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 dysregulated metabolic pathways and inflammation driven by adipokines.
- Insulin resistance, commonly manifested as type 2 diabetes (T2D), is an important driver of NAFLD and its complications and is tightly linked to metabolic and phenotypic changes.
- Endogenous metabolic modulators (EMMs), a broad set of physiologically intrinsic molecules such as amino acids, fatty acids, and other lipids, can be selectively combined to form combinations that target multiple metabolic pathways key to multilobar liver diseases such as NAFLD.
- AXA1125 is a novel, orally administered investigational EMM composition comprising 6 amino acids and a derivative of inosine, valine, alanine, and folic acid; LIVRQNac has the same constituent components at different relative ratios for use in vitro at supraphysiological concentrations.

Aims

- To investigate LIVRQNac in a nonalcoholic primary human hepatocyte (PHH) in vitro model of insulin resistance following an insulin challenge, assessing effects on glucose homeostasis, and insulin sensitivity.
- To analyze the impact of AXA1125 on metabolic and fibroinflammatory markers in subjects with NAFLD and T2D (AXA1125-003; NCT04731588).

Methods

Nonclinical Study

- Phases from 3 healthy human donors were incubated in complete hepatocyte medium.
- Cells were switched to media containing defined custom amino acid concentrations for 25 mM glucose (in an insulin-free medium), then washed and incubated in high-insulin (or insulin-free) medium, glucose output levels were measured for 40-60 sec in cT1 >80 msec in cT1).

Clinical Study

- A total of 50 subjects comprised the safety population, of which 40 (39.2%) had T2D.
- Within the T2D group, 6 subjects received placebo, 12 received AXA1125.
- Baseline characteristics and demographics were similar among the placebo and AXA1125 groups (Table 1).

Table 1. Demographics and Baseline Characteristics in Subjects With T2D

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=6)</th>
<th>AXA1125 (n=12)</th>
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<tbody>
<tr>
<td>Age, yrs</td>
<td>61.7 (14.4)</td>
<td>63.0 (10.5)</td>
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<tr>
<td>Sex, female (%)</td>
<td>6 (60)</td>
<td>10 (83.3)</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>51.3 (35.4)</td>
<td>58.0 (39.0)</td>
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<tr>
<td>BMI, kg/m²</td>
<td>21.2 (6.9)</td>
<td>24.6 (3.2)</td>
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<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>100.1 (68.7)</td>
<td>100.6 (58.3)</td>
</tr>
<tr>
<td>Fasting plasma insulin, µU/mL</td>
<td>16.2 (4.9)</td>
<td>24.7 (6.3)</td>
</tr>
<tr>
<td>Liver fat content by MRI-PDFF (%)</td>
<td>30.7 (12.8)</td>
<td>25.6 (14.6)</td>
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<tr>
<td>Inflammation</td>
<td>5.6 (1.5)</td>
<td>6.8 (2.5)</td>
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- Reduced plasma glucose levels were measured. AXA1125 was generally well tolerated, with no serious adverse drug reactions reported.

Results

Nonclinical Study

- In PHH model with supraphysiological concentrations of saturated FAs (model system to induce lipidotoxicity), LIVRQNac enhanced insulin-induced Akt phosphorylation (Figure 1A) and reduced extracellular glucose levels (Figure 1B).

Clinical Study

- At Week 16, AXA1125 demonstrated consistently greater activity versus placebo across biomarkers of metabolism and fibroinflammation in subjects with T2D (Figures 2–4).

Biological Activity

- At Week 16, AXA1125 demonstrated consistently greater activity versus placebo across biomarkers of metabolism and fibroinflammation in subjects with T2D (Figures 2–4).

Safety

- In the overall population, AXA1125 was generally well tolerated, with no serious adverse drug reactions reported.

Disclosures

- Four subjects had adverse events that led to study discontinuation (1 with placebo, 1 with AXA1125, and 2 with AXA957 high dose).

Conclusions

- A phase II clinical trial (NCT04880187; EMMPACT) of AXA1125 is currently underway to evaluate its efficacy in treating NAFLD and T2D.

References