LIVRQNaC (AXA1125) Enhances Insulin Sensitivity in Primary Human Hepatocytes and in Subjects With NAFLD and T2D

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Introduction

- Nonalcoholic fatty liver disease (NAFLD) is a multifactorial condition that is mediated by dysregulation of lipid metabolism and other metabolic pathways.
- Insulin resistance, commonly manifested as type 2 diabetes (T2D), is an important driver of NAFLD, and targeting these metabolic pathways is a potential therapeutic strategy.
- Endogenous metabolic mediators (EMMs), a broad class of physically and functionally diverse molecules such as amino acids, fatty acids, and other lipids, can be selectively combined to form compositions that target multiple metabolic pathways key to multifactorial liver diseases such as NAFLD.
- AXA1125 is a novel, orally administered investigational EMM composition.

Methods

Aims

- To investigate LIVRQNaC in a nonclinical primary human hepatocyte (PHH) in vitro model of lipotoxicity followed by a clinical proof-of-concept study, assessing effects on glucose homeostasis and insulin sensitivity.
- To analyze the impact of AXA1125 on metabolic and noninflammatory markers in subjects with NAFLD and T2D.
- Positive directional changes related to liver fat, insulin sensitivity, inflammation, and fibrosis were observed; these results have been supported by findings in primary human cell-based systems exposed to AXA1125.

Nonclinical Study

- PHHs from healthy human donors were incubated in complete hepatocyte-defined medium.
- Cells were switched to media containing defined custom amino acid concentrations that matched those found in healthy human plasma; media were supplemented with either (i) LIVRQNaC at specified field concentrations above the plasma level (30x for LVIVQ-NaCl syst, 7.5 mM) or (ii) saline (vehicle).
- After 24 hours of pretreatment, cells were switched to media containing a lipotoxic insult referred to as lipotoxicity, a 0.5 mM maltol saline FFA (2:1 palmitate:1-10,000 nM insulin-mediated Akt activation was determined by a change in the ratio of phosphorylated Akt to total Akt.
- The acute insulin challenge and glucose assay, PHHs were incubated with 22.2 μM glucose (Figure 1B) and insulin (15 μU/mL) in glucose-free medium supplemented with or without 10–100 nM insulin.
- Metabolism
- Glucose homeostasis: glucose and insulin in the fasted state, homeostasis model assessment of insulin resistance (HOMA-IR), and glycosylated hemoglobin (HbA1c).
- Liver fat and inflammation by magnetic resonance imaging (MRI) and proton density fat fraction (PDFF).
- Fibrosis: fibrosis-4 index (FIB-4) and transient elastography (TE).

Clinical Study

- A total of 102 subjects comprised the safety population, of which 40 (39.2%) had T2D within the T2D cohort (Figure 1A).
- Clinical baseline characteristics and demographics were generally similar across the placebo and AXA1125 groups (Table 1).

Results

Nonsurgical Study

- Administration of AXA1125 also led to larger mean reductions from baseline in MRI-PDFF, ALT, cT1, and FIB-4 (Figure 1A).
- AXA1125 demonstrated a favorable safety, tolerability, and biological activity profile in PHHs exposed to supraphysiological concentrations of saturated FFAs (Figure 1B).
- LIVRQNaC enhanced insulin-induced Akt phosphorylation (pAkt/Akt) and reduced extracellular glucose levels (Figure 1B).

Biological Activity

- AXA1125 treatment resulted in larger mean reductions from baseline in HOMA-IR, HbA1c, and MRI-PDFF compared with placebo (Figure 1C).
- AXA1125 treatment resulted in larger mean reductions from baseline in mRNA (AXA1125) compared with placebo (Figure 1C).
- Administration of AXA1125 also led to larger mean reductions from baseline in HOMA-IR, Akt, and HbA1c (Figure 1C) and placebo.

Safety

- There is increasing evidence linking a ≥10-msec absolute reduction in cT1 with improved insulin sensitivity.
- The percentage of subjects achieving these thresholds with AXA1125 was up to 3-fold higher in the T2D population compared with the overall population.

Conclusions

- In the PHH model, LIVRQNaC enhanced glucose homeostasis and improved insulin sensitivity.
- In the clinical study, concurrent changes in multiple biologic activity were consistent with improvements in glucose homeostasis, reductions in liver fat, and decreases in fibroinflammation.
- AXA1125 also led to larger mean reductions from baseline in MRI-PDFF, ALT, and FIB-4 compared with placebo.

Acknowledgments

- Employees of Axcella Health during the time the studies were conducted.
- None.

Disclosures

- Stock ownership or equity: Akero, Cirius, Galectin, Genfit, HistoIndex, Madrigal, Metacrine, NGM Biotech, Regeneron.
- Board: Akcea, Amgen, AstraZeneca, Esperion, Novartis, Regeneron, Sanofi.
- Consulting: BMS, Boehringer Ingelheim, Eli Lilly, Intercept, Janssen, Madrigal, Metacrine, NGM Biotech, Regeneron, Sanofi, 89bio; Speaker’s bureau: Eli Lilly, Merck, Sanofi.

References

- ZHY: Nothing to disclose.
- RP: Nothing to disclose.
- SJB: Stock ownership or equity: Akero, Cirius, Galectin, Genfit, HistoIndex, Madrigal, Metacrine, NGM Biotech, Regeneron.
- NTG: Nothing to disclose.
- Employees of Axcella Health during the time the studies were conducted.
- None.

Table 1: Demographics and Baseline Characteristics in Subjects With T2D

<table>
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<tr>
<th>Age, years</th>
<th>Sex</th>
<th>BMI, kg/m²</th>
<th>Waist, cm</th>
<th>SPPG, mg/dL</th>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
<th>HOMA-IR</th>
<th>HbA1c, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.5 (11.9)</td>
<td>Male, n (%)</td>
<td>22 (66.7)</td>
<td>22.2 (3.2)</td>
<td>103 (12)</td>
<td>130 (15)</td>
<td>80 (10)</td>
<td>0.75 (0.4)</td>
<td>5.0 (0.5)</td>
</tr>
<tr>
<td>45.5 (11.9)</td>
<td>Female, n (%)</td>
<td>9 (75.0)</td>
<td>21.8 (3.4)</td>
<td>100 (11)</td>
<td>126 (15)</td>
<td>78 (10)</td>
<td>0.8 (0.5)</td>
<td>5.2 (0.5)</td>
</tr>
</tbody>
</table>

FIGURE 1. Effects of LIVRQNaC on Akt Activation (A), Glucose Levels in the Presence of Insulin (B), and PDFF Protein Expression (C).

FIGURE 2. Reduction From Baseline in Biomarkers of Glucose Homeostasis at Week 16 in (A) Fasting Glucose, (B) Fasting Insulin, (C) HOMA-IR, (D) and (E) FIB-4.

Table 2: Effects of AXA1125 on Glucose Homeostasis, Liver Fat, Inflammation, and Fibrosis in Subjects With NAFLD and T2D

<table>
<thead>
<tr>
<th></th>
<th>AXA1125</th>
<th>Placebo</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>108 (18)</td>
<td>116 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin, mIU/L</td>
<td>51.7 (12.6)</td>
<td>51.0 (10.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.4 (5.1)</td>
<td>33.6 (5.1)</td>
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<tr>
<td>HOMA-IR</td>
<td>0.74 (0.4)</td>
<td>0.75 (0.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.1 (0.5)</td>
<td>5.2 (0.5)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Results are mean (SD) unless otherwise noted.

Subjects With T2D Achieving Meaningful Reduction Thresholds Associated With Improved Clinical Outcomes

- A ≥10-msec reduction in cT1
- A ≥25% reduction in MRI-PDFF