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SCO-267, a GPR40 Full Agonist, Improves Glycemic and Body Weight Control More Than That by Fasiglifam in Rat Models of Diabetes and Obesity

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Introduction

- GPR40/FFA1 receptor, a G-protein-coupled receptor (GPCR), couples predominantly with the Gq/11 protein, promoting phospholipase C-dependent hydrolysis of phosphatidylinositol 4,5-bisphosphate into diacylglycerol and inositol 1,4,5-triphosphate (Ghislain and Poitout, 2017, *Handb Exp Pharmacol* 236:159-180.)
- GPR40 is expressed in pancreatic beta-cells and intestinal endocrine cells, and its activation stimulates insulin and incretin secretion (Mancini and Poitout, 2013, *Trends Endocrinol Metab* 24:398-407.).
- As insulin and incretin are pivotal for glycemic control (Nauck and Meier, 2018, *Diabetes Obes Metab* 20 Suppl 1:5-21.).
- GPR40 activation is considered a novel option for treating diabetes (Eleazu et al., 2018, *Chem Biol Interact* 289:32-39.).
- GPR40 full agonists can activate the enteroendocrine system while stimulating insulin secretion (Luo et al., 2012, *PLoS One* 7:e46300.).
- As GPR40 partial agonists improve glycemic control in patients with diabetes (Kaku et al., 2016, *Diabetes Obes Metab* 18:925-929.), GPR40 full agonists may provide superior efficacy and additional benefits in patients with metabolic diseases.

Objective

- The current study was conducted to evaluate the pharmacological profiles and efficacy of SCO-267, a novel GPR40 full agonist.

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:e76280.) .
- 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 Kyoto rats (RABICS, LTD. Kanagawa, 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 N-STZ-1.5 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.
- Statistical significance was first analyzed using Bartlett's test for homogeneity of variances, followed by the Williams' test ($P > 0.05$) and Shirley–Williams test ($P \leq 0.05$) for dose-dependent studies, and Dunnett's test ($P > 0.05$) and Steel test ($P \leq 0.05$) for multiple comparisons. Alternatively, statistical significance was analyzed using the F test for homogeneity of variances, followed by Student's t-test ($P > 0.2$) or the Aspin–Welch test ($P \leq 0.2$). The Williams' and Shirley–Williams tests were conducted using a one-tailed significance level of 2.5% (0.025). Other tests were conducted using a two-tailed significance level of 5% (0.05).

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Contact information
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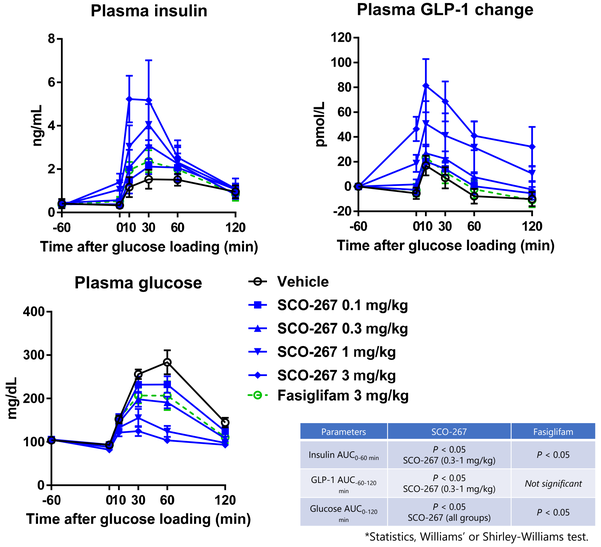
Results

SCO-267 showed full agonistic activity against GPR40

Table 1. Ca^{2+} influx activity in human GPR40-expressing CHO cells.

Test material	CHO cells with high human GPR40 expression		CHO cells with low human GPR40 expression	
	EC_{50} (nmol/L) [95% CI]	E_{max} (%γ-linolenic acid)	EC_{50} (nmol/L) [95% CI]	E_{max} (%γ-linolenic acid)
SCO-267	1.3 [0.97–1.7]	125	12 [11–14]	201
AM-1638	7.1 [5.6–9.2]	110	150 [120–180]	182
Fasiglifam	24 [16–37]	100	>1000	22
γ-linolenic acid	>10000	100	>10000	100

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

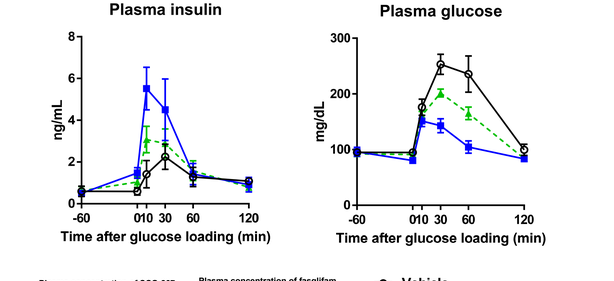


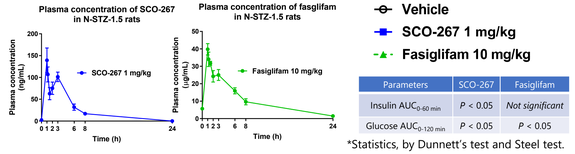
Parameters	SCO-267	Fasiglifam
Insulin $AUC_{0\text{-}60\ min}$	$P < 0.05$ SCO-267 (0.3-1 mg/kg)	$P < 0.05$
GLP-1 $AUC_{60\text{-}120\ min}$	$P < 0.05$ SCO-267 (0.3-1 mg/kg)	*Not significant*
Glucose $AUC_{0\text{-}120\ min}$	$P < 0.05$ SCO-267 (all groups)	$P < 0.05$

*Statistics, Williams' or Shirley-Williams test.

Figure 1. A single dose effects of SCO-267 in N-STZ-1.5 rats
- **Fasiglifam (50 mg, Cmax 5.3 μg/mL) was effective to improve glucose control in T2DM patients (Leifke et al., 2012, *Clin Pharmacol Ther* 92:29-39.).**
- **SCO-267 (0.3 mg/kg) and fasiglifam (3 mg/kg) had C_{max} of 22.7 ng/mL and 6.17 μg/mL, respectively.**

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



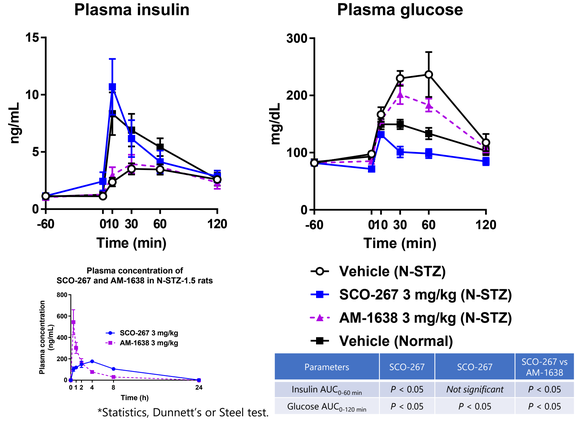


Parameters	SCO-267	Fasiglifam
Insulin $AUC_{0\text{-}60\ min}$	$P < 0.05$	*Not significant*
Glucose $AUC_{0\text{-}120\ min}$	$P < 0.05$	$P < 0.05$

*Statistics, by Dunnett's test and Steel test.

Figure 2. A repeated dose effects of SCO-267 in N-STZ-1.5 rats
- **Low plasma exposure of SCO-267 induced stronger efficacy than that by high dose of fasiglifam. Efficacy on glucose control was durable.**

SCO-267 was more effective to improve glucose tolerance compared to AM-1638 in diabetic rats

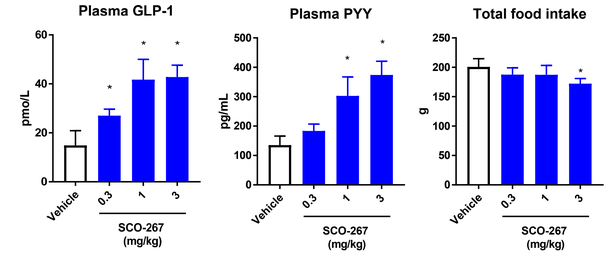


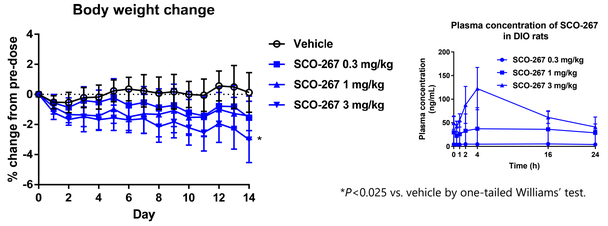
Parameters	SCO-267	SCO-267	SCO-267 vs AM-1638
Insulin $AUC_{0\text{-}60\ min}$	$P < 0.05$	*Not significant*	$P < 0.05$
Glucose $AUC_{0\text{-}120\ min}$	$P < 0.05$	$P < 0.05$	$P < 0.05$

*Statistics, Dunnett's or Steel test.

Figure 3. A single dose effects of SCO-267 and AM-1638 in N-STZ-1.5 rats

SCO-267 effectively decreased body weight in DIO rats





*P<0.025 vs. vehicle by one-tailed Williams' test.

Figure 4. A repeated dose effects of SCO-267 in DIO rats
- **GLP-1 and PYY were higher 16 h after the final dose of SCO-267**
- **Low plasma exposure of SCO-267 induced food intake reduction and body weight loss. Efficacy on body weight control was durable.**

Toxicology

- *In vitro* and *in vivo* toxicological studies demonstrated good safety profiles.
- A wide safety margin of SCO-267 was confirmed [633- (male) to 776- (female) and 421- (female) to 471- (male)-fold in the rat and dog 4-week studies, respectively].
- No concerns in the safety pharmacology studies.

Conclusions

- The GPR40 full agonist, SCO-267 stimulated insulin, GLP-1, and PYY secretion in rats. SCO-267 effectively improved glucose control and exerted 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.

Contact information

- SCO-267 is being prepared for Ph1 SRD study.
- Contact information for research or drug development of SCO-267
https://www.scohia.com/eng/sys/contact_research_or_pipeline/