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

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INTRODUCTION

- Thyroid hormone receptor-beta (THR-β) is the main form of THR expressed in the liver and plays an important role in the metabolism of lipids.[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 demonstrated in preclinical models:
  - High selectivity for THR-β and nanomolar potency[4]
  - High efficacy in diet-induced obese rat/mouse models[4,5]
  - Favorable PK profile with low plasma clearance, metabolic stability, high oral bioavailability and a long plasma half-life[5,6]

AIMS

- To evaluate the safety, PK, and pharmacodynamics (PD) of ALG-055009 in healthy volunteers (HV) and in subjects with mild hyperlipidemia.

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 (CPU) in France (Biotrial, Rennes, FR). Part 1 and 2 evaluate single ascending doses (SAD) in HV and multiple ascending doses (MAD) in subjects with mild hyperlipidemia, respectively.

- Part 1 (SAD) is complete:
  - 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, BMI 18-32.0 kg/m^2
    - Exclusion: TSH or free T4 >upper limit of normal (ULN), ALT or AST >ULN
- Part 2 (MAD) is ongoing:
  - Each cohort is comprised of 10 subjects randomized to receive fourteen (14) once daily oral doses of ALG-055009 (N=8) or placebo (N=2) in a fasted state while confined in the CPU and receiving a standardized diet. Subjects are followed for 2 weeks after the last dose of study drug
  - Key Eligibility Criteria
    - Inclusion: 18-65 years, BMI 18-35.0 kg/m^2, LDL >110 mg/dL
    - Exclusion: TSH or free T4 >ULN, ALT or AST >ULN
- Throughout the study, safety assessments (adverse events [AEs], vital signs, electrocardiogram [ECG] and laboratories (including thyroid hormones), PK, and PD markers (including sex hormone binding globulin [SHBG] and lipids) are collected and analyzed
- Urine and plasma concentrations of ALG-055009 are quantified by validated liquid chromatography–tandem mass spectrometry methods
- PK parameters are determined by non-compartmental analysis using Phoenix WinNonlin

Here we report preliminary results from Part 1 Cohorts 1-5, and Part 2 Cohort 1.

BASELINE CHARACTERISTICS

- The baseline characteristics were similar across treatment groups and are typical for a HV population.

Table 1: Demographics and Baseline Characteristics

	SAD					MAD
Cohort Dose level	Cohort 1 0.1 mg ALG055009/ PBO	Cohort 2 0.3 mg ALG055009/ PBO	Cohort 3 0.9 mg ALG055009/ PBO	Cohort 4 2.6 mg ALG055009/ PBO	Cohort 5 4 mg ALG055009/ PBO	Cohort 1 0.3 mg ALG055009/ PBO
N	N=8	N=8	N=8	N=8	N=8	N=10
Age (years), mean (SEM)	42.1 (2.2)	37.0 (3.6)	36.3 (4.9)	33.3 (4.5)	40.6 (3.9)	40.9 (3.5)
Male, N (%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	9 (90%)
White, N (%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	10 (100%)
BMI, kg/m^2, mean (SEM)	25.0 (1.0)	25.5 (1.5)	23.9 (1.3)	25.0 (0.9)	24.2 (0.7)	27.0 (0.8)
Weight, kg, mean (SEM)	79.5 (4.5)	81.8 (5.1)	72.5 (5.8)	84.1 (4.3)	75.8 (1.3)	84.0 (2.0)
Free T4, ng/dL, mean (SEM)	1.2 (0.1)	1.4 (0.1)	1.3 (0.1)	1.3 (0.1)	1.3 (0.04)	1.2 (0.03)
Free T3, pg/mL, mean (SEM)	3.4 (0.1)	3.2 (0.1)	3.5 (0.2)	3.3 (0.1)	3.3 (0.1)	3.1 (0.2)
TSH, µUI/mL, mean (SEM)	1.9 (0.3)	1.5 (0.2)	2.0 (0.4)	2.2 (0.2)	1.7 (0.2)	1.9 (0.3)
SHBG, nmol/L, mean (SEM)	39.6 (3.9)	34.1 (4.9)	38.4 (5.1)	34.9 (3.6)	36.3 (4.9)	36.7 (12.9)
LDL-C, mg/dL, mean (SEM)	124.7 (12.9)	128.9 (10.1)	121.5 (13.3)	114.2 (10.7)	142.1 (14.4)	145.0 (8.6)
TG, mg/dL, mean (SEM)	113.0 (23.6)	114.7 (16.2)	117.4 (6.9)	86.8 (9.1)	122.9 (17.0)	144.9 (21.0)
Apo-B, mg/dL, mean (SEM)	97.0 (10.6)	100.0 (8.2)	91.5 (8.1)	87.5 (7.3)	108.8 (10.6)	113.8 (4.3)

PBO = Placebo. SEM= Standard Error of the Mean. 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 doses of 0.3 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 treatment emergent AEs (TEAEs)
- In the MAD, there were no TEAEs leading to study drug discontinuation
- TEAEs reported in more than 1 subject:
  - SAD: headache (N=2), rhinopharyngitis (N=2)
  - MAD: insomnia (N=2)
- Treatment emergent laboratory abnormalities:
  - SAD and MAD: all laboratory abnormalities were Grade 1 except for two subjects (SAD, Cohort 4, 2.6 mg; MAD, Cohort 1, 0.3 mg) each with a Grade 2 transient asymptomatic lipase elevation that spontaneously resolved by the following visit
- TSH, free T3 and free T4:
  - SAD: Mean TSH, (free) T3, and (free) T4 levels transiently declined in a generally dose responsive manner
  - MAD: Mean Day 15 TSH, (free) T3, and (free) T4 levels remained in the normal range and declined by <10%
  - No clinical or laboratory evidence of clinically significant hypo- or hyper-thyroidism was observed
- There were no clinically concerning laboratory, ECG, vital sign or physical examination findings

PHARMACOKINETICS

- Plasma ALG-055009 exposures increased in a dose proportional manner across 0.1-4 mg range (Fig. 1A and Fig. 2)
- Rapid absorption (median t_{max} ~ 2 hr); large V_d (Vz/F > 60 L); low clearance (CL/F <3 L/hr)
- Low inter-subject variability (CV <30%)
- Plasma half life ~20-24 h, supporting QD dosing
- Minimal renal excretion of unchanged ALG-055009 (< 3% of total dose) up to 4 mg dose level
- In the MAD cohort, steady-state concentrations achieved by Day 5 with an accumulation ratio of ~ 1.7-fold, consistent with single dose PK

Fig 1A: SAD Pharmacokinetics

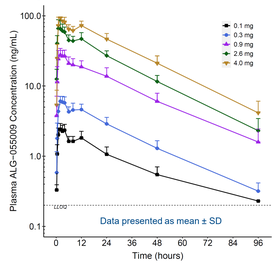


Fig 1B: MAD Pharmacokinetics

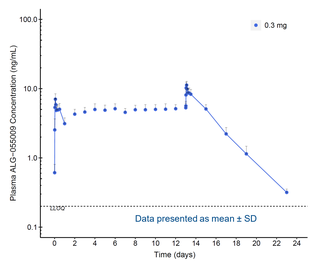


Table 2 : PK Parameters

	SAD					MAD	
Cohort Dose level	Cohort 1 0.1 mg	Cohort 2 0.3 mg	Cohort 3 0.9 mg	Cohort 4 2.6 mg	Cohort 5 4.0 mg	Cohort 1 0.3 mg DAY 1	Cohort 1 0.3 mg DAY 14
N	N=6	N=6	N=6	N=6	N=6	N=8	N=8
AUC_{0-24}, ng•hr/mL	38.3 (22.1)	98.6 (20.1)	440 (23.9)	1020 (20.2)	1510 (17.1)	106 (18.4)	183 (15.7)
T_{max}, hr	2 (2,4)	2 (2,3)	2 (1,3)	1.5 (1,4)	2 (2,2)	2 (2,2)	2 (1,3)
C_{max}, ng/mL	2.42 (20.1)	6.06 (18.5)	28.3 (22.5)	64.9 (30.9)	92.2 (17.6)	6.91 (20.1)	11.2 (13.5)
C_{24}, ng/mL	1.04 (27.2)	2.82 (23.9)	13.2 (32.3)	26.8 (17)	45.8 (20.4)	3.06 (21.1)	5.03 (15.8)
$t_{1/2}$, hr	23.6 (18.2)	21.8 (9.58)	22.8 (13.4)	20.1 (21.1)	21.6 (11.3)	26.6 (19.7)	22.1 (8.04)
CL_{ss}/F, L/hr	2.61 (16.7)	3.04 (20.8)	2.04 (22.9)	2.56 (18.3)	2.65 (16.6)	--	--
V_z/F, L	87.6 (21.2)	95.1 (22.6)	66.7 (15.5)	73 (33.9)	82.2 (13.6)	--	--

AUC_{0-24}=area under the plasma concentration versus time curve from 0 to 24 hours; CL_{ss}/F=apparent clearance; C_{max}=maximum concentration; t_{max}=time to maximum concentration; V_z/F=apparent volume of distribution.
Note: Geometric Mean (Coefficient of Variation [CV]%), except T_{max}: median (minimum, maximum) and $t_{1/2}$: mean (SD).

Fig. 2: Exposure-Dose Relationship

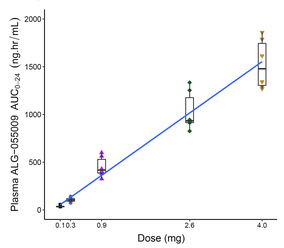
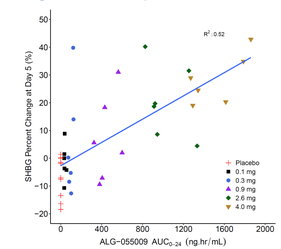


Fig. 3: SHBG-Exposure Relationship



PHARMACODYNAMICS

- SHBG showed a dose responsive increase, consistent with liver target engagement (Fig. 3, Table 3).
- Anti-lipid activity was generally dose responsive in the SAD. Activity was also observed in the MAD after 14 daily 0.3 mg doses.

Table 3 : Change from baseline in SHBG and Lipids

		SAD						MAD	
Cohort Dose level		PBO	Cohort 1 0.1 mg	Cohort 2 0.3 mg	Cohort 3 0.9 mg	Cohort 4 2.6 mg	Cohort 5 4 mg	PBO	Cohort 1 0.3 mg
N		N=10	N=6	N=6	N=6	N=6	N=6	N=2	N=8
SHBG	Baseline, nmol/L	36.4 (4.1)	40.4 (5.0)	33.7 (5.6)	33.7 (5.5)	36.9 (3.8)	39.1 (6.0)	34.0 (9.1)	37.4 (16.3)
	Change, nmol/L	-2.6 (1.1)	-0.2 (0.9)	0.7 (2.6)	1.0 (2.0)	8.3 (2.8)	10.9 (1.8)	1.05 (1.3)	4.1 (2.5)
	% Change	-6.5 (2.3)	-1.4 (2.7)	4.6 (8.0)	6.7 (6.3)	20.5 (5.5)	28.4 (3.7)	4.4 (4.9)	8.5 (2.8)
LDL-c	Baseline, mg/dL	134 (12.4)	123 (12.3)	126 (13.5)	125 (16.0)	115 (14.3)	130 (15.7)	157.8 (18.2)	141.7 (10.0)
	Change, mg/dL	-9.6 (4.0)	7.0 (16.9)	-10.4 (3.2)	-4 .0 (3.3)	-12.6 (3.8)	-20.4 (4.6)	-17.2 (19.5)	-14.6 (6.5)
	% Change	-6.0 (2.7)	13.1 (21.0)	-8.1 (2.6)	-2.3 (2.2)	-11.7 (3.9)	-15.1 (2.5)	-9.6 (11.3)	-9.6 (4.4)
TG	Baseline, mg/dL	128 (11.2)	99.1 (27.1)	116 (22.1)	112 (7.2)	82.1 (9.1)	118 (21.9)	81.5 (5.3)	160.8 (23.1)
	Change, mg/dL	-31.8 (12.2)	- 2.7 (15.2)	-32.8 (13.9)	-38.5 (7.9)	-11.1 (9.7)	-44.6 (9.5)	-6.2 (4.4)	-20.9 (6.7)
	% Change	-22.4 (8.8)	20.0 (26.6)	-25.1 (9.6)	-34.2 (6.3)	-10.7 (10.8)	-37.4 (4.5)	-7.3 (5.0)	-11.6 (3.1)
Apo-B	Baseline, mg/dL	105.7 (9.3)	93.5 (10.8)	98.7 (11.0)	92.3 (9.7)	87.8 (9.8)	97.8 (9.8)	117.0 (15.0)	113.0 (4.6)
	Change, mg/dL	-8.2 (2.4)	0.3 (11.5)	-7.3 (3.2)	-9.2 (2.4)	-6.5 (3.0)	-15.8 (2.0)	-8 .0 (12.0)	-9.1 (3.6)
	% Change	-7.5 (2.0)	5.3 (17.2)	-7.6 (3.2)	-9.4 (2.2)	-7.9 (3.9)	-16.3 (1.7)	-5.6 (9.5)	-8.0 (3.3)

PBO= Placebo. All values are expressed as mean (SEM) changes from Baseline to Day 5 for SAD and Day 15 for MAD.

CONCLUSIONS

- Single ascending oral doses of ALG-055009 up to 4 mg, and multiple doses of 0.3 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 and linear plasma exposures (β=1.02), low variability (CV <30%), and a ~1.7 accumulation ratio after multiple doses.
- Evidence of liver target engagement (SHBG) and anti-lipid activity was observed. The effect on lipids, although highly variable, was generally dose dependent after single doses.
- Additional MAD cohorts evaluating higher doses are ongoing.

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