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ALG-055009, a novel thyroid hormone receptor beta (THR-beta) agonist, demonstrated robust reductions in liver fat at Week 12 across subgroups including glucagon-like peptide-1 (GLP-1) receptor agonist users in non-cirrhotic MASH patients in the Phase 2a HERALD study

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ALIGOS THERAPEUTICS

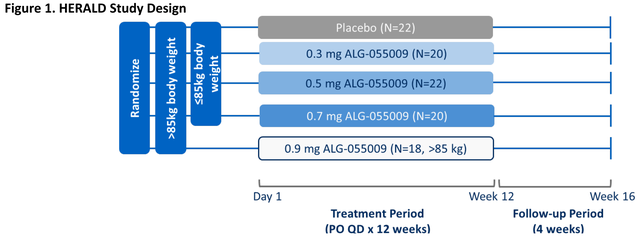
BACKGROUND AND AIMS

ALG-055009, a next generation THR-beta agonist with enhanced beta selectivity and in vitro potency, previously demonstrated favourable Phase 1 safety, pharmacokinetic (PK) and pharmacodynamic (PD) effects in healthy volunteers/hyperlipidemic subjects. In the Phase 2a HERALD (NCT06342947) randomized, double-blind, placebo-controlled study, the efficacy, safety, PK and PD of 12-week once daily ALG-055009 were evaluated in non-cirrhotic adults with presumed MASH and F1-F3 fibrosis. As reported previously, the primary endpoint was met, demonstrating significant reductions in liver fat.[1] Subgroup analyses for the primary endpoint are reported here, including those associated with a worse prognosis (e.g., type 2 diabetes).

METHOD

- In the Phase 2a HERALD study, 102 subjects (~20/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.
- MRI-PDFF measurements were taken at baseline and Week 12 to evaluate the change from baseline in liver fat content.
- The primary endpoint was relative change from baseline in liver fat by MRI-PDFF at Week 12 and was analyzed across subgroups, defined according to baseline characteristics, e.g., gender, body weight, PNPLA3 genotype, GLP-1 agonist use, statin use and type 2 diabetes status.

Figure 1. HERALD Study Design



Subjects >85 kg randomized 1:1:1:1:1 to placebo, 0.3 mg, 0.5 mg, 0.7 mg and 0.9 mg ALG-055009 arms
Subjects ≤85 kg randomized 1:1:1:1 to placebo, 0.3 mg, 0.5 mg and 0.7 mg ALG-055009 arms

BASELINE CHARACTERISTICS

Baseline characteristics were generally comparable across arms and representative of the MASH patient population.

Table 1. Baseline Characteristics

	Placebo (N=22)	ALG-055009			
		0.3 mg (N=20)	0.5 mg (N=22)	0.7 mg (N=20)	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)
Hispanic, n (%)	13 (59.1)	9 (45.0)	8 (36.4)	8 (40.0)	9 (50.0)
BMI, mean (kg/m^2)	42.1	37.8	39.0	37.4	40.2
Weight, mean (kg)	109.1	107.0	115.2	106.4	116.5*
MRI-PDFF, mean (%)	18.6	18.2	17.9	19.4	19.0
Type 2 Diabetes, n (%)	11 (50.0)	9 (45.0)	10 (45.5)	10 (50.0)	7 (38.9)
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)

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 BW restrictions for other dose groups
**Subjects on GLP-1 agonists and statins required to have stable use (≥12 weeks prior to randomization); time of GLP-1 use before first dose of study drug was >1 year for the majority of subjects with stable GLP-1 use

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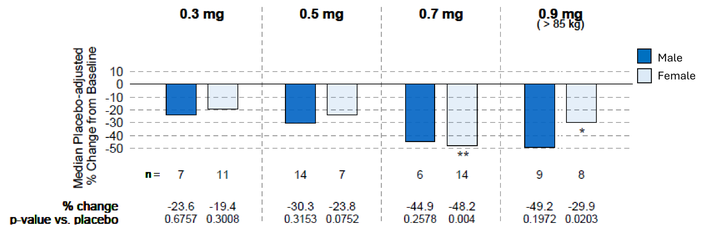
RESULTS: SUBGROUP ANALYSES

- ALG-055009 dose groups met the primary endpoint, with statistically significant placebo-adjusted median relative reductions in liver fat of up to 46.2% at Week 12.
- Efficacy was observed across the baseline factors evaluated (Figures 2-7), with statistically significant median liver fat reductions for ALG-055009 compared to placebo at the highest dose levels evaluated.
- No clinically relevant difference in liver fat reductions were observed defined according to baseline characteristics (e.g., gender, body weight, GLP-1 agonist use, statin use, type 2 diabetes status, PNPLA3 genotype).

GENDER

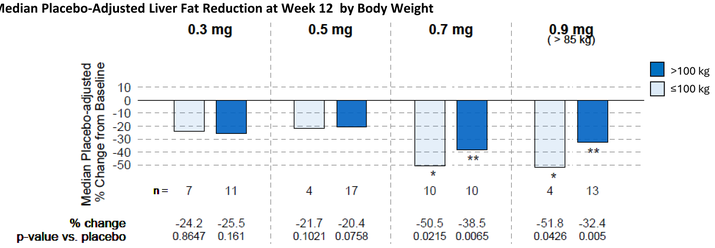
Figure 2. Median Placebo-Adjusted Liver Fat Reduction at Week 12 by Gender



n = number of subjects; *p<0.05, **p<0.01

BODY WEIGHT

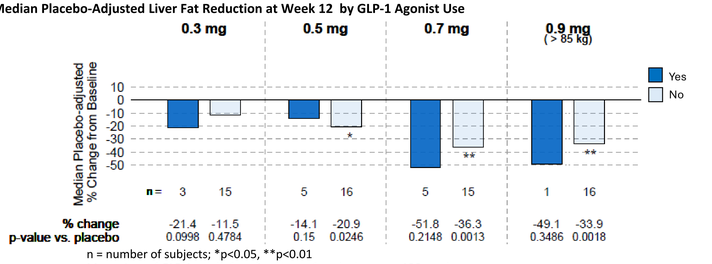
Figure 3. Median Placebo-Adjusted Liver Fat Reduction at Week 12 by Body Weight



n = number of subjects; *p<0.05, **p<0.01

GLP-1 AGONIST USE

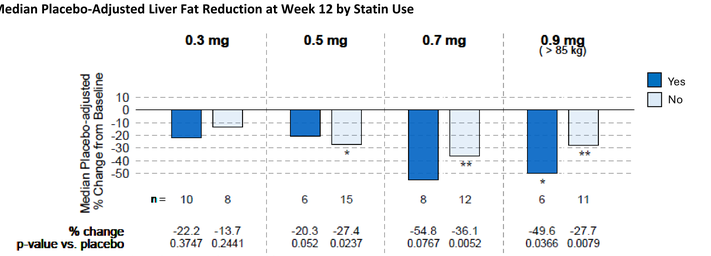
Figure 4. Median Placebo-Adjusted Liver Fat Reduction at Week 12 by GLP-1 Agonist Use



n = number of subjects; *p<0.05, **p<0.01
Mean time of GLP-1 use before first dose of study drug was 130 weeks

STATIN USE

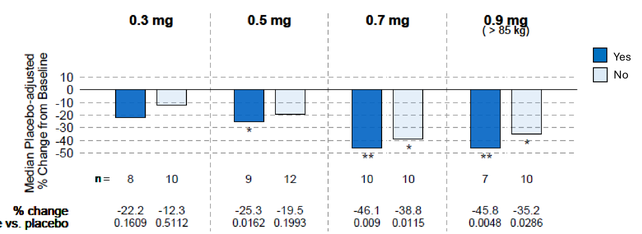
Figure 5. Median Placebo-Adjusted Liver Fat Reduction at Week 12 by Statin Use



n = number of subjects; *p<0.05, **p<0.01

TYPE 2 DIABETES STATUS

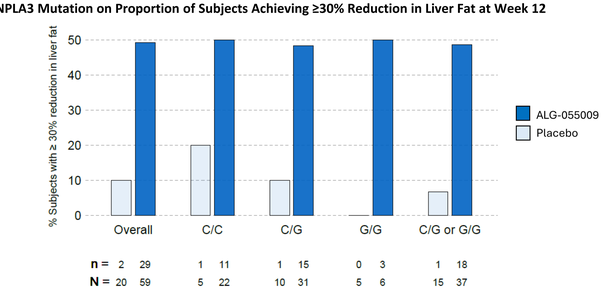
Figure 6. Median Placebo-Adjusted Liver Fat Reduction at Week 12 by Type 2 Diabetes Status



n = number of subjects; *p<0.05, **p<0.01

PNPLA3 GENOTYPE

Figure 7. Effect of PNPLA3 Mutation on Proportion of Subjects Achieving ≥30% Reduction in Liver Fat at Week 12



Pooled ALG-055009 dose groups of 0.3, 0.5, 0.7 and 0.9 mg
n = number of responders; N = number of subjects

CONCLUSION

- **Substantial, dose-dependent reductions (up to 46.2% placebo-adjusted median relative reductions) in liver fat were observed across all key subgroups with 12 weeks of once daily ALG-055009 treatment.**
- **Notably, there was no impact of PNPLA3 genotypes, including the G/G mutation associated with a higher disease severity, on the proportion of subjects with relative reduction of liver fat content ≥30% at Week 12. [2,3]**
- **There were no clinically relevant differences in liver fat reduction among participants with or without GLP-1 agonist use.**
- **These results support evaluation of longer durations of ALG-055009 and indicate liver fat reductions with ALG-055009 may be observed across various baseline characteristics in the MASH patient population, including those associated with a worse prognosis.**

REFERENCES

1. Loomba R et al. AASLD 2024 Late Breaking Abstract #5013.
2. Romeo S et al. Nat Genet 2009; 40:1461-1465.
3. Vilar-Gomez E, et al. Hepatology 2022; 76(5):1482-1494.

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