SCO-267, a GPR40 Full Agonist, Stimulates Islet and Gut Hormone Secretion and Improves Glycemic Control in Humans

Harunobu Nishizaki,[1] Osamu Matsuoka,[2] Tomoya Kagawa,[1] Akihiro Kobayashi,[1] Masanori Watanabe,[1] and Yusuke Moritoh[1]

PHARMACOLOGY AND THERAPEUTICS

SCO-267 is a full agonist of the free fatty acid receptor 1 (GPR40), which regulates the secretion of islet and gut hormones. In this phase 1 study, we aimed to evaluate the clinical profile of single and multiple once-daily oral administration of SCO-267 in healthy adults and patients with diabetes. Plasma SCO-267 concentration was seen to increase in a dose-dependent manner after administration, and its plasma exposure was maintained for 24 h. Repeated dose did not alter the pharmacokinetic profile of SCO-267 in healthy adults. SCO-267 was generally safe and well tolerated at all evaluated single and multiple doses. Single and repeated doses of SCO-267 stimulated the secretion of insulin, glucagon, glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide, and peptide YY in healthy adults. Furthermore, a single dose of SCO-267 stimulated the secretion of these hormones, decreased fasting hyperglycemia, and improved glycemic control during an oral glucose tolerance test in patients with diabetes, without inducing hypoglycemia. This study is the first to demonstrate the clinical effects of a GPR40 full agonist. SCO-267 is safe and well tolerated and exhibits once-daily oral dosing potential. Its robust therapeutic effects on hormonal secretion and glycemic control make SCO-267 an attractive drug candidate for the treatment of diabetes.

Islet and gut hormones work together to regulate the body's metabolism (1–3). Recent studies have identified a G-protein–coupled receptor, free fatty acid receptor 1 (FFAR1 or GPR40), expressed in islet and gut cells as a pivotal player in the regulation of the secretion of these hormones (4). Medium-to-long chain fatty acids act as endogenous ligands for GPR40, and their binding upregulates intracellular responses to Ca^{2+}, thereby stimulating hormonal secretion by islet and gut cells (5–7). Fasiglifam has been found to act as a partial agonist of GPR40, exhibiting therapeutic efficacy for improving glycemic control in patients with type 2 diabetes (8–10). Recent advances in drug discovery research have led to the development of a novel group of small molecules that act as full agonists of GPR40, allowing more effective activation of the downstream signaling of this receptor (11,12).

Full agonists of GPR40 bind to a site that differs from that of GPR40 partial agonists or the endogenous ligand (13). Notably, full agonists of GPR40 increase the secretion of islet and gut hormones (11), in contrast to GPR40 partial agonists, which only upregulate insulin secretion (14). This unique feature of GPR40 full agonists results in more effective glycemic control than that achieved by the partial agonists, as demonstrated in preclinical models (11). In addition to the treatment potential for diabetes, full agonists of GPR40 may also exhibit therapeutic efficacy in the treatment of obesity and nonalcoholic fatty liver disease (15,16). The clinical profiles of full agonists of GPR40 have not yet been evaluated.

SCO-267 is an orally available GPR40 full agonist with first-in-class potential for clinical applications (17). SCO-267 has been shown to stimulate the secretion of islet (insulin and glucagon) and gut (glucagon-like peptide 1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP], and peptide YY [PYY]) hormones in rats (16). It has also been shown to be highly effective at improving glucose

[1]SCOHIA PHARMA, Inc., Kanagawa, Japan
[2]Medical Corporation Heishinkai ToCROM Clinic, Tokyo, Japan

Corresponding author: Yusuke Moritoh, yusuke.moritoh@scohia.com

tolerance in diabetic rats (16). To our knowledge, this is the first report to demonstrate the mechanisms and efficacy of a GPR40 full agonist in a clinical setting. In this study, we report the first-in-human, single ascending dose (SAD) and multiple ascending dose (MAD) phase 1 study of SCO-267. The study was designed to evaluate the safety, tolerability, and pharmacokinetics (primary end points) of once-daily oral doses of SCO-267 in healthy Japanese and Caucasian subjects and in Japanese subjects with glucose intolerance. Pharmacodynamic parameters, including glucoregulatory hormones and glycemic control, were also evaluated as secondary end points.

RESEARCH DESIGN AND METHODS

Trial Design
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 was performed at a center in Japan between November 2019 and August 2020, in accordance with the ethical principles set out in the Declaration of Helsinki and the Guidelines for Good Clinical Practice. The study design was approved by the Institutional Review Boards at the study site in line with local regulations. The clinical trial has been registered under the number JapicCTI-195057 and is available as a completed study at https://www.clinicaltrials.jp.

Participants
The study enrolled a total of 96 male volunteers: 72 healthy Japanese volunteers, 8 healthy Caucasian volunteers, and 16 Japanese volunteers with glucose intolerance (patients with diabetes, glycated hemoglobin [HbA_{1c}] range 6.6–8.8% [48.6–72.7 mmol/mol]). Each cohort consisted of eight subjects: six subjects in the SCO-267 group and two in the placebo group (Fig. 1). Volunteers who had uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, or endocrine disease or other abnormalities that could impact the ability of the subject to participate in the study or confound the results were excluded. Patients with glucose intolerance were of Japanese ethnicity and exhibited an HbA_{1c} level ≤10% (86 mmol/mol) and a plasma glucose concentration ≥230 mg/dL, 2 h after the administration of an oral dose of 75 g glucose (Table 1); these patients were diagnosed with diabetes prior to enrollment in the study. These subjects are hereafter referred to as the patients with diabetes. All participants provided written, informed consent prior to participation in the study.

Preparation of SCO-267 and Placebo, Blinding, and Randomization
The SCO-267 suspension was prepared by adding 20 mL of vehicle (sodium lauryl sulfate solution) into a glass vial containing the active ingredient and shaking vigorously to form a homogeneous solution. Placebo was similarly prepared using a corresponding quantity of sucrose fatty acid ester in place of the active ingredient. As the SCO-267 and placebo suspensions were not distinguishable by their appearance, the investigators and subjects could not distinguish SCO-267 and the placebo. Thus, the suspensions were successfully masked throughout the study. Each vial of the study drug (SCO-267 or placebo) was sequentially numbered. The vial containing the study drug was assigned to subjects in an ascending order of the subject identification code, according to the randomization schedule generated by the sponsor-designee responsible.

Procedures
Participants were admitted to the study site 1 day prior to the administration of the study drug to undergo predefined tests, observations, and assessments. Subjects who met all of the inclusion criteria and did not meet any exclusion criterion were randomly assigned a cohort and administered the study drug. The study consisted of an SAD and MAD part. In the SAD part, healthy Japanese adult male volunteers (hereafter referred to as Japanese subjects) and healthy Caucasian adult male volunteers (hereafter referred to as Caucasian subjects) were administered an oral dose of placebo or SCO-267 (5, 10, 20, 40, 80, 160, and 320 mg). Japanese male 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 0900 h under fasting). An oral glucose tolerance test (OGTT; 75-g glucose) was performed for the patients with diabetes after ≥10 h of fasting and 1 h (1000 h) after the administration of the study drug. In the MAD part, Japanese subjects received once-daily oral doses of placebo or SCO-267 (80 and 160 mg) for 4 days. The meals served during hospitalization were prepared according to the Dietary Reference Intakes for Japanese (2015) (18).

Outcomes
The primary end points of this study were the safety, tolerability, and pharmacokinetics in the SAD and the MAD parts of the study. Adverse events (AEs), vital signs, and weight were monitored, and 12-lead electrocardiograms (ECGs) and laboratory tests were conducted during the study. Continuous digital 12-lead Holter ECGs were performed in Japanese subjects only in the SAD part. Investigators evaluated all clinical AEs in terms of their intensity (mild, moderate, or severe), duration, severity, outcome, and relationship to the study drug. To evaluate the pharmacokinetic profile of SCO-267, blood samples were collected at various time points (as indicated in the figure legends), and pharmacokinetic parameters were estimated. Urine samples were also collected at different time points (as indicated in the figure legends), and the cumulative urinary excretion rates of unchanged SCO-267 (percentage of dose) as well as the renal clearances of individual subjects were determined.
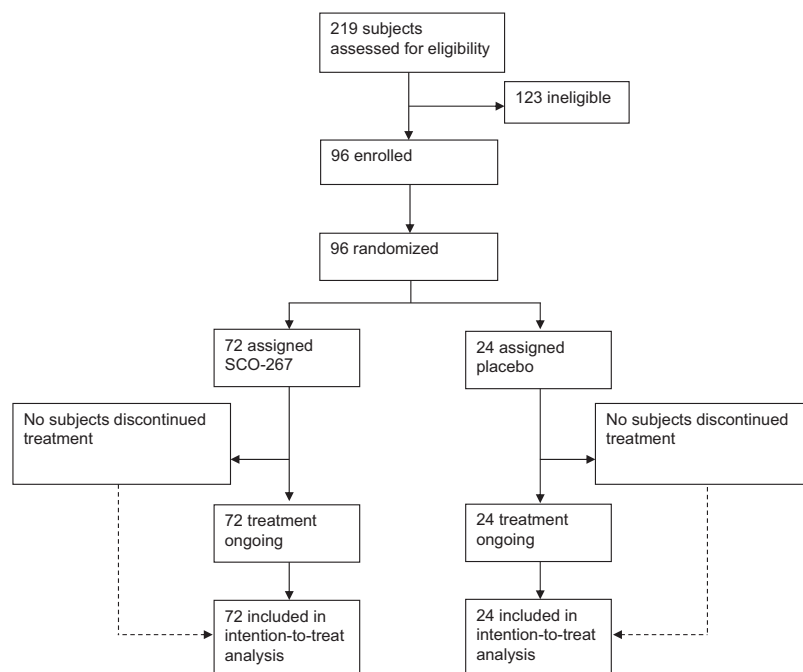
Figure 1 — Subject disposition.

The secondary end points were the pharmacodynamics 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.

Measurements

Plasma SCO-267 levels were determined at the indicated time points by liquid chromatography–tandem mass spectroscopy. Plasma levels of insulin, glucagon, GLP-1, GIP, and PYY at the indicated time points were determined using the ARCHITECT insulin assay (Abbott Laboratories, Chicago, IL), Mercodia Glucagon ELISA Kit (10–1271–01; Mercodia, Uppsala, Sweden), Total GLP-1 (version 2) Assay Kit (Meso Scale Discovery, Rockville, MD), Human GIP (total) ELISA (EZHGIP-54K; Merck Millipore, Burlington, MA), and Human PYY (Total) RIA (PYYT-66HK; Merck Millipore), respectively.

Data Analyses and Statistics

The sample size for this study was consistent with those typically used for first-in-human studies and was sufficient to obtain initial safety and pharmacokinetic data. The numbers and the proportions of subjects with treatment-emergent AEs (TEAEs) were summarized by treatment group, and descriptive statistics of the plasma concentrations and pharmacokinetic parameters of SCO-267 were calculated. The plasma pharmacokinetic and pharmacodynamic parameters of SCO-267 were calculated by noncompartmental analysis based on the plasma SCO-267 concentrations and the actual sampling time after study drug administration, using Phoenix WinNonlin

(Certara, Princeton, NJ). The linear trapezoidal linear interpolation option was used to calculate the area under the concentration curve (AUC). Cumulative urinary excretion rates of unchanged SCO-267 (percentage of dose) and renal clearance of individual subjects were calculated from the urine drug concentrations and urine volumes for each urine pooling period. The differences in the pharmacodynamic parameters were descriptively analyzed using two-sided 95% CIs. When 95% CI did not cross zero, the difference was considered statistically significant and indicated in the results. All data are presented as mean ± SD.

Data and Resource Availability

The individual data reported in this manuscript are subject to access restriction to protect subject confidentiality, except for the data presented in Figs. 2–4, which are available upon reasonable request. Reagents presented in this study may be available upon reasonable request under Material Transfer Agreement.

RESULTS

This trial was conducted between 27 November 2019 and 2 August 2020. A total of 219 subjects provided informed consent to participate in the study. Of them, 96 male volunteers were randomized to the SCO-267 group or placebo group in a 6:2 ratio and administered the respective study drug. All subjects were evaluated for the primary and secondary end point parameters. No subject dropped out of the trial. The demographics for each group are summarized in Table 1.

Table 1—Baseline characteristics of each group

	SAD part													MAD part		
	Healthy Japanese								Healthy Caucasian		Glucose intolerance			Healthy Japanese		
	SCO-267 5 mg (N = 6)	SCO-267 10 mg (N = 6)	SCO-267 20 mg (N = 6)	SCO-267 40 mg (N = 6)	SCO-267 80 mg (N = 6)	SCO-267 160 mg (N = 6)	SCO-267 320 mg (N = 6)	Placebo (N = 14)	SCO-267 320 mg (N = 6)	Placebo (N = 2)	SCO-267 40 mg (N = 6)	SCO-267 80 mg (N = 6)	Placebo (N = 4)	SCO-267 80 mg once-daily (N = 6)	SCO-267 160 mg once-daily (N = 6)	Placebo (N = 4)
Age (years)	27.3 (6.71)	25.5 (5.50)	25.7 (3.83)	23.7 (6.59)	23.0 (3.58)	26.7 (7.37)	27.2 (6.46)	23.4 (4.65)	36.3 (7.74)	31.0 (0.00)	52.5 (15.95)	57.5 (2.95)	63.8 (5.19)	27.3 (5.43)	27.8 (5.42)	29.0 (1.63)
Height (cm)	171.5 (4.74)	170.3 (3.22)	173.6 (7.60)	173.9 (5.54)	171.1 (7.20)	173.6 (8.24)	169.8 (5.45)	172.0 (6.29)	176.0 (6.34)	170.9 (3.82)	168.3 (5.12)	167.8 (6.10)	171.4 (5.59)	169.4 (5.48)	171.6 (6.27)	173.0 (4.64)
Weight (kg)	61.58 (4.385)	62.47 (3.477)	68.85 (9.187)	61.33 (2.787)	61.28 (6.302)	65.43 (11.911)	63.37 (6.557)	63.83 (7.796)	71.95 (6.351)	82.55 (9.122)	66.87 (8.552)	69.28 (5.878)	74.43 (7.288)	60.87 (3.448)	64.85 (7.400)	65.30 (7.535)
BMI (kg/m^2)	20.95 (1.564)	21.53 (0.843)	22.78 (2.035)	20.27 (0.755)	20.93 (1.595)	21.58 (2.447)	21.97 (1.684)	21.56 (2.102)	23.28 (2.188)	28.20 (1.838)	23.57 (2.344)	24.60 (1.339)	25.30 (1.337)	21.23 (1.610)	22.00 (1.489)	21.80 (2.211)
eGFR (mL/min/1.73 m^2)	99.49 (13.355)	105.23 (9.672)	93.91 (6.546)	93.39 (7.371)	91.15 (13.875)	94.18 (13.061)	91.42 (7.471)	96.69 (12.040)	80.65 (7.422)	97.37 (18.448)	96.51 (21.083)	91.38 (23.310)	74.01 (21.296)	95.72 (13.895)	97.04 (7.479)	97.58 (11.447)
C-peptide (ng/mL)	—	—	—	—	—	—	—	—	—	—	1.15 (0.413)	1.30 (0.586)	1.94 (0.485)	—	—	—
HbA$_{1c}$ (%, mmol/mol)	—	—	—	—	—	—	—	—	—	—	7.80, 61.73 (0.777, 8.495)	7.68, 60.46 (0.697, 7.617)	7.35, 56.82 (0.624, 6.826)	—	—	—
Glucose after 2 h from 75-g OGTT (mg/dL)	—	—	—	—	—	—	—	—	—	—	303.67 (54.950)	328.33 (78.360)	267.25 (35.397)	—	—	—

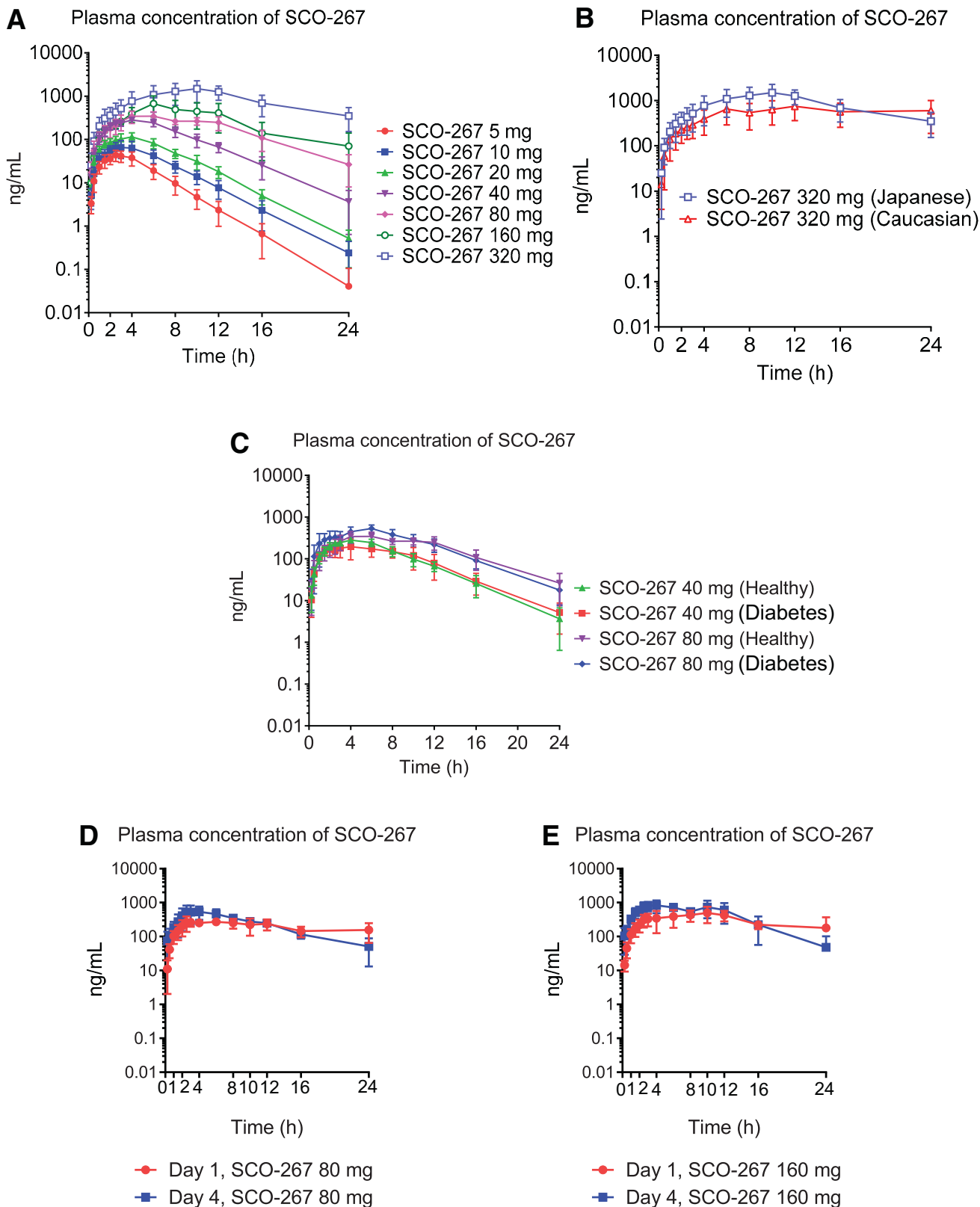Data are presented as mean (SD). eGFR, estimated glomerular filtration rate.

Figure 2—Pharmacokinetic analysis of SCO-267 in healthy adults and in patients with diabetes. *A*: Plasma concentration of SCO-267 in healthy Japanese adults in the SAD part. *B*: Plasma concentration of SCO-267 in healthy Japanese and Caucasian subjects after the administration of a single oral dose of 320 mg SCO-267 in the SAD part. *C*: Plasma concentration of SCO-267 in healthy adults and patients with diabetes after the administration of a single oral dose of SCO-267 in the SAD part. *D* and *E*: Plasma concentration of SCO-267 after administration of the first (day 1) and fourth (day 4) oral doses of SCO-267 in healthy adults in the MAD part. The indicated time points are before dosing (0), and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 h after dosing in the SAD and MAD parts (*A–E*). Values are presented as mean ± SD (*n* = 6 for each group).
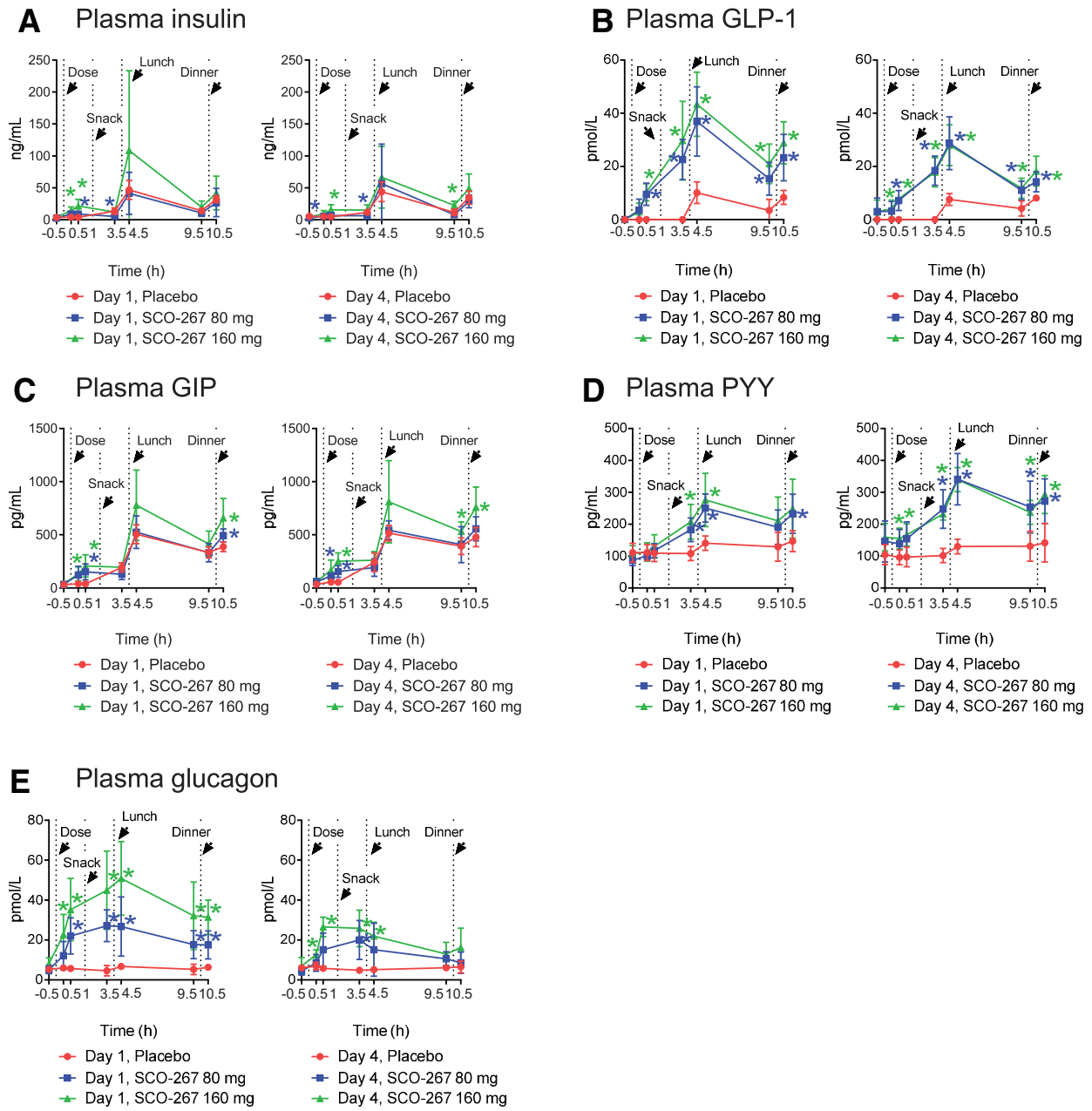
Figure 3—Effects of single and multiple administration of SCO-267 on hormone secretion in healthy adults. Plasma profiles of insulin (*A*), GLP-1 (*B*), GIP (*C*), PYY (*D*), and glucagon (*E*) after the first (day 1) and fourth (day 4) dose of placebo or SCO-267 in healthy adults. Placebo or SCO-267 was administered orally at time 0, and plasma hormone profiles were determined at the indicated time points. In the MAD part, the oral dose of placebo/SCO-267 was administered at 0900 h (time = 0) under fasting; light snacks were given at 1100 h (time = 2 h), lunch at 1300 h (time = 4 h), and dinner at 1900 h (time = 10 h). Values are presented as mean ± SD (*n* = 4, 6, and 6 for placebo, SCO-267 80 mg, and SCO-267 160 mg, respectively). *95% CI did not cross zero at the indicated time points, SCO-267 vs. placebo.

An overview of the TEAEs and those reported in two or more subjects are depicted in Table 2. All TEAEs were mild or moderate in intensity. No severe TEAEs, serious TEAEs, or TEAEs leading to study drug discontinuation were reported in the SAD part of the study. The most common TEAEs reported in the SAD part were gastrointestinal (i.e., diarrhea, nausea, vomiting, and decreased appetite)

and reported to a greater extent in groups receiving higher doses (80 and 320 mg) of SCO-267 compared with the placebo group. All TEAEs were resolved without treatment. All TEAEs reported in the MAD part were also gastrointestinal (i.e., diarrhea and nausea), mild in intensity, and considered to be associated with the study drug. All TEAEs were resolved without treatment within 3 days. No clinically
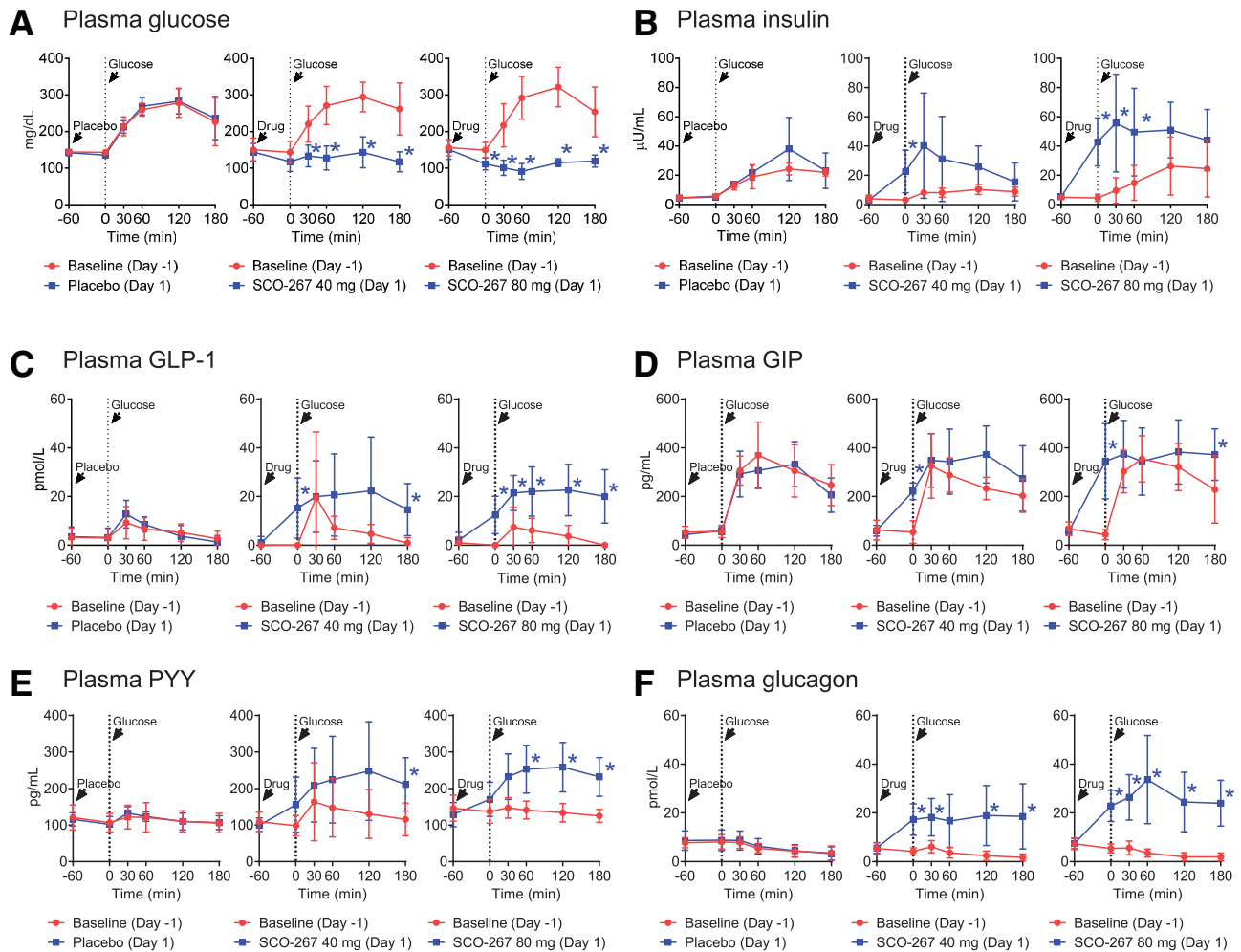
Figure 4—Effects of a single dose of SCO-267 on hormone secretion and glucose tolerance during the OGTT in patients with diabetes. Plasma concentrations of glucose (*A*), insulin (*B*), GLP-1 (*C*), GIP (*D*), PYY (*E*), and glucagon (*F*) in patients with diabetes administered placebo or SCO-267 at baseline (day −1) and day 1. Patients were administered placebo or SCO-267 60 min prior to oral glucose loading (75 g), and the parameters were evaluated at the indicated time points. Values are presented as mean ± SD (*n* = 4, 6, and 6 for placebo, SCO-267 40 mg, and SCO-267 80 mg, respectively). *95% CI did not cross zero at the indicated time points, SCO-267 vs. placebo using the baseline-adjusted (day −1) value.

meaningful changes in the laboratory parameters were observed in the treatment groups, and no significant differences in these parameters were noted between the treatment groups.

Laboratory abnormalities were infrequent and not clinically meaningful across groups, except for the changes reported as TEAEs in the SAD part. The TEAEs associated with abnormalities in laboratory parameters were reported in two or more subjects in the SAD part of the study: increase in ALT (each subject received SCO-267 [10 and 320 mg, healthy Japanese; 320 mg, healthy Caucasian] and placebo), ketone bodies present in urine (each subject received SCO-267 [80 and 160 mg, healthy Japanese], and two subjects received SCO-267 [320 mg, healthy Japanese]), and increase in AST (each subject received SCO-267 [10 and 320 mg, healthy Japanese; 320 mg, healthy Caucasian]). All TEAEs detected through laboratory tests

were mild in intensity and resolved without intervention. No TEAEs associated with abnormalities in laboratory parameters were reported in the MAD part. The 12-lead ECG results at baseline and at all time points after administration of the study drug were found to be normal in all subjects. Continuous digital 12-lead Holter ECGs in subjects receiving SCO-267 did not show QTc prolongation of regulatory concern at any dose level included in this study.

Following single-dose administration of SCO-267 in Japanese subjects, the mean maximum plasma drug concentration (C_{max}) and AUC_{0-72h} of SCO-267 increased nearly dose-proportionately in the dose range of 5–320 mg (Table 3 and Fig. 2*A*). The median time taken to reach C_{max} (T_{max}) of SCO-267 increased as the dose increased (Table 3 and Fig. 2*A*). The mean half-life ($T_{1/2}$) of the drug increased slightly as the dose increased (Table 3). The plasma concentration-time profile of SCO-267 and

Table 2—Safety summary

	SAD part											MAD part		
	Healthy Japanese							Healthy Caucasian	Glucose intolerance			Healthy Japanese		
	SCO-267 5 mg (N = 6)	SCO-267 10 mg (N = 6)	SCO-267 20 mg (N = 6)	SCO-267 40 mg (N = 6)	SCO-267 80 mg (N = 6)	SCO-267 160 mg (N = 6)	SCO-267 320 mg (N = 6)	SCO-267 320 mg (N = 6)	SCO-267 40 mg (N = 6)	SCO-267 80 mg (N = 6)	Placebo (N = 20)	SCO-267 80 mg once-daily (N = 6)	SCO-267 160 mg once-daily (N = 6)	Placebo (N = 4)
Subjects with ≥1 TEAEs	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)
Moderate 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)
TEAEs reported in ≥2 subjects														
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)	3 (50.0)	4 (66.7)	3 (50.0)	3 (50.0)	2 (10.0)	2 (33.3)	1 (16.7)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	1 (16.7)	3 (50.0)	1 (5.0)	1 (16.7)	1 (16.7)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	2 (33.3)	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Feces soft	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Feeling abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)	1 (16.7)	3 (50.0)	2 (33.3)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT increased	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urine ketone body present	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST increased	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cold sweat	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are presented as the number of subjects in the specified category (percentage of the total number of subjects in the treatment group).

Table 3—Pharmacokinetic parameters

	SAD part										MAD part	
	Healthy Japanese							Healthy Caucasian	Glucose intolerance		Healthy Japanese	
	SCO-267 5 mg (N = 6)	SCO-267 10 mg (N = 6)	SCO-267 20 mg (N = 6)	SCO-267 40 mg (N = 6)	SCO-267 80 mg (N = 6)	SCO-267 160 mg (N = 6)	SCO-267 320 mg (N = 6)	SCO-267 320 mg (N = 6)	SCO-267 40 mg (N = 6)	SCO-267 80 mg (N = 6)	SCO-267 80 mg once-daily (N = 6)	SCO-267 160 mg once-daily (N = 6)
Day 1												
AUC_{0-72h} (ng · h/mL)	238.5 (61.737)	452.2 (134.40)	837.3 (132.38)	2,378 (346.86)	4,607 (925.98)	7,567 (3707.2)	23,500 (9,548.0)	20,370 (10,706)	2,132 (503.92)	5,443 (1,104.2)	4,490 (555.40)	8,199 (1,314.3)
AUC_{0-24h} (ng · h/mL)												
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)	1,711 (737.80)	873.3 (412.69)	235.2 (61.111)	554.3 (94.157)	344.8 (98.583)	606.7 (226.89)
T_{max} (h) Median	3.000	3.500	4.000	4.000	6.000	6.000	9.000	12.00	4.000	6.000	6.000	11.00
T_{max} (h) Q1, Q3	2.500, 4.000	3.000, 4.000	4.000, 4.000	4.000, 4.000	4.000, 6.000	6.000, 8.000	6.000, 10.00	6.017, 24.00	4.000, 8.000	6.000, 6.000	4.000, 8.000	10.00, 12.00
$T_{1/2}$ (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)	4.480 (0.83129)	3.879 (0.56820)	3.752 (0.21300)	21.58 (22.158)#	4.472 (1.7870)
Day 4												
AUC_{0-24h} (ng · h/mL)											5,762 (1,848.4)	10,410 (3,503.6)
C_{max} (ng/mL)											590.3 (255.67)	1,004 (287.50)
T_{max} (h) Median											3.500	6.000
T_{max} (h) Q1, Q3											2.500, 6.000	4.000, 10.00
$R(AUC_{0-24h})$*											1.125 (0.098994)	1.316 (0.19087)
$R(C_{max})$†											1.800 (0.82220)	1.787 (0.57587)

Data are presented as mean (SD), except for T_{max}, which is presented as median and the first and third quartiles (Q1, Q3). #$T_{1/2}$ (h) of SCO-267 80 mg once-daily in MAD (day 1) was inconsistent compared with the similarly treated groups. Individual data in this group indicate that unidentified errors in the SCO-267 suspension may affect drug absorption. *$R(AUC_{0-24}) = AUC_{0-24}$ (day 4)/AUC_{0-24} (day 1). †$R(C_{max}) = C_{max}$ (day 4)/C_{max} (day 1).

the pharmacokinetic parameters following single-dose administration of SCO-267 (320 mg) in Caucasian subjects were largely similar to those in the Japanese subjects (Table 3 and Fig. 2B). The plasma concentration-time profiles of SCO-267 (40 and 80 mg) in healthy subjects and patients with diabetes were also largely similar (Fig. 2C). 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, and no accumulation of SCO-267 was observed following repeated administration (Fig. 2D and E). The mean accumulation ratios based on the AUC_{0-24h} at doses of 40 mg and 80 mg were 1.125 and 1.316, respectively (Table 3). The cumulative urinary excretion of SCO-267 was negligible regardless of the dose (Supplementary Table 1). The mean renal clearance of SCO-267 was negligible (0.000–0.0006840 L/h in the SAD part and 0.00004 550–0.0004281 L/h in the MAD part) and similar at all doses, in both ethnic groups, and in both healthy volunteers and those with diabetes (Supplementary Table 1).

A single SCO-267 administration in healthy subjects stimulated the secretion of insulin, GLP-1, GIP, PYY, and glucagon (Fig. 3). The secretion of hormones induced by SCO-267 was further increased by food intake, including lunch and dinner, except for glucagon, the secretion of which slightly decreased upon food intake at some measured time points (Fig. 3E). After administration of the drug for 4 days, SCO-267 retained the ability to stimulate secretion of these hormones (Fig. 3).

The efficacy of the placebo and SCO-267 (40 and 80 mg) was evaluated in patients with diabetes by an OGTT. The changes in the baseline (day −1) levels of glucose, insulin, GLP-1, GIP, PYY, and glucagon during the OGTT were similar in the placebo and SCO-267 groups (Fig. 4 and Table 4). As shown in Fig. 4A and Table 4, at baseline (day −1), patients with diabetes showed elevated fasting glucose levels and impaired glucose tolerance upon oral glucose loading. The administration of placebo on day 1 induced similar changes in all parameters as those observed at baseline (day −1). The administration of SCO-267 (40 and 80 mg) stimulated the secretion of insulin, GLP-1, GIP, PYY, and glucagon in patients with diabetes (Fig. 4B–F and Table 4). An oral glucose load further increased the levels of these hormones in the SCO-267 (40 and 80 mg) groups (Fig. 4B–F and Table 4). It is interesting to note that SCO-267 administration decreased fasting hyperglycemia without inducing hypoglycemia and completely blocked the increase in plasma glucose levels upon glucose loading in patients with diabetes (Fig. 4A and Table 4).

DISCUSSION

To our knowledge, this study is the first to reveal the clinical profile of a full agonist of GPR40. SCO-267 was found to be generally safe and well tolerated at all single and multiple doses evaluated. The plasma drug concentration was found to increase in a dose-proportional manner. No

clinically meaningful changes in the laboratory-tested parameters were observed during the study, although some mild abnormalities were noted in the SAD part. The results of the safety, tolerability, and pharmacokinetic profile analyses collectively suggest the potential of once-daily SCO-267 oral dosing in clinical settings. Overall, this study demonstrated that SCO-267–mediated full agonism of GPR40 harbors significant potential to stimulate islet and gut hormone secretion in humans. Moreover, SCO-267 was found to exhibit remarkable efficacy in improving glucose tolerance in patients with diabetes, without inducing hypoglycemia.

From the pharmacodynamic aspect of the study, the clinical potential of SCO-267 in the regulation of hormonal secretions and blood glucose control was evaluated in patients with diabetes. SCO-267 was demonstrated to stimulate the secretion of insulin, glucagon, GLP-1, GIP, and PYY in humans, which was consistent with the results of the preclinical studies (16). Fasting hyperglycemia in patients with diabetes was corrected by the administration of SCO-267, with no hypoglycemia events observed. Such findings suggest that SCO-267 may induce a safer drug profile. Hormonal secretion was stimulated upon administration of SCO-267 and was further elevated following the subsequent administration of glucose, indicating that both events may contribute to the therapeutic and biological efficacy of SCO-267. SCO-267 remarkably improved glucose intolerance in patients with diabetes. Collectively, this is the first study to demonstrate that SCO-267 acts as a full agonist of GPR40 and is able to stimulate the secretion of islet and gut hormones to improve glucose control in humans, including patients with diabetes.

The plasma AUC and C_{max} of SCO-267 were observed to increase in proportion with the dose administered. The plasma concentration of SCO-267 reached more than a few nanograms per milliliter, 24 h after administration of doses ≥10 mg in the current study. SCO-267 at a dose of 0.3 mg/kg exhibited a C_{max} value of 22.7 ng/mL and was more effective at improving glucose control than the clinically translatable doses of sitagliptin, a dipeptidyl peptidase 4 inhibitor, and fasiglifam in diabetic rats (16,17). In addition, a preclinical study demonstrated that chronic 24-h exposure to SCO-267 was highly effective in improving glycemic control in diabetic rats (19). Therefore, once-daily dosing of ≥10 mg SCO-267 might be sufficient to improve glycemic control for 24 h in clinical settings.

In the MAD part of the study conducted with healthy volunteers, the effects of repeated SCO-267 dosing on the pharmacokinetics and pharmacodynamics were evaluated. The administration of multiple doses of SCO-267 for 4 days did not affect the plasma concentration profile of this molecule. Furthermore, multiple doses of SCO-267 were able to repeatedly simulate the secretion of insulin, glucagon, GLP-1, GIP, and PYY. A preclinical study demonstrated that chronic 24-h exposure to SCO-267 for 5 weeks was highly effective in improving glucose tolerance

Table 4—Pharmacodynamic parameters

	Placebo (N = 4)	SCO-267 40 mg (N = 6)	SCO-267 80 mg (N = 6)
Glucose			
Day −1 (baseline)			
$AUC_{(0-180\ min)}$ (mg · h/dL)	729.5 (79.566)	774.5 (115.58)	813.8 (156.29)
Day 1			
$AUC_{(0-180\ min)}$ (mg · h/dL)	743.41 (88.258)	393.83 (97.719)	321.33 (25.780)
Change from baseline	13.91 (18.347)	−380.6 (109.27)	−492.5 (161.51)
Difference of mean*	—	−394.5	−506.4
95% CI	—	−524.2, −264.9	−697.2, −315.6
Day −1 (baseline)			
At time 0 (mg/dL)‡	143.00 (7.071)	143.50 (30.251)	151.00 (23.399)
Day 1			
At time 0 (mg/dL)‡	135.75 (7.411)	117.83 (27.125)	111.33 (16.609)
Change from baseline	−7.25 (4.031)	−25.67 (24.394)	−38.00 (17.321)
Difference of mean*	—	−18.42	−30.75
95% CI	—	−47.36, 10.52	−51.46, −10.04
Day −1 (baseline)			
At time 120 min (mg/dL)§	278.50 (39.619)	294.33 (40.559)	327.20 (58.649)
Day 1			
At time 120 min (mg/dL)§	283.25 (34.846)	143.00 (42.483)	115.17 (10.647)
Change from baseline	4.75 (24.391)	−151.33 (48.562)	−206.67 (52.929)
Difference of mean*	—	−156.08	−211.42
95% CI	—	−217.40, −94.76	−277.55, −145.28
Insulin			
Day −1 (baseline)			
$AUC_{(0-180\ min)}$ (µU · h/mL)	57.31 (10.646)	25.78 (7.8268)	55.54 (40.260)
Day 1			
$AUC_{(0-180\ min)}$ (µU · h/mL)	74.21 (30.556)	82.76 (62.396)	148.73 (68.574)
Change from baseline	16.90 (23.675)	56.98 (64.023)	93.19 (45.201)
Difference of mean*	—	40.08	76.29
95% CI	—	−38.29, 118.5	18.88, 133.7
Day −1 (baseline)			
At time 0 (µU · h/mL)‡	5.83 (1.289)	3.17 (1.672)	4.74 (2.715)
Day 1			
At time 0 (µU · h/mL)‡	5.18 (1.053)	22.65 (14.510)	42.90 (16.473)
Change from baseline	−0.65 (1.852)	19.48 (13.790)	38.33 (15.175)
Difference of mean*	—	20.13	38.98
95% CI	—	3.82, 36.45	21.05, 56.92
GLP-1			
Day −1 (baseline)			
$AUC_{(0-180\ min)}$ (pmol · h/L)	16.97 (11.518)	20.38 (18.544)	12.00 (10.901)
Day 1			
$AUC_{(0-180\ min)}$ (pmol · h/L)	18.00 (11.350)	58.91 (48.530)	63.10 (28.659)
Change from baseline	1.026 (9.0426)	38.53 (45.716)	51.10 (19.480)
Difference of mean*	—	37.51	50.08
95% CI	—	−16.92, 91.93	25.72, 74.44
Day −1 (baseline)			
At time 0 (pmol · h/L)‡	2.93 (3.399)	0.00 (0.000)	0.00 (0.000)
Day 1			
At time 0 (pmol · h/L)‡	3.20 (3.841)	15.27 (12.371)	12.43 (7.628)
Change from baseline	0.26 (1.393)	15.27 (12.371)	12.43 (7.628)
Difference of mean*	—	15.01	12.16
95% CI	—	0.40, 29.62	3.10, 21.23
GIP			
Day −1 (baseline)			
$AUC_{(0-180\ min)}$ (pg · h/mL)	873.6 (217.34)	727.2 (114.98)	864.1 (214.76)
Day 1			
$AUC_{(0-180\ min)}$ (pg · h/mL)	826.96 (182.844)	997.08 (320.970)	1,099.35 (362.369)
Change from baseline	−46.59 (213.68)	269.9 (321.26)	235.3 (405.00)
Difference of mean*	—	316.5	281.8
95% CI	—	−108.8, 741.8	−233.0, 796.7
Day −1 (baseline)			
At time 0 (pg · h/mL)‡	56.65 (25.485)	54.45 (46.019)	46.10 (22.036)
Day 1			

Table 4—Continued

	Placebo (N = 4)	SCO-267 40 mg (N = 6)	SCO-267 80 mg (N = 6)
At time 0 (pg · h/mL)‡	59.90 (16.895)	221.90 (34.016)	344.77 (154.462)
Change from baseline	3.24 (32.447)	167.45 (46.642)	301.21 (149.009)
Difference of mean*	—	164.2	297.96
95% CI	—	101.86, 226.55	120.14, 475.79
PYY			
Day −1 (baseline)			
$AUC_{(0–180 \ min)}$ (pg · h/mL)	341.6 (92.914)	405.3 (205.56)	410.1 (71.527)
Day 1			
$AUC_{(0–180 \ min)}$ (pg · h/mL)	347.70 (56.861)	664.88 (325.758)	722.54 (177.871)
Change from baseline	6.144 (77.418)	259.6 (273.19)	312.5 (169.45)
Difference of mean*	—	253.5	306.3
95% CI	—	−75.65, 582.6	94.79, 517.8
Day −1 (baseline)			
At time 0 (pg · h/mL)‡	106.50 (25.593)	98.48 (27.794)	126.28 (19.450)
Day 1			
At time 0 (pg · h/mL)‡	102.05 (21.318)	155.83 (75.297)	170.50 (46.552)
Change from baseline	−4.45 (27.216)	57.35 (64.241)	33.27 (42.965)
Difference of mean*	—	61.8	37.72
95% CI	—	−17.76, 141.36	−18.60, 94.04
Glucagon			
Day −1 (baseline)			
$AUC_{(0–180 \ min)}$ (pmol · h/L)	16.11 (7.0570)	10.11 (5.3827)	9.758 (4.9501)
Day 1			
$AUC_{(0–180 \ min)}$ (pmol · h/L)	17.42 (9.016)	54.12 (31.625)	80.60 (35.497)
Change from baseline	1.315 (4.4228)	44.01 (30.730)	70.84 (32.881)
Difference of mean*	—	42.7	69.53
95% CI	—	6.311, 79.08	30.62, 108.4
Day −1 (baseline)			
At time 0 (pmol · h/L)‡	8.12 (2.903)	4.21 (1.397)	5.76 (1.775)
Day 1			
At time 0 (pmol · h/L)‡	8.78 (4.241)	17.26 (6.478)	22.87 (6.395)
Change from baseline	0.66 (1.784)	13.05 (6.339)	17.44 (5.609)
Difference of mean*	—	12.39	16.78
95% CI	—	4.76, 20.03	9.98, 23.58

*Difference from the placebo group (treatment group − placebo group). ‡Before glucose loading. §Two hours from glucose loading.

in diabetic rats (19). Overall, these results suggest that repeated once-daily oral administration of SCO-267 is likely to improve glycemic control in patients with diabetes, and its use should be evaluated for longer periods in clinical trials.

Glucagon secretion was also stimulated by SCO-267 in humans. Considering the recent studies showing that glucagon functions as a physiological insulinotropic hormone, SCO-267–mediated glucagon stimulation may further promote insulin secretion as well as that of other insulinotropic hormones (20–25). However, glucagon is counterregulatory to insulin and elevates plasma glucose levels through its action mediated in the liver (26). Recently, strategies to elevate glucagon function have been explored for the treatment of diabetes and obesity (27). Therefore, coagonists combining glucagon receptor activity with GLP-1R agonism are being developed as antidiabetes and antiobesity medications and have shown promising effects on glycemic control and body weight loss (27). These results provide compelling evidence to support the induction of glucagon activity as a potential therapeutic strategy. In fact, glucagon has been reported to exhibit synergistic effects with GLP-1 in stimulating insulin secretion and reducing food intake in humans (28). Moreover, glucagon plays a pivotal role in lipid metabolism (29). In a preclinical setting, SCO-267, which stimulates the secretion of GLP-1 and glucagon, has been shown to improve liver function parameters in mice with nonalcoholic fatty liver disease (15). These findings suggest the potential for SCO-267–mediated glucagon secretion to play a role in the treatment of hepatic steatosis and nonalcoholic fatty liver disease in clinical settings.

In a previous preclinical study, SCO-267 at a dose of 3 mg/kg (C_{max} reached 122 ng/mL) stimulated the secretion of GLP-1 and PYY and induced loss of body weight in diet-induced obese rats (16). In the current study, SCO-267 stimulated the secretion of GLP-1, PYY, GIP, and glucagon at a dose of at least 40 mg (≤20 mg was not tested). Based

on the recent observations that the multihormone agonism of these hormones might be an effective strategy for the treatment of obesity (30), we propose that SCO-267 may be explored as an oral antiobesity drug.

In this study, the profile of SCO-267 was evaluated in a limited number of subjects for up to 4 days. Therefore, in future studies, it would be important to evaluate the safety, tolerability, and efficacy of SCO-267 in an adequate number of patients for a duration required for clinical application of the treatment for chronic diseases, including diabetes.

In conclusion, 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 potential for once-daily oral dosing and exhibited robust therapeutic effects on hormonal secretion and glycemic control, suggesting that SCO-267 is an attractive drug candidate for the treatment of type 2 diabetes.

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