Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Single and Multiple Ascending Oral Doses of ALG-055009, a Thyroid Hormone Receptor Beta (THR-β) Agonist for the Treatment of Non-Alcoholic Steatohepatitis (NASH), in Healthy Volunteers and Subjects with Hyperlipidaemia

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Abstract #1213

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 fatty liver by decreasing hepatic fat content and improving liver histology[3]
- ALG-055009 is a THR-β agonist that in preclinical models demonstrated:
  - High selectivity for THR-β and nanomolar potency[4]
  - High efficacy in diet-induced obese rat and mouse models[4,5]
  - A favorable PK profile with low plasma clearance, metabolic stability, high oral bioavailability and a long plasma half-life[5,6]

Methods

ALG-055009-301 is a multi-part, double blind, randomized, placebo controlled first-in-human study (NCT05090111) conducted at a single clinical pharmacology unit in France (Biotrial, Rennes, France).

Parts 1 and 2 evaluated single ascending doses (SAD) in healthy volunteers (HV) and multiple ascending doses (MAD) in subjects with mild hyperlipidemia, respectively.

- Part 1 (SAD):
  - Each cohort was comprised of 8 subjects randomized to receive a single oral dose of ALG-055009 (N=6) or placebo (N=2) in a fasted state and followed for 2 weeks after being dosed
  - Key Eligibility Criteria:
    - Inclusion: age 18-55 years, body mass index (BMI) 18-32.0 kg/m^2
    - Exclusion: Thyrotropin (TSH) or Free Thyroxine (T4) >upper limit of normal (ULN), alanine or aspartate aminotransferase (ALT or AST) >ULN
- Part 2 (MAD):
  - 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 last dose.
  - Key Eligibility Criteria:
    - Inclusion: Low Density Lipoprotein cholesterol (LDL-C) >110 mg/dL
    - Exclusion: TSH and T4 >ULN
- Throughout the study, safety assessments, treatment emergent adverse events [TEAEs], vital signs, electrocardiogram [ECG] and laboratories (including thyroid hormones), PK, and pharmacodynamic (PD) markers (including Sex Hormone Binding Globulin [SHBG] and lipids) were collected and analyzed
- Plasma concentrations of ALG-055009 were quantified by validated liquid chromatography–tandem mass spectrometry
- Here we report data from all Part 1 and 2 cohorts

Results

BASELINE CHARACTERISTICS

The baseline characteristics were generally similar across cohorts, except for BMI, LDL-C, triglycerides, and apolipoprotein-B that were more elevated among subjects enrolled in the MAD cohorts.

Table 1: Demographics and Baseline Characteristics

	SAD						MAD				
ALG-055009 Dose Level	**PBO**	**0.1 mg**	**0.3 mg**	**0.9 mg**	**2.6 mg**	**4 mg**	**PBO**	**0.3 mg**	**0.5 mg**	**0.6 mg**	**1 mg**
N	**N=10**	**N=6**	**N=6**	**N=6**	**N=6**	**N=6**	**N=8**	**N=8**	**N=8**	**N=8**	**N=8**
Age (years), mean (SEM)	42.2 (3.3)	41.7 (2.7)	35.7 (4.7)	30.7 (4.5)	35.2 (5.5)	38.8 (4.9)	41.3 (5.5)	39.1 (4.1)	49.4 (3.9)	41.4 (4.1)	33.4 (4.8)
Male, N (%)	10 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	8 (100%)	7 (87.5%)	6 (75%)	8 (100%)	8 (100%)
Non-Hispanic, N (%)	10 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	7 (87.5%)
BMI, kg/m^2, mean (SEM)	25.7 (0.9)	25.4 (1.0)	25.7 (1.9)	23.0 (1.3)	25.0 (1.1)	24.7 (1.0)	25.6 (1.3)	28.1 (0.8)	28.4 (1.3)	27.1 (1.1)	24.7 (1.4)
Weight, kg, mean (SEM)	82.2 (3.1)	80.6 (4.7)	83.3 (6.5)	69.3 (7.1)	83.2 (5.2)	76.2 (1.6)	80.7 (5.6)	85.8 (2.5)	84.5 (4.8)	88.4 (4.5)	78.4 (5.4)
Free T4, ng/dL, mean (SEM)	1.3 (0.1)	1.2 (0.1)	1.3 (0.1)	1.3 (0.1)	1.3 (0.1)	1.3 (0.03)	1.1 (0.1)	1.2 (0.03)	1.1 (0.03)	1.2 (0.1)	1.1 (0.02)
Free T3, pg/dL, mean (SEM)	328.5 (7.9)	343.9 (8.0)	322.2 (10.2)	350.5 (19.9)	325.5 (14.6)	335.5 (15.0)	295.5 (7.8)	318.0 (20.7)	296.7 (7.3)	295.5 (8.0)	300.5 (12.6)
TSH, mIU/L, mean (SEM)	1.6 (0.1)	2.1 (0.3)	1.5 (0.2)	2.2 (0.5)	2.3 (0.3)	1.7 (0.3)	1.3 (0.2)	2.1 (0.3)	1.6 (0.3)	1.4 (0.2)	1.8 (0.2)
SHBG, nmol/L, mean (SEM)	36.4 (4.1)	40.4 (5.0)	33.7 (5.6)	33.7 (5.6)	36.9 (3.9)	39.1 (6.0)	36.6 (3.6)	37.4 (16.3)	42.2 (6.3)	36.3 (3.9)	31.1 (4.2)
LDL-C, mg/dL, mean (SEM)	133.8 (12.4)	123.0 (12.3)	125.9 (13.5)	125.4 (16.0)	144.9 (14.3)	129.6 (15.7)	147.9 (13.9)	141.7 (10.1)	150.5 (10.0)	142.0 (5.9)	125.8 (4.8)
TG, mg/dL, mean (SEM)	127.7 (11.2)	99.1 (27.1)	116.0 (22.1)	111.9 (7.2)	82.1 (9.1)	117.8 (21.9)	125.2 (14.8)	160.8 (22.1)	173.9 (33.2)	153.6 (27.7)	123.4 (10.1)
Apo-B, mg/dL, mean (SEM)	105.7 (9.3)	93.5 (10.8)	98.7 (11)	92.3 (9.7)	87.8 (9.8)	97.8 (9.8)	113.0 (8.4)	113.0 (4.6)	117.6 (5.4)	112.6 (5.2)	96.6 (3.7)

PBO = Placebo. SEM = Standard Error of the Mean. TSH = Thyrotropin. SHBG = Sex Hormone Binding Globulin. LDL-C=Low Density Lipoprotein-Cholesterol. TG = Triglycerides. Apo-B= Apolipoprotein B.

SAFETY

Administration of single doses of up to 4 mg, or up to 1 mg for 14 days of ALG-055009 or placebo was well tolerated:

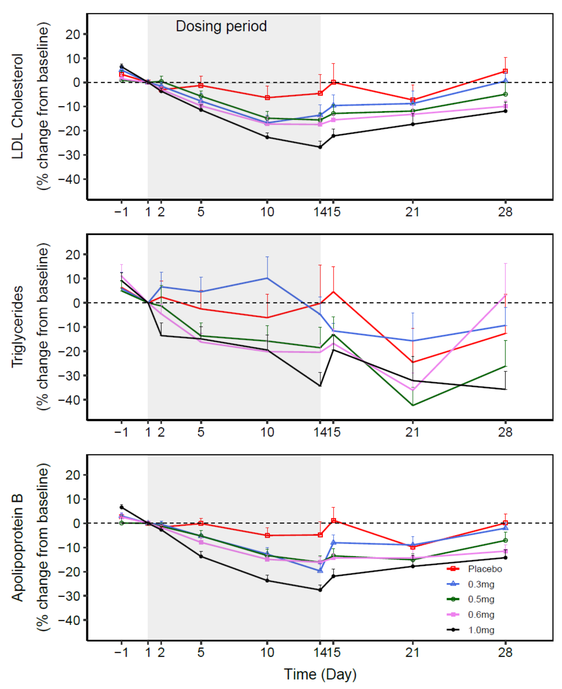
- Across the SAD and MAD, there were no serious adverse events, dose-limiting toxicities, or Grade ≥ 3 TEAEs. In the MAD, there were no TEAEs leading to premature study drug discontinuation
- The most common TEAEs (≥2 subjects) were:
  - SAD:
    - Headache (N=2; N=1 PBO, N=1 0.3 mg)
    - Rhinopharyngitis (N=2; N=1 PBO, N=1 0.1 mg)
  - MAD:
    - 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

Results

PHARMACODYNAMICS: Anti-Lipid Effects

- For SAD and MAD, a generally dose related decline in LDL-C, triglycerides and apolipoprotein B was observed.
  - For SAD, the maximum decline occurred at Day 5
  - For MAD, the maximum decline occurred at Day 14 (Fig 1)

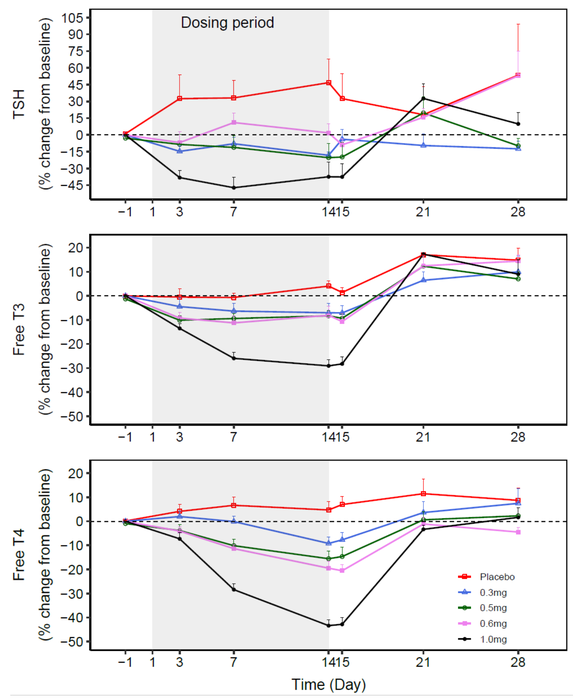
Fig 1: MAD Cohorts, Mean (±SEM) % change from Baseline in Lipids



PHARMACODYNAMICS: Thyroid Hormones

- Mean TSH, (free) T3, and (free) T4 levels declined in a generally dose responsive manner, then returned to (near) baseline within 2 weeks
  - SAD:
    - (Free) T3, (free) T4: maximum mean declines were <~30% for all dose levels
    - TSH: maximum mean declines were <30% at 0.1 mg and 0.3 mg ALG-055009; between 0.9 mg and 4 mg, the maximum mean declines were 46% - 76%
    - The mean values of all parameters remained within the normal range
  - MAD (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: MAD Cohorts, Mean (±SEM) % change from Baseline in Thyroid Hormones



PHARMACODYNAMICS: SHBG

- SHBG increased in a generally dose related manner, confirming liver target engagement
  - For SAD, maximum % increase was observed at Day 5 and was: ~5% (0.3 mg), ~7% (0.9 mg), ~20% (2.6 mg), and ~28% (4 mg). At 0.1 mg, there was no effect compared to placebo.
  - For MAD, maximum % increase 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 across 0.1-4 mg range (Fig. 3A-B)
- Rapid absorption (median tmax ~ 2 hr); large Vd (Vz/F > 30 L); low clearance (CL/F <2 L/hr)
- Low inter-subject variability (CV <30%)
- Plasma terminal half life ~20 h, supporting QD dosing
- In the MAD cohort, steady-state concentrations achieved by Day 5 with an accumulation ratio of ~ 2-fold, consistent with single dose PK

Fig 3A: Mean (±SD) Plasma ALG-055009 Concentrations Following Single Doses in Healthy Volunteers

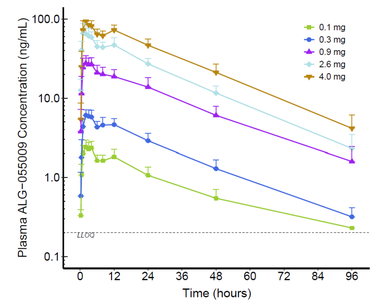


Fig 3B: Mean (±SD) Plasma ALG-055009 Concentrations Following Multiple Doses in Subjects with Hyperlipidaemia

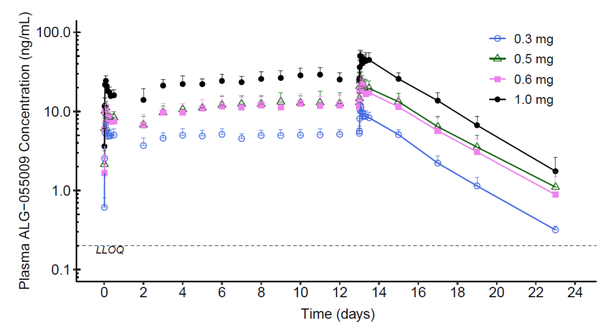


Table 2: Plasma ALG-055009 PK Parameters Following Single Doses in Healthy Volunteers

	SAD				
ALG-055009 Dose Level	**0.1 mg**	**0.3 mg**	**0.9 mg**	**2.6 mg**	**4 mg**
N	**N=6**	**N=6**	**N=6**	**N=6**	**N=6**
$AUC_{0\text{-}24}$, ng•hr/mL	38.1 (19.6)	98.5 (20.7)	440 (23.8)	1013 (19.5)	1508 (17.1)
T_{max}, hr	2 (2,4)	2 (2,3)	2 (1,3)	1.5 (1,4)	2 (2,2)
C_{max}, ng/mL	2.43 (19.1)	6.06 (19)	28.3 (22.5)	64.9 (30.2)	92.2 (18.1)
C_{24}, ng/mL	1.02 (27.4)	2.82 (23.4)	13.2 (32.9)	26.8 (16.7)	45.8 (20.8)
$t_{1/2}$, hr	20.1 (3.34)	20.7 (2.3)	22.7 (3.4)	20.2 (4.4)	20.3 (2.1)
CL_{ss}/F, L/hr	1.36 (31.7)	1.64 (23.9)	1.05 (32.2)	1.45 (17.6)	1.39 (22.1)
V_z/F, L	39.1 (19.1)	48.5 (20.1)	34.1 (18.3)	41.3 (21.2)	40.7 (16.2)

Geometric mean (geometric CV), except for t_{max}: median (min,max), and $t_{1/2}$: mean (SD)

Table 3: Plasma ALG-055009 PK Parameters Following Multiple Doses in Subjects with Hyperlipidaemia

ALG-055009 Dose	Dose No.	AUC_{0_24} (ng.hr/mL)	T_{max} (hr)	C_{max} (ng/mL)
0.3 mg N=8	1st Dose	106 (18.8)	2 (2,2)	6.92 (20.2)
	14th Dose	183 (16.0)	2 (1,2)	11.3 (13.7)
0.5 mg N=8	1st Dose	177 (17.0)	2 (1,3)	11 (20.3)
	14th Dose	423 (25.0)	2 (1,2)	24.9 (26.1)
0.6 mg N=8	1st Dose	166 (22.3)	2 (0.5,2)	11.2 (19.1)
	14th Dose	380 (27.2)	2 (1,2)	23.1 (23.2)
1 mg N=8	1st Dose	354 (15.2)	2 (2,2)	24.1 (15.6)
	14th Dose	922 (20.8)	2 (1,12)	51.3 (15.6)

Geometric mean (geometric CV), except for t_{max}: median (min,max), and $t_{1/2}$: mean (SD)

Conclusions

- Single ascending oral doses of ALG-055009 up to 4 mg, and multiple doses up to 1 mg x 14 days were well tolerated in HV and subjects with hyperlipidemia, respectively. No clinically significant changes in thyroid hormones or cardiovascular system parameters were observed.
- 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.

References

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