Introduction

**GPR40/FFA1 receptor, a G-protein-coupled receptor (GPCR), couples predominantly to phospholipid-hydrolyzed 4,5-bisphosphate into diacylglycerol and inositol 1,4,5-triphosphate (Ghislain and Poitout, 2017, Handb Exp Pharmacol).**


As insulin and incretins are pivotal for glycemic control (Nauck and Meier, 2018, Handb Exp Pharmacol), GPR40 full agonists may provide efficacy on glucose control was durable.

SCO-267 is being prepared for Ph1 SRD study.

Contact information

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Methods

**Cellular response to compound treatment was tested in chinese hamster ovary (CHO) dhfr- cells (Clones #104 and #2) stably expressing human GPR40 (Yabuki et al., 2013, PLoS One 8(6):e67258).**

**Effects of single oral dose of each compound on glucose tolerance were tested in male N-STZ-1.5 Wistar Kyoto rats (N-STZ-1.5 rats, 25-week-old for SCO-267 vs fasiglifam study; 32 week-old for SCO-267 vs AM-1638 study), which are diabetic, were developed via subcutaneous administration of 120 mg/kg streptozotocin (STZ) to Wistar rats (KACTS, LTD, Kyoto, Japan) at 1.5 days after birth.**

**Insulin and glucose response upon oral glucose load after a repeated dosing (~2 weeks) was tested in 27-week-old rats.**

**Effects of SCO-267 on body weight control in obese condition was tested in 49-week-old diet-induced obese (DIO) rats (baseline body weight, 487 g).**

**Toxicological studies were performed according to the guidelines.**

**Table 1**: Ca²⁺ influx activity in human GPR40-expressing CHO cells.

<table>
<thead>
<tr>
<th>Test material</th>
<th>EC₅₀(nM/L)</th>
<th>EC₅₀(μM/L)</th>
<th>Fmax (μmol/L)</th>
<th>Inositol (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasiglifam</td>
<td>0.3±1.7</td>
<td>0.12±0.14</td>
<td>159±20</td>
<td>0.17±0.01</td>
</tr>
<tr>
<td>AM-1638</td>
<td>24±17</td>
<td>100±22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>100±10</td>
<td>100±22</td>
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**GPR40 full agonists can activate the enteroendocrine system while stimulating insulin and incretin secretion (Luu et al., 2012, Endocrinology 153:1460-1469).**

**SCO-267 was much effective in improving glucose tolerance than clinical level exposure of fasiglifam in diabetic rats.**

**Efficacy in improving glucose tolerance was much better to fasiglifam after the repeated administration in diabetic rats.**

**SCO-267 effectively decreased body weight in DIO rats.**

**Table 2**: Efficacy on body weight control and glucose tolerance in N-STZ-1.5 rats

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SCO-267 0.3 mg/kg (N-STZ)</th>
<th>Fasiglifam 3 mg/kg (N-STZ)</th>
<th>Vehicle (N-STZ)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose AUC0-120 mg/dL</strong></td>
<td><strong>[95% CI]</strong></td>
<td><strong>[95% CI]</strong></td>
<td><strong>[95% CI]</strong></td>
</tr>
<tr>
<td>Insulin AUC0-60 min</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&gt;0.05</td>
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<tr>
<td><strong>P</strong></td>
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</table>

**Figure 1**: A single dose effects of SCO-267 and AM-1638 in N-STZ-1.5 rats

**Figure 2**: A repeated dose effects of SCO-267 in N-STZ-1.5 rats

**Figure 3**: A repeated dose effects of SCO-267 in DIO rats

**Figure 4**: A repeated dose effects of SCO-267 in DIO rats

**GPR40 full agonist, SCO-267 stimulated insulin, GLP-1, and PYY secretion in rats. SCO-267 effectively improve glucose control and exert strong efficacy in rats with diabetes. In addition, body weight loss was observed in obese rats. Thus, SCO-267 was effective in improving diabetes and obesity in rats and may induce similar favorable effects in patients with diabetes and obesity.**

**SCO-267 is being prepared for Ph1 SRD study.**

**Contact information**

https://www.scohia.com/eng/sys/contact_research_or_pipeline/