**Introduction**

- Nonalcoholic fatty liver disease (NAFLD) is multifactorial, mediated by dysregulated metabolism, and fibrosis/hematary pathways.
- Because NAFLD and type 2 diabetes (T2D) have a well-established epidemiological and clinical relationship, targeting insulin resistance is a potential strategy for managing NAFLD.
- Endogenous metabolic mediators (EMMs) encompass a broad set of molecules that include vitamin acids (AA), fatty acids and other lipids, bile acids, ketone bodies, hormones, and other molecules. EMMs can be selectively combined to form EMM compositions to simultaneously suppress multiple metabolic nodes and pathways key to liver health and multifactorial diseases.
- As novel, orally administered EMM compositions of AAs and related metabolites and mAbs, 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 carnitine, and-serine (LIRQNaC). 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 in a placebo-controlled non-IND clinical study.

**Methods**

- The full methods for this non-IND clinical study have been previously described.
- Adults with NAFLD and T2D enrolled in this 24-week, multicenter randomized, placebo-controlled clinical study in 73 clinical sites at 44 sites in the U.S. (CX2018015201, 2018015202, and 2018015203; NCT03806206).
- Subjects with T2D were randomized in a 2:2:1 ratio to receive Placebo, AXA1125, or AXA1957 at high dose or low dose.
- Subjects were randomized to receive AXA1125 in three dose levels (n=12 per group).
- AXA1125 showed more than 30% improvements in PDFF in 17 subjects including 6 with diabetes.
- AXA1125 led to a greater relative reduction versus placebo in ALT at Week 16 compared with placebo.
- AXA1125 led to a greater absolute change in MRI-PDFF versus placebo at Week 16.
- AXA1125 led to greater reductions in ELF score compared with placebo.
- AXA1125 led to greater reductions in HbA1c versus placebo at Week 16.
- AXA1125 led to greater reductions in glycated hemoglobin (HbA1c) versus placebo at Week 16.

**Results**

**Baseline Characteristics**

- Of the 102 subjects who received at least one 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 10 received AXA1957 high dose.
- Baseline characteristics and demographics were similar among groups and reflective glycemic control (mean HbA1c 9.4% and T2D-7.4%) (Table 1).

**Baseline Mean fasting plasma glucose, insulin, and triglyceride levels were 150.6 mg/dL, 38.1 mIU/L, and 19.71 mg/dL, respectively.**

**Baseline Mean MRI-PDFF of 22.9 % (15.06% using MRI-PDFF; 13.9 mg/dL using FRS and ProC3 of 4.18 mg/dL, were consistent with previ-ous nonalcoholic steatohepatitis (NASH).**

**AXA1125**

- Placebo-controlled non-IND clinical study was stratified based on T2D status.
- AXA1125 and AXA1957 are calorie-matched and isonitrogenous.
- AXA1125 was selected for further studies based on the findings in the non-IND clinical study.
- AXA1125 and AXA1957 are calorie-matched and isonitrogenous, the full methods for this non-IND clinical study have been previously described.

**AXA1125**

- AXA1125 showed greater reductions from baseline in ProC3 and ELF score versus placebo.
- AXA1125 led to a greater relative reduction versus placebo in ALT at Week 16 compared with placebo.
- AXA1125 led to greater reductions in MRI-PDFF versus placebo at Week 16.
- AXA1125 led to greater reductions in ELF score compared with placebo.
- AXA1125 led to greater reductions in HbA1c versus placebo at Week 16.
- AXA1125 led to greater reductions in glycated hemoglobin (HbA1c) versus placebo at Week 16.

**AXA1957**

- AXA1957 also showed greater reductions from baseline in ProC3 and ELF score versus placebo.
- AXA1957 led to greater reductions in MRI-PDFF versus placebo at Week 16.
- AXA1957 led to greater reductions in ELF score compared with placebo.
- AXA1957 led to greater reductions in HbA1c versus placebo at Week 16.
- AXA1957 led to greater reductions in glycated hemoglobin (HbA1c) versus placebo at Week 16.

**Safety**

- In the overall population, AXA1125 and AXA1957 were generally well tolerated in the study.
- No product-emergent AEs for those administered AXA1125 and AXA1957 were mostly mild to moderate, and no 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 fibrogenic inflammation for both EMM compositions was observed in subjects with T2D, with AXA1125 generating greater biological activity than AXA1957.
- Results for AXA1125 are consistent with those seen in our previous non-IND (AXA1125-002) T2D subjects with NAFLD, and are further supported by preclinical and diabetic data.
- Because AXA1125 and AXA1957 are calorie-matched and isonitrogenous, the differential activity profile is likely due to the distinct mechanisms targeted.
- AXA1125 improved glycemic parameters and showed consistent improvement in liver fat and fibrogenic inflammation without confounding weight or lipid changes.
- The potential for AXA1125 to simultaneously address multifactorial biology of NAFLD and improve insulin resistance, a critical driver of NAFLD pathogenesis, supports the unique multitargeted mechanism of action of this EMM composition and warrants additional studies.
- Additionally, the results from the program for AXA1125 for the treatment of adult and pediatric subjects with NAFLD through IND-enabled clinical trials.

**References**

- Front Pharmacol. 2019;10: 1264A.
- Madrigal, NGM Bio, Novo Nordisk, Zydus; Consultant: Gilead; Sponsored lectures: Intercept.
- 1 dose of AXA1125.
- 1 dose of AXA1957 Low.
- 1 dose of AXA1957 High.
- All values are mean (SE). *P < 0.05 vs. Placebo at Week 16.
- **P < 0.01 vs. Placebo at Week 16.
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