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# First in human, single and repeated-dose study of SCO-267, a GPR40 full agonist, in healthy adults and subjects with glucose intolerance

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## Introduction

- 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.).
- 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.
- SCO-267 has been shown to stimulate secretion from the islet (insulin and glucagon) and gut (glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and peptide YY (PYY)) hormones in rats, and to be highly effective at improving glucose tolerance in diabetic rats (Ueno et al., J Pharmacol Exp Ther 2019; 370(2): 172–81.). Here, we report the first-in-human, single and multiple ascending dose phase 1 study of SCO-267.

## Objective

- The current study was conducted to evaluate to investigate safety, tolerability, pharmacokinetics, and pharmacodynamics of SCO-267, a novel GPR40 full agonist.

## Methods

- This study was a phase 1, placebo-controlled, randomized, double-blind, single- and multiple-dose study of SCO-267, conducted in healthy adult volunteers, as well as in patients with diabetes.
- The study enrolled a total of 96 adult male volunteers: 72 healthy Japanese volunteers, 8 healthy Caucasian volunteers, and 16 Japanese volunteers with glucose intolerance (patients with diabetes, glycated hemoglobin (HbA1c) range 6-6-8-8%). Each cohort consisted of 8 subjects: 6 subjects in the SCO-267 group and 2 in the placebo group.
- The study consisted of a single ascending dose (SAD) and a multiple ascending dose (MAD). In the SAD part, healthy Japanese and healthy Caucasian were administered an oral dose of placebo or SCO-267 (5, 10, 20, 40, 80, 160, and 320 mg). Japanese patients with diabetes were administered an oral dose of placebo or SCO-267 (40 and 80 mg) under regulated food intake conditions (oral dose of placebo/SCO-267 at 9:00 under fasting). An oral glucose tolerance test (OGTT, 75 g glucose) was performed for the patients with diabetes after more than 10 h of fasting, and 1 h (10:00) after the administration of the study drug. OGTT was also performed on the day before the drug administration as baseline. In the MAD part, Japanese subjects received once daily oral doses of placebo or SCO-267 (80 and 160 mg, respectively) for 4 days.
- The primary endpoints of this study were the safety, tolerability, and pharmacokinetics in the SAD and the MAD parts of the study. The secondary endpoints were the pharmacodynamics such as plasma levels of insulin, glucagon, GLP-1, GIP, and PYY at the indicated time points of a single oral dose of SCO-267 in patients with diabetes in the SAD part, and of multiple doses of SCO-267 in Japanese subjects in the MAD part.

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## Results

### Pharmacodynamics

- SCO-267 decreased fasting hyperglycemia without inducing hypoglycemia, and completely blocked the increase in plasma glucose levels upon glucose loading in patients with diabetes (Figure 1A).
- SCO-267 (40 and 80 mg) stimulated the secretion of insulin, glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), ) peptide YY (PYY), and glucagon in patients with diabetes (Figure 1B-F).
- A single SCO-267 (80 and 160 mg) in healthy subjects stimulated the secretion of insulin, GLP-1, GIP, PYY, and glucagon compared to the placebo. After administration of the drug for 4 days, SCO-267 still exhibited the ability to stimulate the secretion of these hormones.

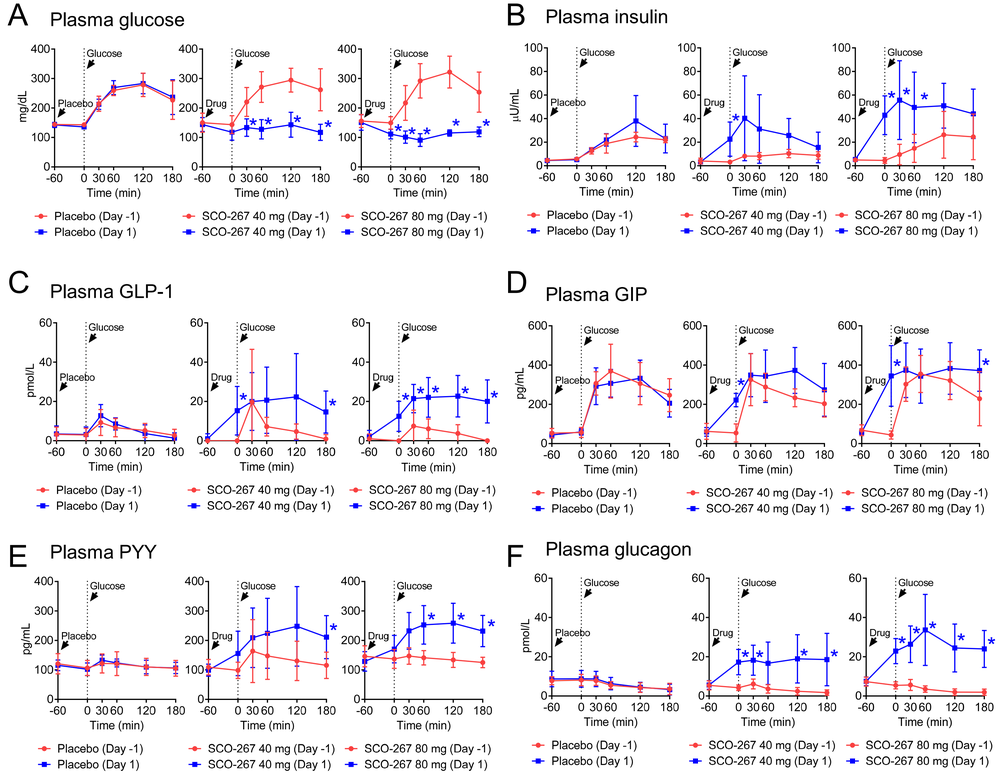



**Figure 1. Effects of a single dose of SCO-267 on hormone secretion and glucose tolerance during OGTT in patients with diabetes.**

- Plasma concentrations of (A) glucose, (B) insulin, (C) glucagon-like peptide 1 (GLP-1), (D) glucose-dependent insulinotropic polypeptide (GIP), (E) peptide YY (PYY), and (F) glucagon in patients with diabetes administered placebo (red) or SCO-267 (blue). Patients were administered SCO-267 or placebo 60 min prior to oral glucose loading (75 g), and the parameters were evaluated at the indicated time points.
- Values are presented as mean ± S.D. (n = 4, 6, 6 for placebo, SCO-267 40 mg, SCO-267 80 mg, respectively). *95% CI of the point estimate difference in the mean change for drug versus placebo, using baseline (Day −1)-adjusted values at the indicated time point did not cross zero.

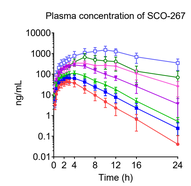
### Safety

- All TEAEs were mild or moderate in intensity. No severe TEAEs, serious TEAEs, or TEAEs leading to study drug discontinuation were reported in the study.
- No hypoglycemia was reported.

| | SAD Part | | | | | | | | | | | MAD Part | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Japanese Subjects | | | | | | | Caucasian Subjects | Patients with Diabetes | | | Japanese Subjects | | |
| | SCO-267 | | | | | | | SCO-267 | SCO-267 | | | SCO-267 | | |
| System Organ Class Preferred Term | 5 mg (N=6) | 10 mg (N=6) | 20 mg (N=6) | 40 mg (N=6) | 80 mg (N=6) | 160 mg (N=6) | 320 mg | 320 mg (N=6) | 40 mg (N=6) | 80 mg (N=6) | Placebo (N=20) | 80 mg (N=6) | 160 mg (N=6) | Placebo (N=4) |
| Subjects with ≥1 Treatment-Emergent Adverse Events | 0 (0.0) | 1 (16.7) | 1 (16.7) | 2 (33.3) | 3 (50.0) | 1 (16.7) | 4 (66.7) | 5 (83.3) | 3 (50.0) | 4 (66.7) | 4 (20.0) | 2 (33.3) | 1 (16.7) | 0 (0.0) |
| Drug-Related TEAEs | 0 (0.0) | 1 (16.7) | 1 (16.7) | 1 (16.7) | 2 (33.3) | 1 (16.7) | 4 (66.7) | 5 (83.3) | 3 (50.0) | 4 (66.7) | 4 (20.0) | 2 (33.3) | 1 (16.7) | 0 (0.0) |
| Serious TEAEs | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Severe TEAEs | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Modelate TEAEs | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (16.7) | 0 (0.0) | 1 (16.7) | 3 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| TEAEs Leading to Study Drug Discontinuation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

### Pharmacokinetics

- Following single-dose administration of SCO-267 in Japanese subjects, the plasma SCO-267 concentration increased dose-proportionately in the dose range of 5 - 320 mg (Figure 2).
- In the 4-day repeated administration of SCO-267 (80 and 160 mg), the plasma SCO-267 concentration profiles reached a steady state within 48 h after administration of the first dose.
- SCO-267 was hardly detected in urine, suggesting that it is eliminated by non-renal mechanisms.




| | SAD Part | | | | | | |
|---|---|---|---|---|---|---|---|
| | Japanese Subjects | | | | | | |
| | SCO-267 | | | | | | |
| | 5 mg (N=6) | 10 mg (N=6) | 20 mg (N=6) | 40 mg (N=6) | 80 mg (N=6) | 160 mg (N=6) | 320 mg (N=6) |
| $AUC_{0\text{-}72h}$ (ng·h/mL) | 238.5 (61.737) | 452.2 (134.40) | 837.3 (132.38) | 2378 (346.86) | 4607 (925.98) | 7567 (3707.2) | 23500 (9548.0) |
| $C_{max}$ (ng/mL) | 44.88 (12.247) | 72.65 (28.787) | 116.8 (26.938) | 282.3 (36.037) | 379.2 (64.042) | 701.5 (321.06) | 1711 (737.80) |
| $T_{max}$ (h) | 3 | 3.5 | 4 | 4 | 6 | 6 | 9 |
| $T_{1/2}$ (h) | 2.052 (0.36561) | 2.203 (0.37526) | 2.316 (0.20495) | 2.762 (0.62787) | 3.853 (1.5408) | 3.397 (0.45972) | 3.732 (0.75724) |
| Cumulative Urinary Excretion Rate (% of dose) | 0.000 (0.000) | 0.000 (0.000) | 0.000 (0.000) | 0.000 (0.000) | 0.000 (0.000) | 0.002466 (0.0034437) | 0.004860 (0.0020099) |

Data are presented as mean (SD), except for Tmax, which is presented as median

**Figure 2. Plasma concentration of SCO-267 in SAD part**

## Conclusions

- SCO-267 was generally found to be safe and well tolerated in healthy adults and patients with diabetes, in the dose range studied.
- SCO-267 showed the potential of once-daily oral dosing and the robust therapeutic effects on hormonal secretion and glycemic control suggest that SCO-267 is an attractive drug candidate for the treatment of type 2 diabetes.

## Contact information

- SCO-267 is being prepared for Ph2 study.
- Contact information for research or drug development of SCO-267
https://www.scohia.com/eng/sys/contact_research_or_pipeline/