Biological Activity of AXA1125 and AXA1957 on Glucose, Insulin, HOMA-IR, and HbA1c and Measures of Liver Fat and Fibroinflammation in a Prospective 16-Week Randomized, Placebo-Controlled Study in Subjects With NAFLD and Type 2 Diabetes

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Introduction

- Nonalcoholic fatty liver disease (NAFLD) is multifactorial, mediated by dysregulated metabolic and fibroinflammatory pathways[1]
- Because NAFLD and type 2 diabetes (T2D) have a well-established bidirectional link, with insulin resistance serving as a common metabolic driver,[2] targeting insulin resistance is a potential strategy for managing NAFLD
- 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
- As novel, orally administered EMM compositions of AAs and related metabolites and precursors, AXA1125 and AXA1957 are specifically designed to support pathways related to liver metabolism, inflammation, and fibrosis in a multitargeted manner
- AXA1125 is composed of leucine, isoleucine, valine, arginine, glutamine, and N-acetylcysteine (LIVRQNac)
- A previous non-IND clinical study (AXA1125-002) assessed the safety, tolerability, and biological activity of AXA1125 on liver structure and function in subjects with NAFLD and T2D and demonstrated positive directional changes in biomarkers related to liver fat, insulin sensitivity, inflammation, and fibrosis,[3] results that were supported by targeted plasma metabolomic and lipidomic data[4–6]
- Composed of leucine, isoleucine, arginine, glutamine, N-acetylcysteine, carnitine, and serine (LIRQNacCarS), AXA1957 is isonitrogenous to AXA1125 and was developed to examine additional biological activity

Aim

- To assess the safety, tolerability, and biological activity on liver structure and function with AXA1125 and AXA1957 in subjects with NAFLD and T2D (AXA1125-003; NCT04073368)

Methods

- The full methods for this non-IND clinical study have been previously described[7]
- 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
- Subjects with T2D were eligible to enroll in the study if they were receiving stable treatment for T2D and related comorbidities
- Activity was assessed by measuring change from baseline in key measures of glucose homeostasis (glucose and insulin in fasted states and during oral glucose tolerance tests [oGTT], homeostasis model assessment of insulin resistance [HOMA-IR], glycosylated hemoglobin [HbA1c]), as well as measures of liver fat (magnetic resonance imaging proton density fat fraction [MRI-PDFF]), inflammation (alanine aminotransferase [ALT] and corrected T1 [cT1]), and fibrosis (N-terminal type III collagen propeptide [ProC3])
  - Key thresholds of activity included proportion of subjects achieving reductions of ≥80 mSec in cT1, ≥30% in MRI-PDFF, and ≥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
- Two-sample t-test for continuous endpoints and chi-square test for binary endpoints were applied, and summary statistics were reported based on the data available 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 the subjects with T2D who received ≥1 dose of study product based on the dose received on Day 1 (safety population)

Results

Baseline Characteristics

- Of the 102 subjects who received ≥1 dose of study drug, 40 (39.2%) had T2D
- Within the T2D group, 6 subjects received placebo, 12 received AXA1125, 10 received AXA1957 low dose, and 12 received AXA1957 high dose
- Baseline characteristics and demographics were similar among groups and reflected stable glycemic control (mean fasted HOMA-IR 15.2 and HbA1c 7.4%) (Table 1)
- Baseline mean fasting plasma glucose, insulin, and triglyceride levels were 150.6 mg/dL, 38.1 mIU/L, and 172.7 mg/dL, respectively
- Baseline mean MRI-PDFF of 22.4%, cT1 of 1005.4 mSec, FibroScan of 13.9 kPa, and ProC3 of 18.13 ng/mL were consistent with presumed nonalcoholic steatohepatitis (NASH)

Table 1: Subject Demographics and Baseline Characteristics in Subjects With T2D

	Placebo (n=6)	AXA1125 (n=12)	AXA1957 Low (n=10)	AXA1957 High (n=12)
Age, years	51.7 (12.64)	51.0 (10.80)	49.6 (10.79)	49.7 (11.44)
Sex				
Female, n (%)	4 (66.7)	9 (75.0)	6 (60.0)	6 (50.0)
Male, n (%)	2 (33.3)	3 (25.0)	4 (40.0)	6 (50.0)
Weight, kg	122.4 (38.94)	101.2 (13.91)	102.9 (22.20)	110.0 (27.59)
BMI, kg/m^2	41.4 (11.09)	38.6 (5.76)	36.5 (6.47)	41.4 (9.36)
Metabolism				
Fasting plasma glucose, mg/dL	130.28 (24.45)	160.92 (58.29)	150.11 (38.71)	151.19 (38.17)
Fasting plasma insulin, mIU/L	40.6 (12.02)	42.3 (44.69)	31.3 (18.49)	38.4 (22.18)
Fasting triglycerides, mg/dL	148.80 (56.14)	174.48 (104.60)	174.48 (89.90)	180.68 (73.51)
Liver fat content by MRI-PDFF, %	23.05 (5.21)	23.58 (4.54)	20.44 (5.27)	22.61 (6.69)
HOMA-IR	12.9 (3.64)	19.2 (25.76)	11.9 (7.98)	15.0 (12.29)
HbA1c, %	6.9 (0.46)	7.8 (0.95)	7.3 (1.37)	7.5 (0.88)
Inflammation				
ALT, U/L	51.3 (42.31)	60.8 (26.19)	70.4 (33.51)	48.8 (22.71)
AST, U/L	36.7 (23.53)	45.1 (29.44)	47.8 (24.21)	33.8 (16.64)
cT1, mSec	1040.0 (204.68)	999.3 (105.15)	957.5 (97.34)	1034.2 (187.17)
Fibrosis				
FibroScan score, kPa	14.2 (5.70)	9.9 (1.34)	19.8 (19.49)	13.0 (5.00)
ProC3, ng/mL	13.78 (3.97)	18.35 (10.64)	19.71 (10.95)	18.05 (10.38)
ELF score	9.24 (1.29)	9.37 (0.73)	9.61 (0.90)	9.57 (0.99)
FIB-4	1.07 (0.35)	1.25 (0.79)	1.38 (0.74)	0.98 (0.59)

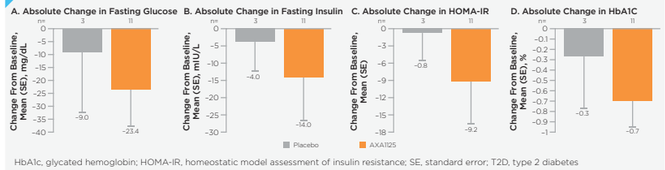
All values are mean (SD) unless otherwise noted.
ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; cT1, corrected T1; ELF, Enhanced Liver Fibrosis; FIB-4, fibrosis 4; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; MRI-PDFF, magnetic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

Biological Activity

- AXA1125 showed consistently greater activity across markers of glucose homeostasis, liver fat, and fibroinflammation compared with placebo in subjects with T2D (Figures 1–4)
- At Week 16, a numerically greater reduction from baseline was seen with AXA1125 versus placebo for fasting glucose (Figure 1A), which was not observed with either dose of AXA1957
- AXA1125 administration also led to greater numerical reductions relative to placebo in fasting insulin at Week 16 (Figure 1B). For AXA1957, neither the low or high dose showed reductions from baseline that were greater than those observed with placebo
- For HOMA-IR, AXA1125 showed greater absolute reductions from baseline versus placebo at Week 16 (Figure 1C), whereas with AXA1957, HOMA-IR either increased (high dose) or was largely unchanged (low dose)
- A greater absolute mean reduction from baseline in HbA1c was seen with AXA1125 compared with placebo by Week 16 (Figure 1D), but not with either dose of AXA1957

FIGURE 1

Reduction From Baseline in Biomarkers of Glucose Homeostasis at Week 16 in Subjects With T2D: (A) Fasting Glucose, (B) Fasting Insulin, (C) HOMA-IR, and (D) HbA1c

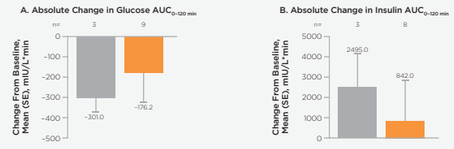


HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; SE, standard error; T2D, type 2 diabetes

- At Week 16, glucose excursions during 120 minutes of oGTT tended to be lower with AXA1125 compared with placebo (Figure 2A)
- Consistent with the lowered glucose excursion, insulin area under the curve from 0 to 120 minutes ($AUC_{0-120\ min}$) tended to be concomitantly decreased with AXA1125 relative to placebo at Week 16 (Figure 2B)
- These findings, in the setting of glucose ingestion, suggest improved glucose handing (ie, improved glucose/insulin ratio) and likely reduced insulin resistance, further supported by the observations noted with fasting HOMA-IR (Figure 1C)

FIGURE 2

Change From Baseline at Week 16 in Subjects With T2D in (A) Glucose $AUC_{0-120\ min}$ and (B) Insulin $AUC_{0-120\ min}$

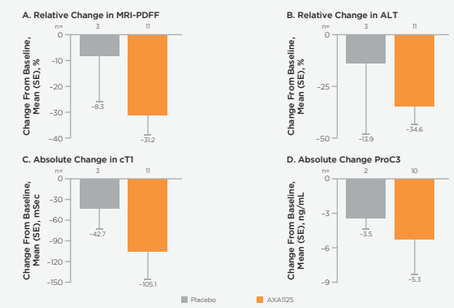


$AUC_{0-120\ min}$, area under the curve from 0 to 120 minutes; SE, standard error; T2D, type 2 diabetes.

- Compared with placebo, larger relative reductions in MRI-PDFF were seen with AXA1125 at Week 16 (Figure 3A). AXA1957 low dose also reduced MRI-PDFF versus placebo at both time points, though changes were less marked than with AXA1125
- Administration of AXA1125 led to a greater relative reduction versus placebo in ALT at Week 16 (Figure 3B). For AXA1957, only the low dose showed greater reductions from baseline compared with placebo for ALT at Week 16
- Fibroinflammatory marker cT1 showed an absolute reduction from baseline at Week 16 with AXA1125 that was greater than with placebo (Figure 3C). Administration of both doses of AXA1957 led to reductions in cT1 at both time points but were not greater than those observed with placebo
- At Week 16, the absolute change from baseline in ProC3 was greater with AXA1125 than with placebo (Figure 3D). Both doses of AXA1957 also showed greater reductions from baseline in ProC3 than placebo at Week 16

FIGURE 3

Reduction From Baseline in Subjects With T2D at Week 16 in Biomarkers of Metabolism by (A) MRI-PDFF, Inflammation by (B) ALT and (C) cT1, and Fibrosis by (D) ProC3

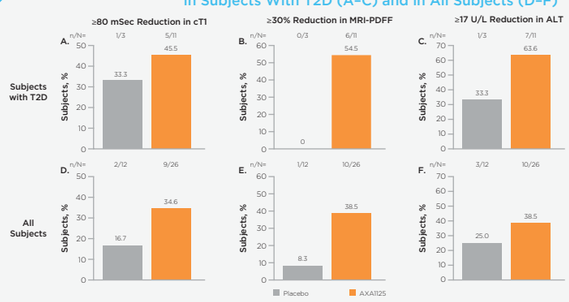


ALT, alanine aminotransferase; cT1, corrected T1; MRI-PDFF, magnetic resonance imaging proton density fat fraction; ProC3, N-terminal type III collagen propeptide; SE, standard error; T2D, type 2 diabetes.

- There is increasing evidence linking a ≥30% relative reduction in MRI-PDFF and ≥17 U/L absolute reduction in ALT with improved histologic outcomes[8–11]; ≥80 mSec absolute reduction in cT1 may also correlate with a 2-point NAFLD score improvement[9,10]
- At Week 16, 46%–64% of subjects with T2D who received AXA1125 achieved ≥80 mSec absolute reduction in cT1, ≥30% relative reduction in MRI-PDFF, or ≥17 U/L absolute reduction in ALT (Figures 4A–4C)
- The percentage of subjects achieving these thresholds with AXA1125 was up to ~1.7-fold higher in the T2D population (Figures 4A–4C) compared with the overall population (Figures 4D–4F)
- Improvements in activity across markers of glucose homeostasis, liver fat, and fibroinflammation in subjects with T2D were seen without confounding body weight or serum lipid changes in the overall population

FIGURE 4

Subjects Achieving a Key Reduction Threshold in cT1, and Reduction Thresholds Associated With Improved Histologic Outcomes in MRI-PDFF and ALT at Week 16 in Subjects With T2D (A–C) and in All Subjects (D–F)



ALT, alanine aminotransferase; cT1, corrected T1; MRI-PDFF, magnetic resonance imaging proton density fat fraction; 2D, type 2 diabetes.

Safety

- In the overall population, AXA1125 and AXA1957 were generally well tolerated in the study
- Product-emergent AEs for those administered AXA1125 and AXA1957 were mostly mild to moderate, and few subjects discontinued study product because of AEs

Conclusion

- Multitargeted and coordinated activity on glucose, insulin, HOMA-IR, and HbA1c and markers of liver fat and fibroinflammation for both EMM compositions was observed in subjects with T2D, with AXA1125 generating greater biological activity than AXA1957 or placebo
  - Results for AXA1125 are consistent with those seen in our previous non-IND clinical study (AXA1125-002) in T2D subjects with NAFLD,[3] and are further supported by phenotypic and mechanistic data[4–6]
  - Because AXA1125 and AXA1957 are calorie-matched and isonitrogenous, the differential activity profile is believed to reflect differences in the components within each EMM composition, underscoring that EMM composition matters for optimal activity
- AXA1125 improved glucose homeostasis and showed concordant improvement in liver fat and fibroinflammation without confounding weight or lipid changes
- The potential for AXA1125 to simultaneously address the multifactorial biology of NASH and improve insulin resistance, a critical driver of NASH pathogenesis, supports the unique multitargeted mechanism of action of this EMM composition and warrants additional studies
- Axcella has decided to advance the program for AXA1125 for the treatment of adult and pediatric subjects with NASH through IND-enabled clinical trials

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Disclosures

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