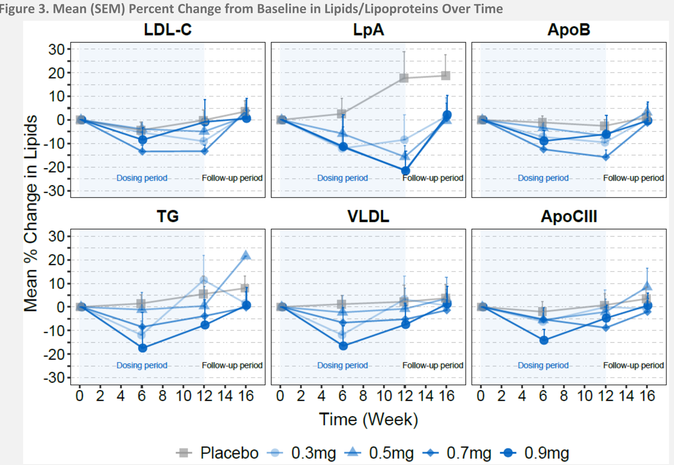
- Statistically significant median reductions compared to baseline at Week 12 in levels of LDL-C, Lp(a) and apoB for ALG-055009 vs. placebo were observed at the highest ALG-055009 dose levels evaluated; reductions in triglycerides, VLDL and apoCIII were also observed (Figure 2). Continuous declines in Lp(a) observed during the dosing period at the highest ALG-055009 dose levels (Figure 3).

Figure 2. Median Percent Change from Baseline in Lipids/Lipoproteins at Week 12



n: number of subjects with available data at week 12; N: number of subjects in Full Analysis Set; *p<0.05 **p<0.01.

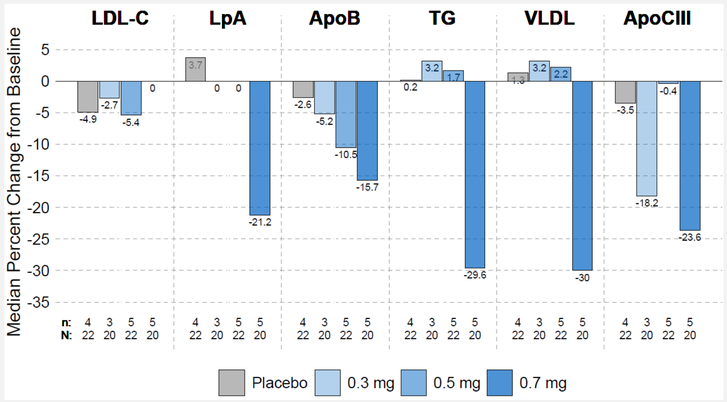
Figure 3. Mean (SEM) Percent Change from Baseline in Lipids/Lipoproteins Over Time



SEM = standard error of the mean

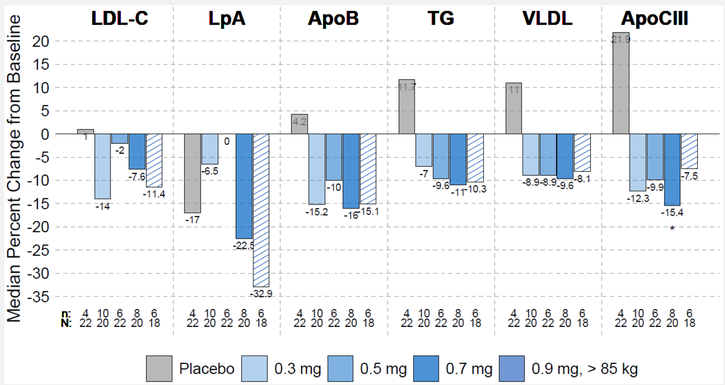
- Additional lipid/lipoprotein reductions were observed in subjects with stable GLP-1 agonist (Figure 4) or statin (Figure 5) use.

Figure 4. Median Percent Change from Baseline in Lipids/Lipoproteins at Week 12 for Subjects with Stable GLP-1 Agonist Use



n: number of subjects with available data at week 12; N: number of subjects in Full Analysis Set; data for 0.9 mg group not presented as there was not sufficient data (n=1 subject at this dose level)

Figure 5. Median Percent Change from Baseline in Lipids/Lipoproteins at Week 12 for Subjects with Stable Statin Use



n: number of subjects with available data at week 12; N: number of subjects in Full Analysis Set

CONCLUSIONS

- **Statistically significant improvements in atherogenic lipids were achieved with 12 weeks of ALG-055009 treatment.**
- **Reductions in lipids/lipoproteins were observed even in the context of stable GLP-1 agonist or statin use.**
- **This data suggests an added benefit of ALG-055009 for patients at risk for CVD in addition to the previously reported liver fat lowering properties in a MASLD/MASH population.**
- **This data supports evaluation of longer duration ALG-055009 treatment in a dedicated clinical trial of patients with dyslipidemia (including those with MASLD/MASH) to better characterize the extent of reduction in atherogenic lipids/lipoproteins.**

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