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A multipart phase 1 study of the safety, pharmacodynamics and pharmacokinetics of ALG-055009, a novel thyroid hormone receptor beta (THR-β) agonist for metabolic dysfunction-associated steatohepatitis (MASH), in healthy participants

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Abstract

ALG–055009 is an oral thyroid hormone receptor beta (THR-β) agonist being evaluated for treating metabolic dysfunction–associated steatohepatitis (MASH). This study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of ALG-055009 and bioavailability/food effect. Part 1 was a single–ascending dose study in healthy participants randomized to ALG-055009 (0.1 to 4.0 mg) or placebo. Part 2 was a multiple–ascending dose study in participants with mild hyperlipidemia randomized to ALG-055009 (0.3 to 1.0 mg) or placebo once daily for 14 days. Part 3 was an open–label study to determine relative bioavailability and food effect of 0.6 mg ALG-055009 solution versus soft gelatin (softgel) capsule formulation. Among 78 participants, ALG-055009 was well tolerated, and most adverse events were mild or moderate with no clinically meaningful safety issues. Transient reductions in thyroid hormone levels were observed with no clinical manifestation of hypo/hyperthyroidism. Plasma ALG-055009 exposure increased in a dose–proportional manner with rapid absorption, low variability, accumulation ranging from 1.6-2.6-fold, and $t_{1/2}$ of 20 h. Relative bioavailability of the softgel capsule was 86% versus solution, with no food effect. Dose–dependent decreases in atherogenic lipids and increases in sex hormone binding globulin were observed. These results support further development of ALG-055009 for patients with MASH.

Keywords

lipids, metabolic dysfunction–associated steatohepatitis, pharmacokinetics, thyroid hormone receptor beta

Metabolic dysfunction–associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease worldwide with a substantial and growing global prevalence of 30% as of 2019 compared to

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25% in 2015.[1,2] Previously known as nonalcoholic fatty liver disease (NAFLD), MASLD is defined as fat accumulation in the liver with the presence of at least one cardiometabolic risk factor, which include excess body weight, insulin resistance, hypertension, high triglyceride levels, and low high–density cholesterol levels.[3] Metabolic dysfunction–associated steatohepatitis (MASH; previously known as non–alcoholic steatohepatitis or NASH) is the most severe form of MASLD with excessive fat deposits that can lead to inflammation that may progress to liver fibrosis, cirrhosis, hepatocellular carcinoma or death.[4,5] Among adult liver transplant candidates in the U.S., MASH is the second leading cause of liver disease[6] and the leading cause of hepatocellular carcinoma.[7] MASH is closely associated with lifestyle factors and the high prevalence of obesity and type 2 diabetes mellitus,[5,8,9] which are related to poor diet and lack of physical activity.[10,11] Lifestyle changes are recommended as the first–line therapy,[12,13] although overweight and obese adults who adopt recommended lifestyle changes require modest (7-10%) or greater (≥10%) weight loss to significantly improve liver histology.[14,15] Improvement of all histologic parameters is most apparent in individuals with weight reductions ≥10%.[15] Despite the benefits of weight loss, lifestyle modifications alone are insufficient for most patients with advanced disease therefore other treatment modalities are needed.

Thyroid dysfunction may be associated with the pathogenesis of NAFLD and NASH,[16,17] where the prevalence of hypothyroidism was common and associated with increased NAFLD activity. The two subtypes of thyroid hormone receptor (THR), THR alpha (THR-α), and THR beta (THR-β), are expressed at various levels in most tissues. THR-α expression is predominant in bone, gastrointestinal tract, cardiac and skeletal muscle, and central nervous system.[18] THR-β is mainly expressed in the liver, kidneys, pituitary gland, and brain but importantly is the predominant receptor subtype in the liver and is responsible for the effects of thyroid hormone on lipid metabolism.[19–21] Resmetirom, a THR-β agonist, is approved in the United States for treating MASH. Data from the 52-week Phase 3 study of resmetirom showed significant reductions in both hepatic fat content and LDL–C, demonstrating that the mechanism of THR-β agonists is efficacious for the treatment of MASH.[22] While resmetirom demonstrated robust activity and is currently the only approved treatment for MASH, gastrointestinal (GI)–related adverse events (e.g. diarrhea and nausea) occurred more frequently in the resmetirom treatment groups than in the placebo group. Reduction of these GI–related effects with the next generation of THR-β agonists may result in fewer discontinuations and potentially offer an advantage over resmetirom as a treatment for MASH.

ALG-055009, a potent THR-β agonist, is being developed as a treatment for MASH. The nonclinical properties of this drug include high potency, approximately 50-fold greater than that observed for resmetirom in head–to–head in vitro biochemical and cell–based assays assessing THR-β activation, and a 4- to 6-fold higher selectivity for the beta subunit of THR compared to the alpha subunit.[23] Because THR-α is predominantly expressed in the heart, brain, and skeletal muscle, while THR-β is expressed primarily in the liver and plays a role in hepatic lipid metabolism, a selective specificity and potency for THR-β, as demonstrated by ALG-055009, is advantageous for both safety (e.g. less effects of THR-α stimulation such as cardiac and bone toxicity) and efficacy (e.g. greater reduction of fat deposits in the liver). Rapid absorption and a dose proportional pharmacokinetic (PK) profile of ALG-055009 supporting once daily dosing was also observed in nonclinical studies.[24–28] Overall, the toxicology profile of ALG-055009 was consistent with the exaggerated pharmacologic actions of thyromimetics, including significant modulation of thyroid hormones along with hepatocellular and cardiovascular effects observed at supratherapeutic exposures in rats and/or dogs. ALG-055009 significantly decreased triglycerides in young healthy rats and dogs and total cholesterol in young healthy dogs in the repeat–dose toxicology studies. No adverse histopathological findings were noted in either rat or dog chronic toxicology studies up to the highest doses tested up to 6- or 9-months in duration, respectively, and all non–adverse clinical pathology or histopathological effects were reversible.

Based on the promising nonclinical profile, ALG-055009 is being evaluated as a treatment for MASH. We report here the findings of this phase 1 first–in–human trial evaluating the safety, tolerability and PD activity of single and multiple doses of ALG-055009.

Methods

This study was conducted at one investigational site in Rennes, France between December 2021 and June 2023 in accordance with the principles of the International Council for Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and all relevant regulations. The study protocol was reviewed and approved by an Ethics Committee and was also approved by the French National Agency for the Safety of Medicines and Health Products. All the participants provided written informed consent prior to any study participation. The protocol was amended twice with no impact on the overall study design. No significant

protocol deviations were noted that would impact the interpretation of study results.

Study design

This was a three–part, phase 1 first–in–human trial (NCT05090111) to evaluate oral ALG-055009 after single–ascending doses (SAD) and multiple–ascending doses (MAD) in healthy or hyperlipidemic participants which are further described in subsequent sections. The starting dose in Part 1 (0.1 mg) was selected based on safety margins based on the human–equivalent dose (≥14.5-fold) and exposures (≥16.2-fold) compared with the nonclinical no–observed–adverse–effect levels (NOAELs) from the initial 14-day repeat–dose rat and dog toxicology studies. The starting dose in Part 2 (0.3 mg) was selected based on the projected steady–state $AUC_{0\text{-}24}$ that approximately matched the lowest efficacious exposures observed in the diet–induced obesity mouse model. The dose in Part 3 (0.6 mg) was selected based on PK data in order to achieve exposures that were expected to result in PD activity. The maximum exposures for Parts 1 and 2 were capped based on the nonclinical 14-day repeat–dose toxicology studies (mean C_{max} of 250 or 553 ng/mL and mean $AUC_{0\text{-}24}$ of 4500 or 7400 ng•h/mL, respectively) and did not exceed exposures for Part 3 that had been studied in Parts 1 and 2 for Part 3.

For Part 1, the dose escalations were determined based on review of all available safety, tolerability, and PK data from previous cohorts including at least 3 days of blinded safety data and at least 24 h of PK data from at least 6 participants. For Part 2, dose escalations required at least 7 days of blinded safety data and at least 24 h of PK data following the first dose from at least 8 participants. No dose escalations were conducted in Part 3. These reviews took place during data safety review meetings (DRMs) conducted by the Study Review Committee (SRC), including the Medical Monitor from Aligos and the Principal Investigator. Subsequent cohorts were only dosed if considered safe to do so by the SRC.

Part 1 – single–ascending dose. Part 1 was a double–blind, randomized, placebo–controlled SAD study to investigate the safety, tolerability, and PK of ALG-055009. Participants were screened on Days -42 through -2, confined to the clinic site on Day -2, received a single oral dose of ALG-055009 or placebo on Day 1, and released from the clinic site on Day 3. Participants were followed for approximately 2 weeks after the study drug was administered.

Five cohorts of eight healthy participants per cohort were randomized in a 3:1 ratio to a single, oral dose of ALG-055009 (0.1, 0.3, 0.9, 2.6, or 4.0 mg) or placebo administered in a fasted state. A sentinel group of two participants was administered ALG-055009 or placebo (1:1 ratio) at least 24 h before the remaining six participants (5 ALG-055009 and 1 placebo) were randomized and treated. The Sponsor and Principal Investigator reviewed available safety data for adverse events (AEs) in the sentinel group before the remaining participants in the ALG-055009 and placebo groups received study medication.

Part 2 – multiple–ascending dose. Part 2 was a double–blind, randomized, placebo–controlled multiple–ascending dose study conducted in participants with mild hyperlipidemia (low–density lipoprotein cholesterol [LDL–C] >110 mg/dL) to investigate the safety, tolerability, PK, and PD of oral ALG-055009. Participants were screened on Days -42 through -3, confined to the clinic site on Day -3, received an oral dose of ALG-055009 or placebo once daily on Day 1 through Day 14, and were discharged from the clinic site on Day 17. Participants were followed for approximately 2 weeks after the last dose of study drug. Five cohorts of 10 participants were randomized in a 4:1 ratio to receive a daily dose of 0.3, 0.5, 0.6, 0.75, or 1.0 mg ALG-055009 or placebo for 14 days in a fasted state.

Part 3 – bioavailability and food effect. Part 3 was an open–label study to assess the relative bioavailability of a single, oral dose of ALG-055009 administered as a solution formulation or a soft gelatin capsule formulation to participants in a fasted state and to determine the effect of food on ALG-055009 PK following the soft gelatin capsule administration in the fed state. ALG-055009 was administered in three single oral doses of 0.6 mg in a fixed sequence with a 10-day washout period between each dose: solution formulation in fasted state, soft gelatin capsule in fasted state, and soft gelatin capsule in fed state.

ALG-055009 and matching placebo used in Parts 1 and 2 were supplied as a solution. The soft gelatin capsule formulation contained 0.3 mg ALG-055009 and was used in Part 3 only. In Part 1 and when fasting was required in Part 3, participants fasted ≥10 h overnight before dosing and until 4 h post dose. Participants in Part 2 fasted ≥8 h overnight before dosing and until 2 h post dose. When ALG-055009 was administered in a fed state, participants consumed a high–fat, high–calorie meal[29] within 30 min before dosing. In Parts 2 and 3, site staff administered each dose of ALG-055009 at approximately the same time on each dosing day.

Participant selection

In Parts 1 and 3, male or female participants aged 18-55 years with a body mass index (BMI) of 18 to 32 kg/m^2 were eligible. Participants were nonsmokers for at least 3 months prior to randomization and considered healthy, i.e. had no clinically significant abnormality based on physical examination, medical history,

vital signs, and clinical laboratory testing performed at screening and on Day-1.

In Part 2, male or female participants aged 18-65 years with a BMI of 18 to 35 kg/m^2 were eligible. Participants were nonsmokers for at least 3 months prior to randomization or light smokers (<10 cigarettes, or equivalent, per day), and smoking status had to remain stable throughout the study. Participants were on a stable diet for the 3 months prior to screening with a fasting low–density lipoprotein cholesterol (LDL–C) level >110 mg/dL at screening and Day -1. LDL–C was included as a potential pharmacodynamic biomarker based on clinical data with resmetirom in shorter duration studies[30] and subsequent translation of LDL–C reductions to more clinically relevant endpoints (magnetic resonance imaging proton density fat fraction; MRI–PDFF) in longer duration studies.[22,31]

In Parts 1-3, participants were excluded for a medical history of thyroid disorder, abnormal levels of thyroid stimulating hormone (TSH) or free T4 during screening or on Day -1 or known sensitivity to thyroid medications. Participants also were excluded for alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin levels greater than the upper limit of normal, unless Gilbert's syndrome was suspected in the case of total bilirubin. A complete list of inclusion and exclusion criteria are provided in Tables S3 and S4.

Safety assessments

Safety assessments included monitoring of AEs, clinical laboratory tests (biochemistry, hematology, urinalysis, Table S5), serology, physical examination, 12-lead electrocardiogram (ECG), vital signs (blood pressure, heart rate, respiratory rate, temperature), and pregnancy test at prespecified intervals throughout the study. A treatment–emergent adverse event (TEAE) was any event that met the criteria for an AE/serious AE and occurred on or after the time the participant received the first dose of study drug. Adverse events were evaluated and documented using the grading scales contained in the Division of AIDS (DAIDS) version 2.1, July 2017, and a separate study specific scale for laboratories not graded in the DAIDS system. The relationship between plasma concentration of ALG-055009 and placebo–corrected change from baseline QTcF ($\Delta\Delta$QTcF) was also included as an exploratory endpoint.

Pharmacokinetics and pharmacodynamics

Samples were collected to assess the PK of ALG-055009 in plasma and urine (Parts 1 and 2 only). Concentrations of ALG-055009 in human plasma and urine were measured with liquid chromatography–tandem mass spectrometry (LC/MS/MS). For plasma, concentrations were calibrated over the range of 0.200 to 400 ng/mL and for urine over the range from 0.500 to 500 ng/mL. Quality control samples were prepared at multiple concentration levels and met predefined validation criteria for accuracy, precision, and stability. Stability was 24 h at ambient temperature for both plasma and urine, and 373 days and 378 days at −20 °C for plasma and urine, respectively. For plasma, inter–run precision and accuracy were 4.96% and 4.17% and for urine were 5.58% and 1.60%, respectively. In plasma, intra–run precision and accuracy were 6.65% and −7.50%, respectively, and in urine were 8.92% and 4.00%, respectively. PK parameters included area under the concentration–time curve (AUC), T_{max}, C_{max}, C_{min}, C_0 (predose), $t_{1/2}$, urinary excretion, and renal clearance (Table S6). Plasma was collected to evaluate the effect of ALG-055009 compared with placebo on PD markers such as total cholesterol, LDL–C, HDL–C, triglycerides, apolipoprotein B, lipoprotein A, non–HDL–C, sex hormone–binding globulin (SHBG), and thyroid hormones (Table S5).

Statistical analysis

No formal sample size calculation was performed. Up to 72 participants with normal LDL–C levels and up to 80 participants with mild hyperlipidemia were considered sufficient to satisfy the study objectives. The safety analysis included participants who received at least one dose of any study drug. Safety data were listed by participant and summarized using descriptive statistics. The PD population was all participants who received at least one dose of study drug and had at least one available PD assessment. The PK population was all participants who received ALG-055009 and had quantifiable PK concentration data. PK parameters were calculated by non–compartmental methods. The linear dose–proportionality of C_{max}, $AUC_{0\ last}$, and $AUC_{0\text{-}inf}$ was assessed using a power model. The log–transformed PK parameter and dose values were analyzed using a mixed effects model with log–transformed dose as a fixed effect. Linear dose–proportionality will be concluded if the two–sided 90% CI for the slope value of the log–transformed dose is within the critical [(1+ln(LL)/ln(r)); (1+ln(UL)/ln(r))] region, where r = dose maximum/dose minimum, LL = 0.8 and UL = 1.25.[32] The dose group comparisons were conducted for Day 1 in Part 1 and Days 1 and 14 in Part 2. In Part 2, steady–state was assessed with a one–way analysis of variance (ANOVA) using log–transformed pre–dose plasma concentrations of ALG-055009 from Days 1 to 15. Food effect with the soft gelatin capsule formulation and the relative bioavailability of a soft gelatin capsule versus solution formulation were assessed with an ANOVA on log–transformed data for C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ with treatment as

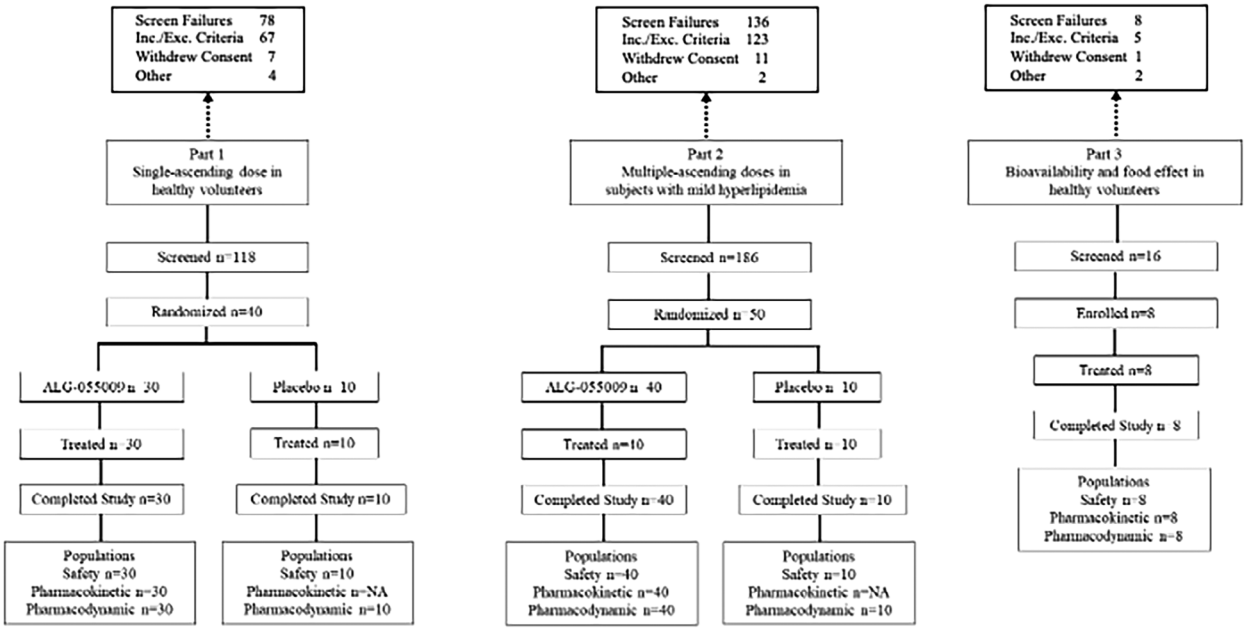

Figure 1. Flow diagram of participants.

fixed effect and participant as random effect. Geometric mean ratios (GMR) between formulation/food condition of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ and the corresponding 90% CI were constructed. Equivalent bioavailability and absence of food effect will be concluded if the 90% CI of GMRs lies within the bioequivalence/equivalence range of [0.80-1.25].[33] Exposure–response analyses were conducted for heart rate, blood pressure, body temperature, and change from baseline in QTc using a linear mixed effect model to examine the relationship between these endpoints and time–matched plasma ALG-055009 concentrations.

Results

All randomized participants completed the study (Figure 1). In Part 1, 118 participants were screened and 40 were randomized and completed the study. At baseline, all participants were male, Caucasian, mean age was 37.9 years, mean weight was 79.4 kg, and mean BMI at baseline was 25.0 kg/m^2 (Table S7). In Part 2, 186 participants with mild hyperlipidemia were screened and 50 participants were randomized and completed the study. The majority of participants were male (94.0%) and Caucasian (96%), mean age was 40.7 years, mean weight was 83.2 kg, and mean BMI was 26.5 kg/m^2. No relevant differences were observed between dose groups for baseline characteristics across Parts 1 and 2. In Part 3, 16 participants were screened and 8 were enrolled and completed the study. The majority of participants were male (75.0%), all were Caucasian, mean age was 39 years, mean weight was 74.9 kg, and mean BMI was 24.7 kg/m^2.

Safety and tolerability

All TEAEs were mild (Grade 1) or moderate (Grade 2) in severity, and all participants who experienced a TEAE were resolved by the end of the study (Table S8). Across Parts 1-3, no serious AEs, deaths, dose–limiting toxicities or TEAEs leading to study drug discontinuation occurred. No clinically relevant changes were observed for clinical laboratory testing, and no clinically significant abnormalities for blood pressure and heart rate (Figures S2 and S3) or physical examinations were reported. A concentration–QTc analysis using ECG data showed that the upper bound of the two–sided 90% CI of the predicted placebo–corrected mean QTcF change from baseline ($\Delta\Delta$QTcF) was <10 ms at the C_{max} of a supratherapeutic dose of 4 mg, suggesting no clinically relevant effects on the QT interval (Figure S4).

In Part 1, TEAEs were reported by four (13.3%) participants in the ALG-055009 dose cohorts and three (30%) participants with placebo (Table S8). All TEAEs were considered unrelated to ALG-055009. In Part 2, nine (22.5%) participants across the ALG-055009 dose cohorts and five (50%) participants with placebo experienced TEAEs. The most commonly reported TEAEs (≥2 participants treated with ALG–055009) were abdominal distension (3), diarrhea (4), headache (3), and insomnia (2) (Table S8). Seven (17.5%) participants experienced TEAEs considered related to ALG-055009 (abdominal distention, 2; diarrhea, 2; headache, 3), and three (30.0%) participants with placebo experienced related events (abdominal pain, diarrhea, headache).

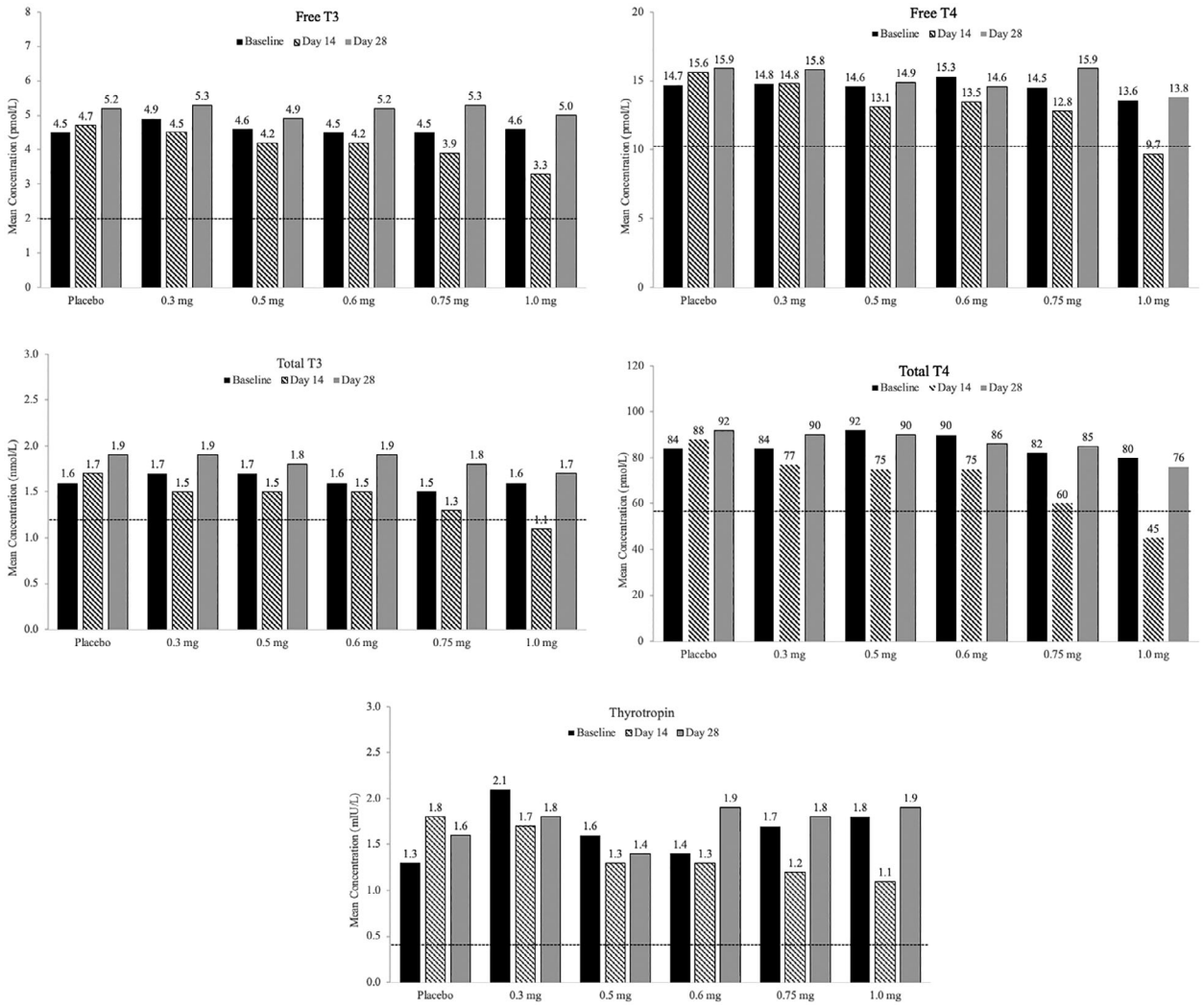

Figure 2. Mean concentrations of total triiodothyronine (T3), free triiodothyronine, free thyroxine (T4), total thyroxine, and thyrotropin at baseline, Day 14 (end of treatment), and Day 28 following 14 daily doses of ALG-055009. Dashed line represents the lower limit of normal.

In Part 3, six (75%) participants experienced 10 TEAEs. The most commonly reported (≥2 participants) TEAEs were nasopharyngitis (n = 3) and diarrhea (n = 2). Two TEAEs (abdominal distention, diarrhea) were unlikely related, and one (diarrhea) was possibly related. Notably, the solution formulation evaluated in this study uses a diluent containing 60% polyethylene glycol 400 (PEG400), a known laxative.

Thyroid hormones

In Part 1, dose–dependent decreases in TSH, total T3, and free T3 were observed across all dose levels on Day 2 (Table S9). Dose–dependent decreases in total T4 and free T4 also were observed at 0.9, 2.6, and 4.0 mg doses of ALG-055009. Decreases were transient, with mean values remaining within the normal range and returning to baseline by Day 14. In Part 2, multiple–ascending doses of ALG-055009 induced a transient, dose–dependent decrease in thyroid parameters with mean levels of thyroid hormones at the end of treatment (Day 14) remaining within or slightly below the normal range (Figure 2). However, following treatment completion, thyroid hormone levels for all doses of ALG-055009 returned to baseline or near baseline, all in the normal range, by Day 28. In Part 3, the effects of a single 0.6 mg dose were consistent with those observed among participants in Part 1. Across all parts, none of the reductions in thyroid hormone levels were associated with symptoms or with significant changes in heart rate, blood pressure or body temperature. Moreover, the slope of the exposure–response relationship for heart rate, diastolic and systolic blood pressure, and

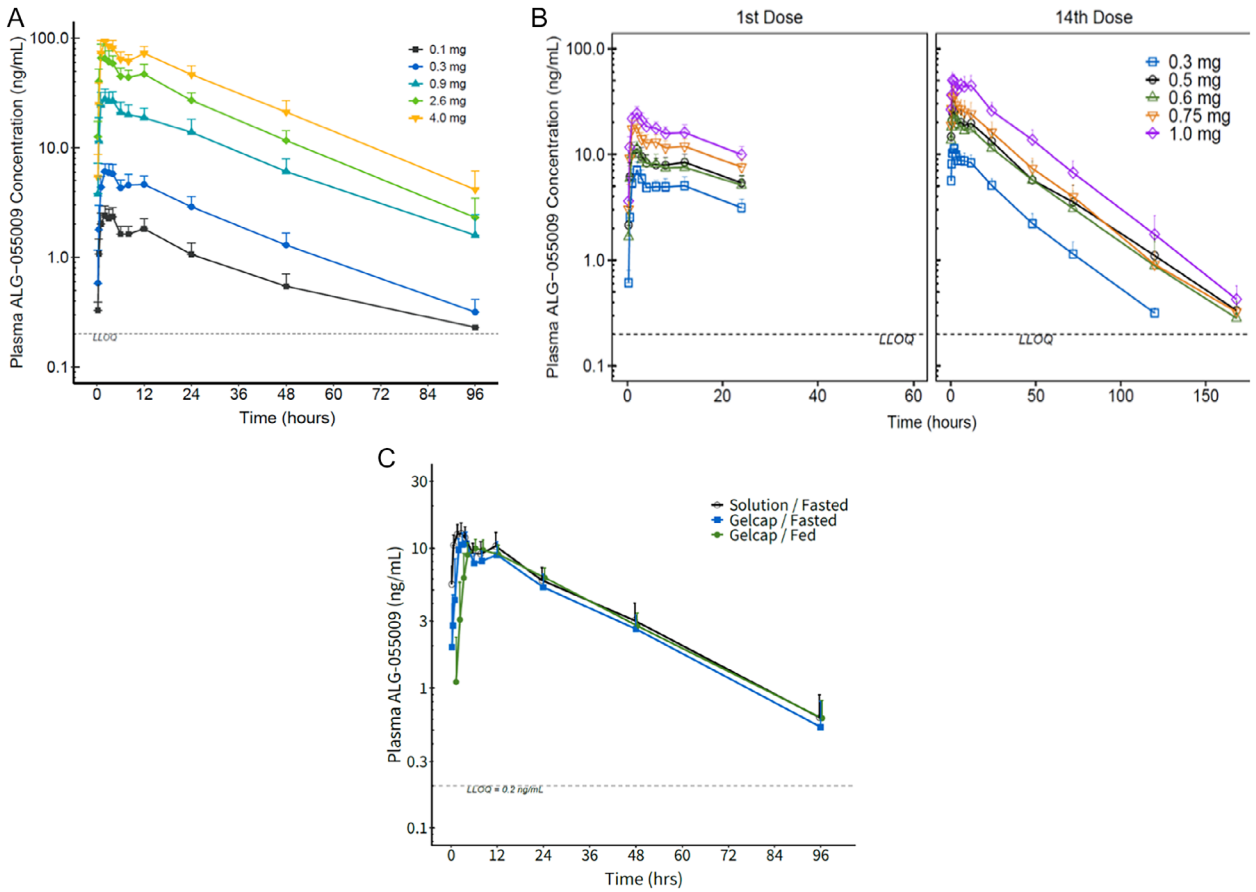

Figure 3. Mean (SD) plasma concentrations of ALG-055009 after single doses in healthy volunteers (A), multiple doses on Day 1 and Day 14 in mild hyperlipidemic participants (B), and after single oral 0.6 mg doses of solution or soft gelatin capsule formulation in fasted or fed conditions in healthy volunteers (C).

Table 1. Geometric Mean (% Geometric CV) Plasma PK Parameters for ALG-055009 in Healthy Volunteers Following Single–Ascending Doses (Part 1).

Dose (mg)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (ng·h/mL)	C_{24h} (ng/mL)	AUC_{inf} (ng·h/mL)	CL_{ss}/F (L/h)	Vz/F (L)	$t_{1/2}$ (h)[a]
0.1	2.4 (17.3)	38.1 (19.6)	1.0 (24.8)	73.4 (37.2)	1.36 (37.2)	39.1 (20.6)	20.1 (3.3)
0.3	6.1 (19.0)	98.5 (20.7)	2.8 (23.2)	183 (23.9)	1.64 (23.9)	48.5 (20.1)	20.7 (2.3)
0.9	28.3 (22.5)	440 (23.8)	13.2 (32.9)	856 (32.2)	1.05 (32.2)	34.1 (18.3)	22.7 (3.4)
2.6	64.9 (30.2)	1014 (19.5)	26.8 (16.7)	1794 (17.6)	1.5 (17.6)	41.3 (21.2)	20.2 (4.4)
4.0	92.2 (18.1)	1508 (17.1)	45.8 (20.8)	2867 (22.1)	1.4 (22.1)	40.7 (16.2)	20.3 (2.1)

$AUC_{0\text{-}24}$, area under the concentration–time curve from 0 to 24 h; $AUC_{0\text{-}inf}$, area under the concentration–time curve from 0 to infinity; C_{24}, concentration at 24 h postdose; C_{max}, maximum concentration; CL_{ss}/F, apparent clearance; N, 6/cohort; $t_{1/2}$, plasma terminal half–life; Vz/F, apparent volume of distribution.
[a] Arithmetic Mean (SD).

body temperature was flat and not statistically different than zero ($P > 0.05$), indicating that the thyroid hormone changes were not clinically relevant.

Pharmacokinetics

Following single doses (Part 1), absorption of ALG-055009 was rapid with a median time to reach maximum plasma concentration (T_{max}) ranging between 1.5 and 2.0 h. A second peak in plasma ALG-055009 at around 12 h postdose in all cohorts were also observed (Figure 3). Plasma distribution/elimination phase appears to be one–phasic with a terminal half–life of ALG-055009 of approximately 20 h, which supports once daily dosing (Table 1). Mean ALG-055009 C_{max} ranged from 2.4 to 92.2 ng/mL and mean $AUC_{0\text{-}inf}$ ranged from 73.4 to 2866.5 h·ng/mL with low PK variability (CV $\leq$30% for C_{max} and AUC) across all dose levels. The 90% CI of the slope of the power model was slightly wider than the reference

Table 2. Geometric Mean (% Geometric CV) Plasma PK Parameters for ALG-055009 in Participants with Mild Hyperlipidemia Following Multiple–Ascending Doses (Part 2).

Dose (mg)	Dose number	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (ng· h/mL)	C_{24h} (ng/mL)
0.3	1st dose	6.9 (20.2)	106 (18.8)	3.1 (24.7)
0.3	14th dose	11.3 (13.7)	183 (16.0)	5.0 (16.4)
0.5	1st dose	11.0 (20.3)	177 (17.0)	5.3 (15.3)
0.5	14th dose	24.9 (26.1)	423 (25.0)	12.9 (26.8)
0.6	1st dose	11.2 (19.1)	167 (22.3)	5.0 (25.3)
0.6	14th dose	23.1 (23.2)	380 (27.2)	10.8 (35.5)
0.75	1st dose	17.9 (19.5)	261 (17.7)	7.4 (20.7)
0.75	14th dose	33.9 (28.7)	533 (26.5)	15.4 (27.2)
1.0	1st dose	24.1 (15.6)	354 (15.2)	9.8 (19.0)
1.0	14th dose	51.3 (15.7)	922 (20.8)	25.3 (21.3)

$AUC_{0\text{-}24}$, area under the concentration–time curve from 0 to 24 h; C_{24}, concentration at 24 h postdose; C_{max}, maximum concentration; N, 8/cohort.

confidence interval [0.940; 1.060]. However, the slope was approximately equal to and not statistically different from 1 ($P > 0.10$), indicating that ALG-055009 exposure increase was dose–proportional. Dose-normalized PK parameters were also generally similar at all doses, except for a slightly higher trend in dose–normalized AUC and C_{max} for the 0.9 mg dose. No trend of dose dependent changes in dose–normalized PK parameters across 0.1 to 4.0 mg dose levels was observed, further confirming dose–proportional PK of ALG-055009. Urine recovery of ALG-055009 was 1.9% to 2.5% of total dose at all dose levels, indicating low rate of elimination by the renal route.

Following multiple doses (Part 2), PK of ALG-055009 was similar to what was observed following single doses ($T_{max} \sim 1.5$-2.0 h and terminal half–life ~20 h), indicating PK was time independent (Table 2 and Figure 3). On both Day 1 and Day 14 across all dose levels (0.3 to 1.0 mg), plasma ALG-055009 increased in a dose–proportional manner. Steady–state trough plasma concentrations were reached between Days 7 and 9 for 0.3, 0.5, 0.6 and 0.75 mg doses of ALG-055009 and at Day 13 for 1.0 mg (Figure 3). Accumulation ratios on Day 14 were 1.63 to 2.60, consistent with the observed plasma half–life of ALG-055009. ALG-055009 was minimally recovered in urine (<3.2% of total dose) indicating low renal clearance.

Plasma concentrations over time were comparable for both formulations (solution and soft gelatin capsule) and in the fed and fasted state (Part 3, Figure 3). ALG-055009 C_{max} was reached at a median T_{max} of 3.0 h with the solution and soft gelatin capsule formulation in the fasted state but was 6.0 h with the capsule formulation in the fed state; half–life of ALG-055009 was approximately 20 h. A comparison of PK parameters for solid versus capsule formulations found geometric mean ratios for C_{max}, AUC_{last}, and AUC_{inf} of 0.86, and between 0.97-1.06 for the capsule formulation in fed versus fasted states (Table 3). The 90% CIs of the ratio for all PK parameters were within the reference CI. Thus, the bioavailability for solution and soft gelatin capsule formulations was similar and an absence of food effect was observed.

Pharmacodynamics

A generally dose–dependent, decrease in mean lipid parameters was observed with all single and multiple doses of ALG-055009 except the 0.1 mg single dose (Table 4 and Table S9). Mean values for apolipoprotein B and LDL–C decreased throughout the dosing period with multiple doses of ALG-055009 (Figure 4). Mean values for lipoprotein (a), very low–density lipoprotein (VLDL), and triglycerides also decreased throughout the dosing period (not shown). Mean maximum reductions for all doses versus placebo were 27.6% versus 9.3%, 26.8% versus 7.7%, 47.4% versus 13.9%, 42.2% versus 25.4%, and 42.4% versus 25.2% from baseline for apolipoprotein B, LDL–C, lipoprotein (a), very low–density lipoprotein (VLDL), and triglycerides, respectively. For other lipids evaluated (apolipoprotein A, and HDL cholesterol), there was no effect or the effect was modest for ALG-055009 versus placebo. Following treatment completion, lipid parameters generally returned to baseline or near baseline at the follow–up visit.

Following single and multiple doses, dose–dependent increases in SHBG were observed, with a return to baseline or near baseline at the follow–up visit after treatment completion (Table S9). Following multiple dosing, the largest increase occurred on Day 15, 24 h after the last dose, across all dose levels with the greatest change from baseline (95%) observed with the highest dose of 1.0 mg (Table 4 and Figure 5).

Table 3. Statistical Comparison of PK Parameters for ALG-055009 Following Single Oral 0.6 mg Dose of Solution and Soft Gelatin Capsule Formulations Under Fed and Fasted Condition in Healthy Participants in Part 3.

	Geometric mean		Geometric mean ratio	
Parameter	Test	Reference	Estimate	90% confidence interval
Soft gelatin capsule versus solution (fasted)				
C_{max} (ng/mL)	11.1	12.8	0.86	0.82-0.91
AUC_{last} (ng•h/mL)	329	382	0.86	0.82-0.91
AUC_{inf} (ng•h/mL)	345	402	0.86	0.81-0.91
Fed versus fasted for soft gelatin capsule				
C_{max} (ng/mL)	10.7	11.1	0.97	0.91-1.03
AUC_{last} (ng•h/mL)	348	329	1.06	0.99-1.12
AUC_{inf} (ng•h/mL)	367	345	1.06	1.00-1.13

AUC_{inf}, area under the concentration–time curve from 0 to infinity; AUC_{last}, area under the concentration–time curve from 0 to last time point; C_{max}, maximum concentration; N, 8.

Discussion

ALG-055009 is a THR-β agonist in clinical development being evaluated as a treatment for MASH. THR-β has become a potential target for MASH given its role in hepatic lipid metabolism, specifically modulating levels of cholesterol and triglycerides. THR-β agonists cause selective stimulation in the liver resulting in reduced fat deposits. This reduction in liver fats, in principle, should prevent the downstream consequences of MASLD (inflammation, fibrosis, hepatocellular carcinoma). Resmetirom received FDA approval in March 2024 for the treatment of non–cirrhotic NASH with liver fibrosis and is currently the only approved treatment for MASH. Side effects of resmetirom are primarily GI–related (e.g. diarrhea and nausea) and the label includes warnings for increased risk of drug–induced liver toxicity and gallbladder issues. Additionally, multiple dosage levels are available based on the patient's body weight, along with adjustments to dose levels if used concomitantly with moderate cytochrome P450 2C8 inhibitors. Improvements in the side effect profile as well as superior potency against THR-β and selectivity over THR-α may potentially offer benefits over resmetirom.

Following single and daily multiple dose settings, ALG-055009 demonstrated favorable PK including dose–proportionality, time–independence, and low variability in healthy participants and in participants with mild hyperlipidemia across all dose levels. The second peak in plasma ALG-055009 in all cohorts was observed may be as a result of enterohepatic recirculation. Single oral doses of ALG-055009 up to 4.0 mg in healthy volunteers and multiple daily doses up to 1.0 mg for 14 days in participants with mild hyperlipidemia resulted in dose–dependent reductions in lipid levels, particularly LDL–C, apolipoprotein–B, lipoprotein (a), triglycerides, and VLDL. 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.[31] In accordance with these Phase 2 results, data from the 52–week Phase 3 study of resmetirom demonstrated significant reductions in both hepatic fat content and LDL–C[34] correlating to histological improvements. ALG-055009–induced decreases in LDL–C and apolipoprotein–B may therefore correspond to a reduction in liver fat content in MASH patients in studies of longer treatment duration.

Dose–dependent increases in SHBG, a liver–specific marker of target engagement for THR-β,[35] were observed in healthy participants after single doses and in participants with mild hyperlipidemia administered multiple–ascending doses of ALG-055009. The 1.0 mg solution dose level of ALG-055009 was associated with the largest increase in SHBG levels (95% change from baseline). Importantly, data shows that NASH patients with a higher percent change from baseline in SHBG exhibit better efficacy in terms of liver fat reduction. Specifically, in the previously described Phase 2 study of resmetirom, those NASH patients with SHBG change from baseline $\geq$75% at Week 12 and 88% at Week 36 had greater relative liver fat reductions from baseline (40% and -41%, respectively) compared with those patients with lower SHBG levels.[31] High SHBG groups in this study also had more robust reductions in liver enzymes, lipids, NAS (on liver biopsy) and fibrosis biomarkers. Notably, the significant liver fat reductions observed for resmetirom in Phase 2 have translated into significant improvements in NASH liver histology in Phase 3.[34] Therefore, these PD findings are useful for designing studies with a longer duration to determine whether ALG-055009–induced increases in SHBG and improved lipoprotein levels after dosing may correlate with a reduction in liver fat content and improved histology in patients with MASH.

Table 4. Mean (SD) Percent Change From Baseline for Lipoproteins and Sex–Hormone Binding Globulin at End–of–Treatment (EOT) Visit Following Multiple Doses of ALG-055009 (Part 2).

	Mean (± standard deviation)					
	Placebo	0.3 mg	0.5 mg	0.6 mg	0.75 mg	1.0 mg
Apolipoprotein A1, g/L						
Baseline	1.2 ± 0.18	1.2 ± 0.18	1.3 ± 0.30	1.2 ± 0.09	1.2 ± 0.22	1.2 ± 0.24
Day 14 (EOT)	1.1 ± 0.18	1.0 ± 0.13	1.2 ± 0.24	1.1 ± 0.09	1.1 ± 0.11	1.1 ± 0.19
Mean % change	−10.3 ± 6.5	−11.3 ± 7.3	−10.3 ± 6.1	−12.6 ± 3.6	−8.2 ± 10.5	−13.9 ± 6.6
Day 28 (follow–up visit)	1.3 ± 0.21	1.3 ± 0.19	1.3 ± 0.24	1.3 ± 0.16	1.3 ± 0.13	1.3 ± 0.22
Mean % change	11.1 ± 8.6	8.3 ± 10.2	2.6 ± 8.5	9.7 ± 6.4	6.0 ± 16.3	2.0 ± 8.0
Apolipoprotein B, g/L						
Baseline	1.1 ± 0.2	1.1 ± 0.1	1.2 ± 0.2	1.1 ± 0.1	1.0 ± 0.2	1.0 ± 0.1
Day 14 (EOT)	1.0 ± 0.2	0.9 ± 0.1	1.0 ± 0.2	0.9 ± 0.1	0.9 ± 0.1	0.7 ± 0.1
Mean % change	−5.5 ± 14.1	−19.7 ± 8.6	−16.1 ± 7.1	−16.1 ± 6.4	−16.0 ± 9.0	−27.6 ± 6.0
Day 28 (Follow–up visit)	1.1 ± 0.2	1.1 ± 0.1	1.1 ± 0.2	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.2
Mean % change	−0.9 ± 10.5	−2.0 ± 6.2	−7.1 ± 9.5	−11.5 ± 7.5	0.4 ± 9.8	−14.2 ± 9.2
HDL cholesterol, mmol/L						
Baseline	1.1 ± 0.3	1.0 ± 0.3	1.2 ± 0.5	1.1 ± 0.1	1.0 ± 0.2	1.2 ± 0.3
Day 14 (EOT)	1.0 ± 0.3	0.9 ± 0.2	1.1 ± 0.3	1.0 ± 0.1	0.9 ± 0.1	1.1 ± 0.3
Mean % change	−9.8 ± 8.1	−9.3 ± 12.2	−6.0 ± 13.7	−9.0 ± 4.8	−5.6 ± 10.5	−7.1 ± 7.9
Day 28 (Follow–up visit)	1.3 ± 0.3	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.2	1.1 ± 0.2	1.3 ± 0.3
Mean % change	15.3 ± 9.4	13.9 ± 10.6	13.4 ± 15.8	8.9 ± 8.5	14.8 ± 19.3	9.4 ± 7.4
LDL cholesterol, mmol/L						
Baseline	3.7 ± 0.9	3.7 ± 0.7	3.9 ± 0.7	3.7 ± 0.4	3.4 ± 0.5	3.3 ± 0.4
Day 14 (EOT)	3.5 ± 0.9	3.1 ± 0.6	3.3 ± 0.8	3.0 ± 0.4	2.8 ± 0.3	2.4 ± 0.4
Mean % change	−5.9 ± 19.9	−13.6 ± 12.1	−15.5 ± 8.3	−17.4 ± 8.6	−17.9 ± 10.8	−26.8 ± 6.8
Day 28 (Follow–up visit)	3.8 ± 0.9	3.7 ± 0.7	3.7 ± 0.8	3.3 ± 0.4	3.5 ± 0.4	2.9 ± 0.6
Mean % change	2.1 ± 15.9	0.5 ± 9.7	−4.9 ± 13.6	−9.9 ± 6.9	3.4 ± 14.2	−11.9 ± 10.2
Lipoprotein–A, g/L						
Baseline	0.045 ± 0.032	0.020 ± 0.010	0.034 ± 0.022	0.037 ± 0.027	0.024 ± 0.008	0.014 ± 0.008
Day 14 (EOT)	0.055 ± 0.035	0.026 ± 0.009	0.031 ± 0.018	0.037 ± 0.026	0.022 ± 0.013	0012 ± 0.009
Mean % change	2.4 ± 20.6	6.5 ± 2.3	0.6 ± 29.5	1.9 ± 15.9	−10.4 ± 24.5	−34.9 ± 32.7
Day 28 (Follow–up visit)	0.042 ± 0.034	0.022 ± 0.006	0.026 ± 0.018	0.027 ± 0.028	0.015 ± 0.013	0.013 ± 0.004
Mean % change	−13.9 ± 18.5	−7.2 ± 6.4	−23.9 ± 21.8	−34.4 ± 16.1	−42.0 ± 34.9	−44.9 ± 10.5
Triglyceride, mmol/L						
Baseline	1.4 ± 0.4	1.8 ± 0.7	2.0 ± 1.1	1.7 ± 0.9	1.5 ± 0.4	1.3 ± 0.3
Day 14 (EOT)	1.3 ± 0.5	1.7 ± 0.6	1.5 ± 0.6	1.4 ± 0.7	1.2 ± 0.4	0.9 ± 0.3
Mean % change	2.7 ± 40.1	−4.8 ± 20.1	−18.5 ± 23.6	−20.4 ± 10.0	−23.1 ± 13.6	−34.4 ± 15.7
Day 28 (Follow–up visit)	1.1 ± 0.3	1.6 ± 0.5	1.3 ± 0.5	1.6 ± 0.8	1.1 ± 0.5	0.9 ± 0.3
Mean % change	−7.4 ± 41.9	−9.3 ± 20.9	−26.2 ± 29.9	3.0 ± 37.7	−29.5 ± 25.5	−35.7 ± 20.9
VLDL, mmol/dL						
Baseline	0.6 ± 0.2	0.8 ± 0.3	0.9 ± 0.5	0.8 ± 0.4	0.7 ± 0.2	0.6 ± 0.1
Day 14 (EOT)	0.6 ± 0.3	0.8 ± 0.3	0.7 ± 0.3	0.6 ± 0.3	0.5 ± 0.2	0.4 ± 0.1
Mean % change	2.6 ± 39.5	−4.3 ± 20.7	−18.6 ± 23.4	−20.4 ± 10.2	−23.0 ± 13.5	−34.5 ± 15.4
Day 28 (Follow–up visit)	0.5 ± 0.1	0.7 ± 0.2	0.6 ± 0.2	0.7 ± 0.4	0.5 ± 0.2	0.4 ± 0.1
Mean % change	−7.9 ± 41.3	−9.1 ± 21.5	−26.3 ± 29.7	2.9 ± 37.7	−29.3 ± 26.1	−35.7 ± 21.0
SHBG, nmol/L						
Baseline	41.7 ± 15.2	37.4 ± 46.1	42.2 ± 17.9	36.3 ± 10.9	40.2 ± 18.9	31.1 ± 11.9
Day 28 (follow–up)	38.2 ± 13.1	32.1 ± 38.1	49.4 ± 26.7	39.6 ± 12.2	41.4 ± 20.0	34.2 ± 13.5
Mean % change	−6.4 ± 15.2	−12.0 ± 5.8	14.3 ± 20.8	9.8 ± 17.0	3.0 ± 13.2	10.2 ± 13.9

LDL, low density lipoprotein; SHBG, sex hormone binding globulin; VLDL, very low density lipoprotein.
Values are at baseline for the final completion visit and the mean percent change from baseline to the final completion visit.

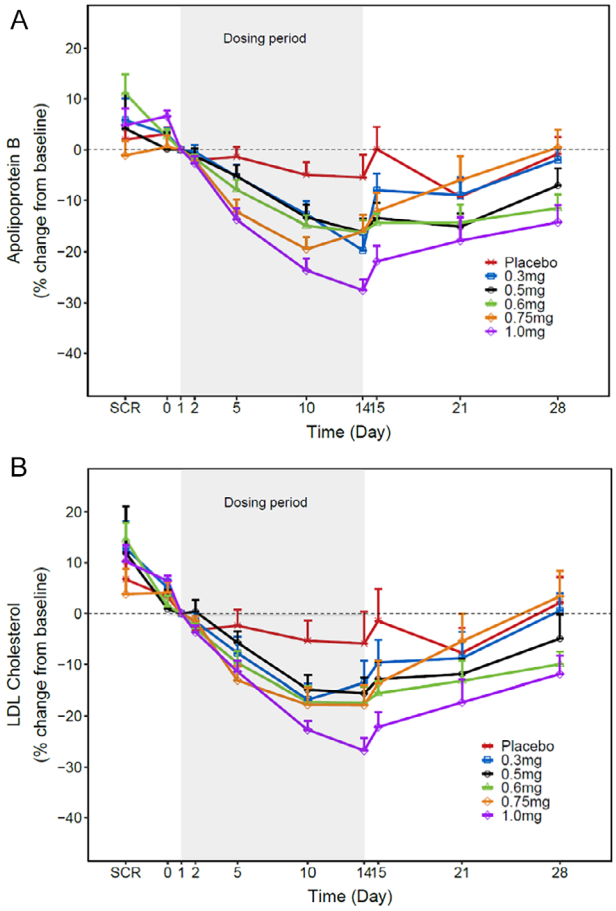

Figure 4. Mean (standard error) percent change from baseline in (A) apolipoprotein–B and (B) LDL–cholesterol following daily oral doses of ALG-055009 for 14 days in participants with mild hyperlipidemia (Part 2).

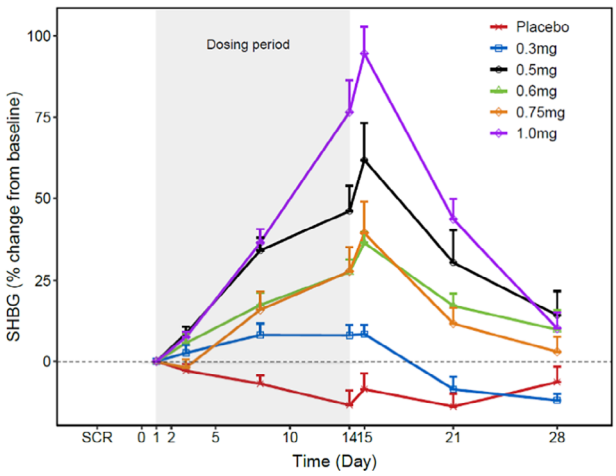

Figure 5. Mean percent change from baseline (standard error) for SHBG following daily oral doses of ALG-055009 for 14 days in participants with mild hyperlipidemia (Part 2).

As expected for a drug with thyromimetic properties, dose–related decreases in thyroid hormones (free T3, free T4, and TSH) were observed after multiple doses of ALG-055009; all values returned to baseline levels after study drug was discontinued and the thyroid hormone decreases were not associated with clinical hypo– or hyperthyroidism. Specifically, no participants experienced symptoms or clinically relevant abnormal vital sign measurements or ECG findings, and there was no association between ALG-055009 exposures and changes from baseline in heart rate, blood pressure, or body temperature based on PK/PD analysis.

Limitations of this trial include small sample size and short duration of evaluation that preclude comparison of the side effect profile of ALG-055009 and any potential advantages over resmetirom, particularly related to GI–mediated effects. In addition, the majority of participants were male, even though selection criteria specified inclusion of both males and females. This imbalance limits generalization of the study results to females. Participation of female participants will be important in future studies with ALG-055009 to treat MASH considering that females have a somewhat higher prevalence of MASH than males, 54% and 46%, respectively.[9]

Taken together, these data demonstrate that ALG-055009 can safely be dosed once daily without regard to food and across a wide dose range (up to 1.0 mg following repeated dosing). Additionally, the PK/PD relationship between expected thyromimetic effects (changes in thyroid hormone, lipid, and SHBG levels) was established across this dose range. Importantly, the high dose of 1.0 mg in the MAD established the upper limits of thyroid hormone modulation that were acceptable under the criteria defined in this study. The PK achieved across the dose range in this study can be used to correlate ALG-055009 doses in the clinic with efficacious exposures identified in diet–induce obesity mouse models and therefore determine the appropriate dose range and maximal exposures for subsequent larger and longer duration studies.

In summary, oral ALG-055009 demonstrated a favorable PK and PD profile along with the high selectivity for THR-β and nanomolar potency (approximately 50-fold more potent than resmetirom) that is consistent with activity in MASH patients based on the currently available data. The favorable safety, PK, and PD profile of ALG-055009 in this Phase 1 study support continued evaluation of once daily doses of ALG-055009 with the soft gelatin capsule formulation in longer–term and larger clinical studies including more meaningful clinical endpoints (e.g. MRI–PDFF, liver biopsy). Currently, a 12-week Phase 2a study is ongoing in non–cirrhotic adults with presumed MASH and liver fibrosis

across four ALG-055009 dose levels (NCT06342947). These data will ultimately be used along with emerging nonclinical data to determine the overall risk–benefit profile and potential for continued evaluation of ALG-055009 in longer duration clinical trials in subjects with MASH.

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Conflicts of Interest

Hakim Charfi was the Principal Investigator and is employed by Biotrial, Rennes, France. All other authors are or were employees of and may hold stock in Aligos Therapeutics, Inc.

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Data Availability Statement

Qualified academic investigators and researchers can request additional patient–level, de–identified clinical data and supporting documents (statistical analysis plan) pertaining to this study. For details regarding data availability, instructions for requesting information, and data disclosure policy, please contact the corresponding author.

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Supplemental Information

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