Safety, Tolerability, and Biological Activity of AXA1125 and AXA1957 in a Prospective 16-Week Randomized, Placebo-Controlled Study in Subjects With NAFLD With and Without Type 2 Diabetes

Poster

Virtual Cafe

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Introduction

- Nonalcoholic fatty liver disease (NAFLD) is associated with a spectrum of histologic manifestations, including isolated steatosis, steatohepatitis, fibrosis, and cirrhosis[1]
- Patients with complex multifactorial diseases like NAFLD and nonalcoholic steatohepatitis (NASH) may benefit from approaches that concordantly address multiple metabolic and fibroinflammatory pathways[2]
- 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 multifactorial diseases and liver health
- 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 isonitrogenous to AXA1125 and is composed of leucine, isoleucine, arginine, glutamine, N-acetylcysteine, carnitine, and serine (LIRQNacCarS); it was designed to examine additional biological activity
- In a prior pilot, open-label, non-IND clinical study of AXA1125 (AXA1125-002), AXA1125 demonstrated positive trends in biomarkers related to liver structure (steatosis, fibrosis) and function (insulin sensitivity, inflammation) in subjects with NAFLD and type 2 diabetes (T2D)[3]; these results were supported by targeted plasma metabolomic and lipidomic data[4–6]
  - Additionally, nonclinical data from primary human cells and NASH rodent models confirm multitargeted activity of LIVRQNac on core NASH pathophysiologic features[5,6]
- There is increasing evidence linking reductions in specific biomarkers (corrected T1 [cT1], N-terminal type III collagen propeptide [ProC3], magnetic resonance imaging-proton density fat fraction [MRI-PDFF], and alanine aminotransferase [ALT]) with improved histologic or clinical outcomes[7–11]

Aim

- To assess the safety, tolerability, and biological activity on liver structure and function with AXA1125 and AXA1957 in subjects with NAFLD with and without T2D (AXA1125-003; NCT04073368)

Methods

- The full methods for this non-IND clinical study have been previously described[12]
- Adults with NAFLD ± T2D enrolled in this 16-week, multicenter, randomized, placebo-controlled non-IND clinical study 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, AXA1957 20.3 g (calorie-matched and isonitrogenous to AXA1125), or a calorie-, excipient-, and color-matched placebo 24 g twice daily
- Activity on liver structure and function was assessed by measuring change from baseline in key measures of metabolism (MRI-PDFF and homeostasis model assessment of insulin resistance [HOMA-IR]), inflammation (ALT and cT1), and fibrosis (ProC3 and fibrosis 4 [FIB-4])
  - Key thresholds of activity were captured indicating the proportions of subjects achieving reductions of either ≥80 mSec in cT1, ≥2 ng/mL in ProC3, ≥30% in MRI-PDFF, or ≥17 U/L in ALT
- Safety and tolerability were evaluated through adverse events (AEs), safety laboratory tests (including fasting lipid profiles), physical examinations (including body weight), and other safety parameters
- 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 results from all subjects who received ≥1 dose of study product based on the dose received on Day 1 (overall safety population), with a particular focus on AXA1125 versus placebo. Of note, while both AXA1125 and AXA1957 were well tolerated and demonstrated relevant biological activity, AXA1125 had more consistent results across the 3 critical biological nodes relevant for NASH pathogenesis, and coupled with the results from the prior AXA1125-002 study, will be the candidate advancing in development

Results

Baseline Characteristics

- Of the 488 subjects screened, 102 were randomized and received ≥1 dose of study product (placebo, n=15; AXA1125, n=29; AXA1957 low dose, n=26; AXA1957 high dose, n=32)
- Baseline mean MRI-PDFF of 21.8%, cT1 of 987.1 mSec, FibroScan of 13.0 kPa, and ProC3 of 16.8 ng/mL were consistent with presumed NASH; baseline mean HOMA-IR of 10.9 was consistent with insulin resistance (Table 1)
- Comorbid T2D was present among 40 subjects (39.2%); mean glycated hemoglobin was 7.4% among the T2D group (Table 1)

Table 1: Subject Demographics and Baseline Characteristics in the Overall Safety Population

	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 (%)	10 (66.7)	17 (58.6)	16 (61.5)	19 (59.4)
Male, n (%)	5 (33.3)	12 (41.4)	10 (38.5)	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 (%)	6 (40.0)	12 (41.4)	10 (38.5)	12 (37.5)
HbA1c, %	6.9 (0.46)	7.8 (0.95)	7.3 (1.37)	7.5 (0.88)
Metabolism				
Liver fat content by MRI-PDFF, %	21.19 (5.86)	22.35 (5.01)	21.01 (5.93)	22.27 (5.23)
HOMA-IR	8.59 (4.86)	13.51 (17.91)	9.62 (6.88)	10.82 (9.93)
Inflammation				
ALT, U/L	50.5 (33.81)	55.2 (26.33)	60.6 (28.87)	50.5 (23.25)
AST, U/L	41.3 (34.29)	37.3 (22.69)	40.6 (21.0)	34.9 (16.56)
cT1, mSec	1022.3 (160.16)	960.6 (90.71)	959.5 (110.52)	1017.2 (137.46)
Fibrosis				
FibroScan score, kPa	13.51 (5.69)	11.73 (6.67)	16.31 (15.76)	11.18 (3.82)
ProC3, ng/mL	15.85 (6.29)	17.07 (8.09)	17.02 (9.48)	16.76 (9.14)
ELF score	9.42 (1.23)	9.24 (0.89)	9.18 (0.85)	9.30 (0.91)
FIB-4	1.42 (0.98)	1.05 (0.63)	1.17 (0.66)	1.0 (0.58)

All values are mean (SD) unless otherwise noted.

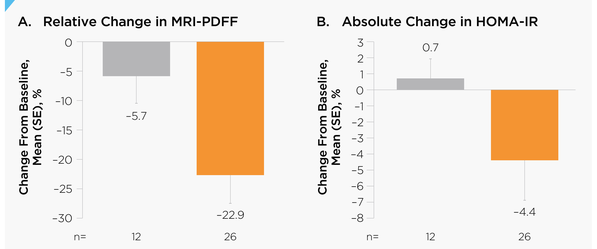
ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; cT1, corrected T1; ELF, Enhanced Liver Fibrosis; FIB-4, fibrosis 4; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; MRI-PDFF, magnetic resonance imaging proton density fat fraction; ProC3, N-terminal type III collagen propeptide; SD, standard deviation.

Biological Activity

- AXA1125 consistently resulted in greater reductions from baseline in liver fat and markers of fibroinflammation versus placebo, which were evident as early as Week 8 and were sustained or further reduced through Week 16 (Figures 1–3)
  - AXA1125 led to a greater relative reduction in liver fat by MRI-PDFF at Week 16 versus placebo (Figure 1A)
  - At Week 16, a greater absolute mean reduction from baseline HOMA-IR was seen with AXA1125 versus placebo (Figure 1B)
  - Relative changes over time for ALT showed that reductions from baseline with AXA1125 compared with placebo occurred as early as Week 2 and were sustained to Week 16 (Figure 2)
  - At Week 16, AXA1125 significantly reduced absolute cT1 from baseline versus placebo (p<0.05; Figure 3A)
  - Fibrosis biomarkers ProC3 and FIB-4 showed greater reductions from baseline with AXA1125 versus placebo at Week 16 (Figures 3B and 3C)

FIGURE 1

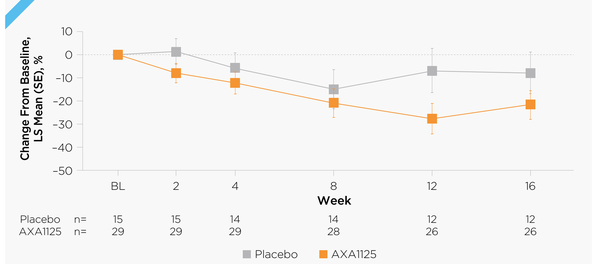
Reduction From Baseline in Biomarkers of Metabolism at Week 16 in the Overall Safety Population: (A) Liver Fat by MRI-PDFF and (B) Insulin Resistance by HOMA-IR



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

FIGURE 2

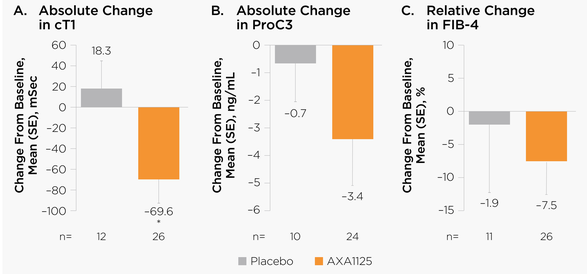
Change From Baseline ALT Over Time in the Overall Safety Population



ALT, alanine aminotransferase; BL, baseline; LS, least squares; SE, standard error.

FIGURE 3

Reduction From Baseline in Biomarkers of Fibroinflammation at Week 16 in the Overall Safety Population: Inflammation by (A) cT1 and Fibrosis by (B) ProC3 and (C) FIB-4



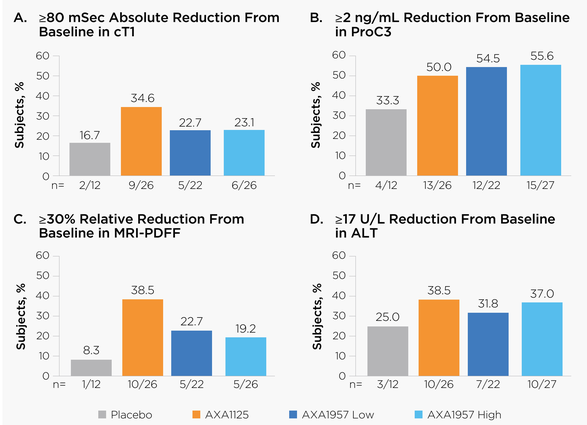
*p<0.05 versus placebo.

cT1, corrected T1; FIB-4, fibrosis 4; ProC3, N-terminal type III collagen propeptide; SE, standard error.

- AXA1957 led to numerically greater reductions from baseline compared with placebo at Weeks 8 and 16 in some measures; however, changes were less robust and consistent than those observed with AXA1125
  - AXA1957 led to reductions from baseline versus placebo in MRI-PDFF, ALT, cT1, and ProC3
  - AXA1957 did not lead to reductions relative to placebo in HOMA-IR or FIB-4
- Greater activity was observed with AXA1125 than with AXA1957 in MRI-PDFF, HOMA-IR, ALT, cT1, and FIB-4
- As the study was stratified on T2D status, analysis of subjects with T2D showed that AXA1125 resulted in greater reductions from baseline versus placebo in subjects with T2D compared with the overall population for MRI-PDFF (–31.2% vs –8.3%), absolute HOMA-IR (–9.2 vs –0.8), and ALT (–34.6% vs –13.9%)
- More subjects who received AXA1125 versus placebo achieved ≥80 mSec absolute reduction in cT1 (Figure 4A), ≥2 ng/mL reduction in ProC3 (Figure 4B), ≥30% relative reduction in MRI-PDFF (Figure 4C), and ≥17 U/L absolute reduction in ALT (Figure 4D)
- A greater proportion of subjects who received AXA1125 achieved key thresholds of reduction in cT1 (Figure 4A), MRI-PDFF (Figure 4C), and ALT (Figure 4D) compared with subjects who received placebo and AXA1957

FIGURE 4

Subjects in the Overall Safety Population at Week 16 Achieving Key Reduction Thresholds for (A) cT1 and (B) ProC3 and Reduction Thresholds Associated With Improved Histologic Outcomes for (C) MRI-PDFF and (D) ALT



ALT, alanine aminotransferase; cT1, corrected T1; MRI-PDFF, magnetic resonance imaging proton density fat fraction; ProC3, N-terminal type III collagen propeptide.

Safety

- AXA1125 and AXA1957 were both generally well tolerated in the study (Table 2)
- All product-emergent AEs for those administered 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, decreased appetite), upper respiratory tract infection, and headache (Table 2)
- Gastrointestinal AEs were generally mild and transient, self-resolving without intervention (eg, no antidiarrheal, antiperistaltic, or antiemetic agents required) within 2 to 3 weeks
- The 2 serious AEs reported were determined to be unrelated to study product administration (Table 2)
- Rates of discontinuation due to AEs were low (Table 2)
- There were no meaningful changes in lipids or weight profiles

Table 2: AEs at Week 16 in the Overall Safety Population

	Placebo (n=15)	AXA1125 (n=29)	AXA1957 Low (n=26)	AXA1957 High (n=32)
Total PEAEs	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[c]	1 Upper abdominal pain[d]	0	2 Laryngeal cancer[e,f] Nephrolithiasis[f]
Any serious AE[f]	0	1 (3.4)	0	1 (3.1)
Death	0	0	0	0
Severity of AEs among subjects with PEAEs[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 within each category reported during the product administration period; [b]Safety data presented are based on what subject received on Day 1 of dosing; [c]Related; [d]Possibly related; [e]Also a serious AE; [f]Unlikely related.

AE, adverse event; PEAE, product-emergent adverse event.

Conclusions

- AXA1125 and AXA1957 were safe, well tolerated, and demonstrated clinically relevant multitargeted activity on biomarkers of metabolic and fibroinflammatory pathways, which are associated with NAFLD and NASH
  - In subjects with presumed NASH (as indicated by baseline characteristics), greater biological activity was consistently observed with AXA1125 than with AXA1957 or placebo in subjects with and without T2D, all of whom had presumed NASH as indicated by baseline characteristics
  - This activity with AXA1125 was generally of a higher magnitude in the prespecified analysis of T2D subjects; these data are expanded further in a separate GHAPP 2021 Conference Poster
  - As AXA1125 and AXA1957 are calorie-matched and isonitrogenous, the greater activity with AXA1125 underscores the differentiated activity that can be generated via novel EMM compositions
  - Results for AXA1125 from this study closely replicate those seen in our previous non-IND clinical study (AXA1125-002)[3]
- 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 multitargeted mechanism of action
- Axcella has decided to advance the AXA1125 program for the treatment of adult and pediatric subjects with NASH through IND-enabled clinical trials

References

1. Do A, Lim JK. *Clin Liver Dis.* 2016;7:106–108.
2. Friedman SL, et al. *Nat Med.* 2018;24:908–922.
3. Marukian S, et al. *Hepatology.* 2018;68(Suppl 1):67A. Abstract 106.
4. Chakravarthy MV, et al. *Hepatology.* 2019;70(Suppl 1): 1264A. Abstract 2134.
5. Lee CW, et al. Poster P02-05 presented at: EASL NAFLD Summit 2017.
6. Marukian S, et al. Oral presentation at: Keystone Symposia 2019.
7. Ratziu V, et al. *Hepatology.* 2020;72:892–905.
8. Harrison SA, et al. *Hepatology.* 2020;71:1198–1212.
9. McDonald N, et al. *Sci Rep.* 2018;8:9189.
10. Loomba R, et al. *Hepatology.* 2020;72:1219–1229.
11. Loomba R, et al. *Gastroenterology.* 2019;156:88–95.e5.
12. Harrison SA, et al. Poster presented at: European Association for the Study of the Liver 2020.

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