Remogliflozin etabonate reduces insulin resistance and liver function enzymes: role for treatment of NASH

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Chief Operating Officer, Islet Sciences
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Remogliflozin Etabonate (RE) Development: Sodium Glucose Transporter 2 (SGLT2) Inhibitor

• Clinical development
  • 21 clinical studies performed
  • Over 850 subjects have received RE
  • Doses up to 4 g and 12 weeks
  • Safe and well-tolerated

• Preclinical development
  • DMPK complete
  • Long term safety (52 wk dog; 26 wk rat; 13 wk mouse) completed
  • NOAELs: 650 mg/kg/day lowest level
  • Two year carcinogenicity completed, no significant findings
  • CMC/formulation work completed, novel formulation in progress
Study Group
Colleagues/Collaborators

Clinical Study

**BHV Pharma**
- Bentley Cheatham
- Sue Walker

**Islet Sciences**
- Bill Wilkison

- Financial support from Kissei Pharmaceuticals (preclinical) and GlaxoSmithKline (clinical)
Clinical Study Results

• Study Design
  • Randomized, double-blind, placebo-controlled, parallel-group trial

• Subjects were type 2 diabetics
  • 930 screened, 336 randomized, 288 subjects (86%) completed

• Dosing
  • Remogliflozin etabonate (RE) 50, 100, 250, 500, 1000 mg and placebo twice daily (bid)
  • Pioglitazone 30 mg once daily

• Duration: 12 weeks

• Efficacy/safety assessments performed at 0, 4, 8 and 12 weeks.

• Results presented are primary analysis of effect of RE on weight and insulin resistance

• Additional results shown as post hoc analysis on LFTs

Remogliflozin
Insulin Sensitization and Weight Loss

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Remogliflozin etabonate (BID)</th>
<th>Pio (QD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>n(^{a})</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>(\Delta)HOMA IS</td>
<td>3.4</td>
<td>6.3</td>
</tr>
<tr>
<td>(\Delta)HOMA BCF</td>
<td>-2.5</td>
<td>23.1</td>
</tr>
<tr>
<td>n(^{a})</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>(\Delta)AUC OGTT</td>
<td>-0.4</td>
<td>-3.2</td>
</tr>
</tbody>
</table>

\(\Delta\Delta\) Mean

(95% CI) (-4.7, -0.9) (-3.8, -0.4) (-5.0, -1.3) (-4.9, -1.3) (-5.2, -1.9) (-4.6, -0.7)

<table>
<thead>
<tr>
<th>(\Delta) weight (kg)</th>
<th>Remogliflozin etabonate (BID)</th>
<th>PIO (QD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>50 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>n</td>
<td>47</td>
<td>46</td>
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<tr>
<td>(\Delta) vs Placebo</td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-1.36</td>
<td>-2.14</td>
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<tr>
<td>p-value</td>
<td>0.015</td>
<td>&lt;0.001</td>
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</table>
Remogliflozin
ALT Reduction and Anti-Oxidant Activity

Change from Baseline in ALT - Subjects with Baseline ALT >=30

![Graph showing mean change from baseline in ALT (U/L) for different treatments over weeks.]

- Placebo (N=13)
- 50mg (N=17)
- 100mg (N=12)
- 250mg (N=17)
- 500mg (N=21)
- 1000mg (N=12)
- Pio 30mg (N=12)

p-value=0.049*  
*Using a repeated measure analysis of all doses of remo versus placebo while controlling for baseline ALT, age, sex, race, BMI
Remogliflozin effectively addresses major pathological events leading to NASH in one molecule:

- Obesity
- Oxidative Stress

**Insulin Resistance**

**Obesity Dyslipidemia**

**Clinical**

**Remogliflozin**

**Clinical/Pre-clinical**

**Oxidative Stress Hepatocellular injury**

**Pro-Inflammatory Pathways Cytokines/Chemokines**

**NAFLD (Steatosis)**

**NASH (Steatohepatitis)**
Summary

• Remogliflozin caused weight loss, reversed insulin resistance and reduced ALT levels in patients treated for 12 weeks

• Remogliflozin suppressed the increase in liver TG content, oxidizing stress and inflammatory markers in the NAFLD model

• Remogliflozin is safe and well tolerated

• Remogliflozin demonstrated strong potential for safe and effective treatment of NAFLD/NASH

• Islet Sciences is planning a phase 2b NASH study to start in 2H 2015