Multifactorial Effects of AXA1125 and AXA1957 Observed on Markers of Metabolism, Inflammation and Fibrosis: A 16-Week Randomized Placebo-Controlled Study in Subjects With Nonalcoholic Fatty Liver Disease (NAFLD) With and Without Type 2 Diabetes (T2D)

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Introduction

- Nonalcoholic fatty liver disease (NAFLD) is associated with a spectrum of histologic manifestations, including simple steatosis, steatohepatitis, fibrosis, and cirrhosis[1]
- Because multiple metabolic and fibroinflammatory pathways are dysregulated in NAFLD and nonalcoholic steatohepatitis (NASH),[2] patients may benefit from approaches that support multiple pathways related to normal health processes
- Endogenous metabolic modulators (EMMs) encompass a broad set of molecular families that include amino acids (AAs), fatty acids and other lipids, bile acids, ketone bodies, hormones, and other molecules. EMMs can be selectively combined to form EMM compositions to simultaneously support multiple metabolic nodes and pathways key to liver health and multifactorial diseases
- AXA1125 and AXA1957 are novel, orally administered EMM compositions of AAs and related metabolites and precursors specifically designed to simultaneously support pathways related to liver metabolism, inflammation, and fibrosis
  - AXA1125 is composed of leucine, isoleucine, valine, arginine, glutamine, and N-acetylcysteine (LIVRQNac)
  - AXA1957 is a distinct EMM composition that is isonitrogenous to AXA1125 and was developed to examine additional biological activity; it is composed of leucine, isoleucine, arginine, glutamine, N-acetylcysteine, carnitine, and serine (LIRQNacCarS)
- In a prior non-IND clinical study (AXA1125-002) that assessed the safety, tolerability, and biological activity on liver structure and function with AXA1125 in subjects with NAFLD and type 2 diabetes (T2D), AXA1125 demonstrated positive trends in biomarkers related to liver structure (steatosis, fibrosis) and function (insulin sensitivity, inflammation)[3]
  - Additionally, nonclinical data in primary human cells and rodents confirm the simultaneous activity of LIVRQNac on core pathophysiological features of NASH[4,5]

Aim

- To assess the safety, tolerability, and biological activity on liver structure and function with AXA1125 and AXA1957 in subjects with NAFLD (AXA1125-003; NCT04073368)

Methods

- This was a 16-week, placebo-controlled, multicenter, randomized, single-blind, multi-arm, non-IND clinical study of adults with NAFLD
- Subjects were eligible for inclusion if they had proton density fat fraction (PDFF) ≥10%, corrected T1 (cT1) ≥830 mSec by multiparametric magnetic resonance imaging (MRI), and fasting aspartate aminotransferase (AST) >20 IU/L; subjects with a diagnosis of T2D were eligible to enroll in the study
- Key exclusion criteria included current or history of significant alcohol consumption, liver disease (other than NAFLD or NASH), and/or hepatic decompensation
- Subjects were stratified based on T2D status and randomized in a 2:2:2:1 ratio to receive orally administered AXA1125 24 g; AXA1957 13.5 g or 20.3 g; or a calorie, excipient, and color-matched placebo 24 g twice daily for 16 weeks
- Changes in diet, physical activity, and body weight were recorded at every visit, with the expectation that subjects would maintain their body weight within 5% of baseline
- Assessments were carried out on Day 1 (baseline) and at Weeks 1, 2, 4, 8, 12, and 16; a follow-up visit occurred 2 weeks after each subject's last visit
- Safety and tolerability were evaluated through adverse events (AEs), clinical safety laboratory tests, vital signs, body weight, electrocardiograms, and other safety parameters
- Activity on liver structures and functions was assessed by measuring change from baseline in key parameters of metabolism (eg, MRI-PDFF and homeostasis model assessment of insulin resistance [HOMA-IR]) and fibroinflammation (eg, alanine aminotransferase [ALT], cT1, cytokeratin-18 [CK-18] M65, N-terminal type III collagen propeptide [ProC3])
  - Key thresholds of activity were also assessed: proportion of subjects achieving reductions of ≥30% in MRI-PDFF, ≥17 U/L in ALT, and ≥40 mSec in cT1
- Analysis of covariance for continuous endpoints and the Cochrane–Mantel–Haenszel test for binary endpoints were applied (both adjusted for baseline T2D status), and summary statistics were reported based on the observed data collected at each visit
- This non-IND clinical study was exploratory in nature and not designed to evaluate impact on disease nor to have statistical power to compare biological assessments versus placebo
- Here, we report top-line results from all subjects who received ≥1 dose of study product based on the dose received on Day 1 (safety population)

Results

Baseline Characteristics

- Of the 488 subjects screened, 102 were randomized and received ≥1 dose of study product; 15 subjects received placebo, 29 received AXA1125, 26 received AXA1957 low dose, and 32 received AXA1957 high dose
- Baseline characteristics among the overall population were suggestive of presumed NASH (mean MRI-PDFF 21.8, cT1 987.1 mSec, FibroScan 13.0 kPa, and ProC3 16.8 ng/mL) and insulin resistance (mean HOMA-IR 10.9) (Table 1)
- Forty subjects (39.2%) had comorbid T2D; in these subjects, the mean glycosylated hemoglobin (HbA1c) was 7.4%

Table 1: Subject Demographics and Baseline Characteristics

	Placebo (n=15)	AXA1125 (n=29)	AXA1957 Low (n=26)	AXA1957 High (n=32)
Age, years	53.2 (9.62)	49.2 (12.79)	49.6 (10.74)	50.1 (12.79)
Sex Female, n (%) Male, n (%)	 10 (66.7) 5 (33.3)	 17 (58.6) 12 (41.4)	 16 (61.5) 10 (38.5)	 19 (59.4) 13 (40.6)
Weight, kg	118.25 (31.75)	102.86 (23.82)	106.24 (23.50)	102.31 (26.14)
BMI, kg/m^2	42.0 (9.39)	36.8 (7.32)	37.4 (6.11)	38.5 (8.49)
Type 2 diabetes, n (%) HbA1c, %	6 (40.0) 6.9 (0.46)	12 (41.4) 7.8 (0.95)	10 (38.5) 7.3 (1.37)	12 (37.5) 7.5 (0.88)
Metabolism				
Liver fat content by MRI-PDFF, % HOMA-IR	21.19 (5.86) 8.59 (4.86)	22.35 (5.01) 13.51 (17.91)	21.01 (5.93) 9.62 (6.88)	22.27 (5.23) 10.82 (9.93)
Inflammation				
ALT, U/L AST, U/L cT1, mSec	50.5 (33.81) 41.3 (34.29) 1022.3 (160.16)	55.2 (26.33) 37.3 (22.69) 960.6 (90.71)	60.6 (28.87) 40.6 (21.0) 959.5 (110.52)	50.5 (23.25) 34.9 (16.56) 1017.2 (137.46)
Fibrosis				
FibroScan score, kPa ProC3, ng/mL ELF score FIB-4	13.51 (5.69) 15.85 (6.29) 9.42 (1.23) 1.42 (0.98)	11.73 (6.67) 17.07 (8.09) 9.24 (0.89) 1.05 (0.63)	16.31 (15.76) 17.02 (9.48) 9.18 (0.85) 1.17 (0.66)	11.18 (3.82) 16.76 (9.14) 9.30 (0.91) 1.0 (0.58)

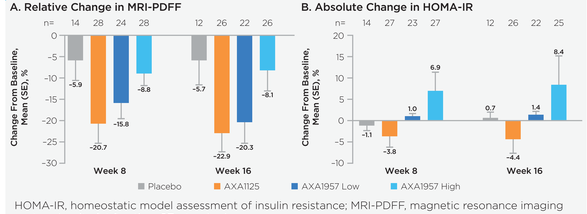
All values are mean (SD) unless otherwise noted.
ALT, alanine aminotransferase; BMI, body mass index; cT1, corrected T1; ELF, Enhanced Liver Fibrosis; FIB-4, fibrosis-4; HOMA-IR, homeostasis model assessment of insulin resistance; MRI-PDFF, magnetic resonance imaging proton density fat fraction; ProC3, N-terminal type III collagen propeptide; SD, standard deviation.

Biological Activity

- AXA1125 consistently resulted in numerically greater reductions from baseline in biomarkers of liver fat and fibroinflammation versus placebo, and AXA1957 showed activity in a number of key biomarkers but with less consistent directional change than AXA1125 (Figures 1–3)
- Both AXA1125 and AXA1957 reduced liver fat biomarker MRI-PDFF at Weeks 8 and 16 compared with placebo, though reductions with AXA1125 were more marked (Figure 1A)
- At Weeks 8 and 16, greater absolute mean reductions from baseline HOMA-IR were seen with AXA1125 compared with placebo, but not with AXA1957 (Figure 1B)

FIGURE 1

Reduction From Baseline in Biomarkers of Metabolism: (A) Liver Fat by MRI-PDFF and (B) Insulin Resistance by HOMA-IR

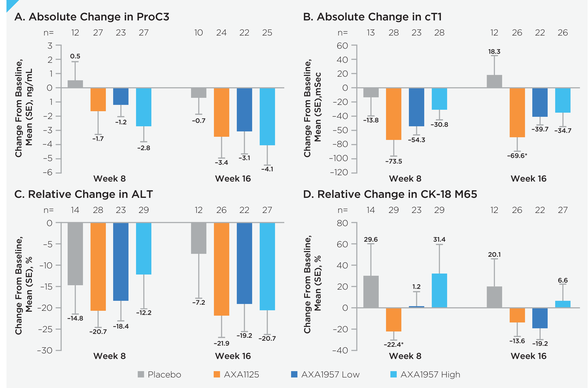


HOMA-IR, homeostatic model assessment of insulin resistance; MRI-PDFF, magnetic resonance imaging proton density fat fraction; SE, standard error.

- Fibrosis biomarker ProC3 was also reduced more markedly by both AXA1125 and AXA1957 than placebo at Weeks 8 and 16 (Figure 2A)
- Reductions in cT1 were seen with AXA1125 and AXA1957 at Weeks 8 and 16, though those with AXA1125 were greater—at Week 16, AXA1125 significantly reduced absolute cT1 versus placebo (p<0.05; Figure 2B)
- Compared with placebo, larger reductions in inflammation marker ALT were seen with AXA1125 and AXA1957 low dose at Weeks 8 and 16 and with AXA1957 high dose at Week 16 (Figure 2C)
- Inflammation as measured by CK-18 M65, which reflects overall cell death, was significantly reduced from baseline at Week 8 with AXA1125 (p<0.05) and numerically reduced with AXA1125 and AXA1957 low dose at Week 16 compared with placebo. CK-18 M65 increased less with AXA1957 high dose than placebo at Week 16 (Figure 2D)

FIGURE 2

Reduction From Baseline in Biomarkers of Fibrosis by (A) ProC3 and Inflammation by (B) cT1, (C) ALT, and (D) CK-18 M65

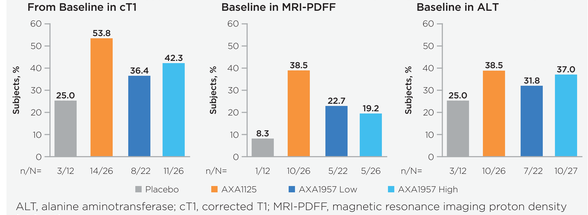


*p<0.05 versus placebo.
ALT, alanine aminotransferase; CK-18 M65, cytokeratin-18 measured using M65 enzyme-linked immunosorbent assay; cT1, corrected T1; ProC3, N-terminal type III collagen propeptide; SE, standard error.

- There is increasing evidence linking key thresholds of reductions in MRI-PDFF, ALT, and cT1 with improved histologic outcomes[6-9]
- A greater proportion of subjects who received AXA1125 and AXA1957 (high and low doses) achieved ≥40-mSec absolute reduction in cT1, ≥30% relative reduction in MRI-PDFF, and ≥17-U/L absolute reduction in ALT compared with placebo, though a higher percentage of subjects achieved these reductions with AXA1125 compared with both doses of AXA1957 (Figure 3)

FIGURE 3

Subjects Achieving a Key Reduction Threshold in (A) cT1, and Reduction Thresholds Associated With Improved Histologic Outcomes in (B) MRI-PDFF and (C) ALT at Week 16



ALT, alanine aminotransferase; cT1, corrected T1; MRI-PDFF, magnetic resonance imaging proton density fat fraction.

Safety

- AXA1125 and AXA1957 were both generally well tolerated in the study (Table 2)
- All product-emergent AEs for those treated with AXA1125 and AXA1957 were mild or moderate (Table 2)
- The most common product-emergent AEs (experienced by ≥10% of subjects in any arm) were gastrointestinal (diarrhea, nausea, reduced appetite), upper respiratory tract infection, and headache
- Gastrointestinal AEs were generally mild and transient, self-resolving in 2 to 3 weeks on average
- Two serious AEs were reported, both of which were determined to be unrelated to study product administration
- Rates of discontinuation due to adverse events were low (Table 2)
- There were no meaningful changes in lipids or weight profiles

Table 2: Adverse Events at Week 16

	Placebo (n=15)	AXA1125 (n=29)	AXA1957 Low (n=26)	AXA1957 High (n=32)
Total product-emergent AEs	22	71	43	61
Subjects[a,b]				
All PEAEs	10 (66.7)	24 (82.8)	19 (73.1)	19 (59.4)
All PEAEs reported in >10% for any arm:				
Diarrhea	1 (6.7)	10 (34.5)	3 (11.5)	6 (18.8)
Nausea	1 (6.7)	4 (13.8)	3 (11.5)	3 (9.4)
Upper respiratory infection	1 (6.7)	4 (13.8)	0	2 (6.3)
Decreased appetite	0	3 (10.3)	2 (7.7)	1 (3.1)
Headache	1 (6.7)	1 (3.4)	4 (15.4)	2 (6.3)
AE leading to discontinuation	1 Dry mouth[d]	1 Upper abdominal pain[e]	0	2 Laryngeal cancer[c,f] Nephrolithiasis[f]
Any serious AE	0	1 (3.4)	0	1 (3.1)
Death	0	0	0	0
Severity of AEs among subjects with product-emergent AE[a,b]				
Mild	6 (40.0)	16 (55.2)	8 (30.8)	6 (18.8)
Moderate	3 (20.0)	8 (27.6)	11 (42.3)	13 (40.6)
Severe	1 (6.7)	0	0	0

Data are n or n (%). [a]Subjects were counted only once if they had more than 1 event reported during the product administration period; [b]Safety data presented are based on what subject received on Day 1 of dosing. [c]Also a serious AE; [d]Related; [e]Possibly related; [f]Unlikely related. AE, adverse event; PEAE, product-emergent adverse event.

Conclusions

- AXA1125 and AXA1957 were safe, well tolerated, and resulted in clinically relevant multitargeted activity on biomarkers of metabolic and fibroinflammatory pathways, which are associated with NAFLD and NASH
- The potential of these EMM compositions to simultaneously address the multifactorial pathogenesis of NASH and its key comorbidities (eg, T2D) represents a novel modality with a unique mechanism of action
- Biological activity was consistently greater among those treated with AXA1125 than with both doses of AXA1957, warranting further study of AXA1125
- Future development of AXA1125 for the treatment of adult and pediatric subjects with NASH are planned in IND-enabled clinical trials

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Disclosures

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