SCO-240, a small molecule antagonist for somatostatin receptor type 5 (SSTR5), stimulates growth hormone secretion in humans

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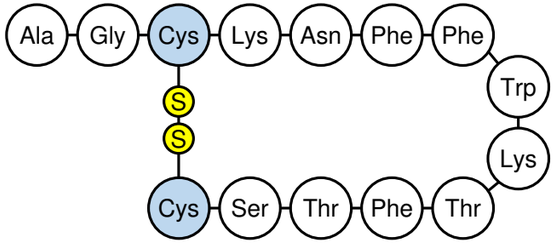
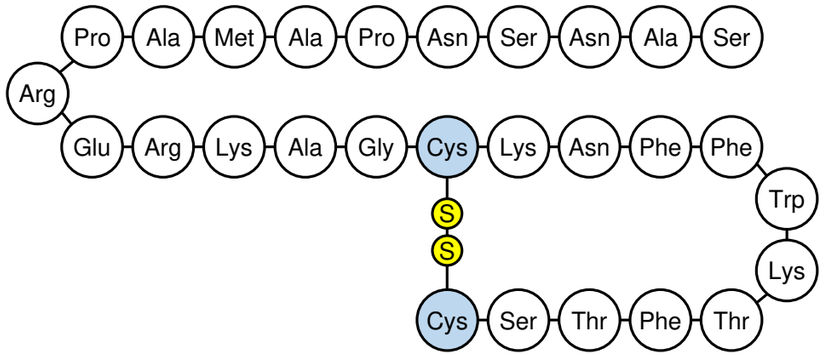
Somatostatin and Somatostatin Receptors (SSTR1-5)

- Somatostatin (SST, SRIF) is a 14 or 28 amino acid peptide located in brain, pituitary, pancreas, stomach and gut, etc.
- SST suppresses endocrine and exocrine hormone secretion via five G-protein-coupled receptors (GPCRs) coupling with Gi/Go (SSTR1-5)
- The difference of tissue localization of SSTR1-5 defines the physiological function of each SSTR



SST-14



SST-28

Hormone changes by SSTRs activation

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
GH		↓			↓
Glucagon		↓			
Insulin					↓
GLP-1					↓
PYY					↓
GIP		↓			
CCK		↓			↓

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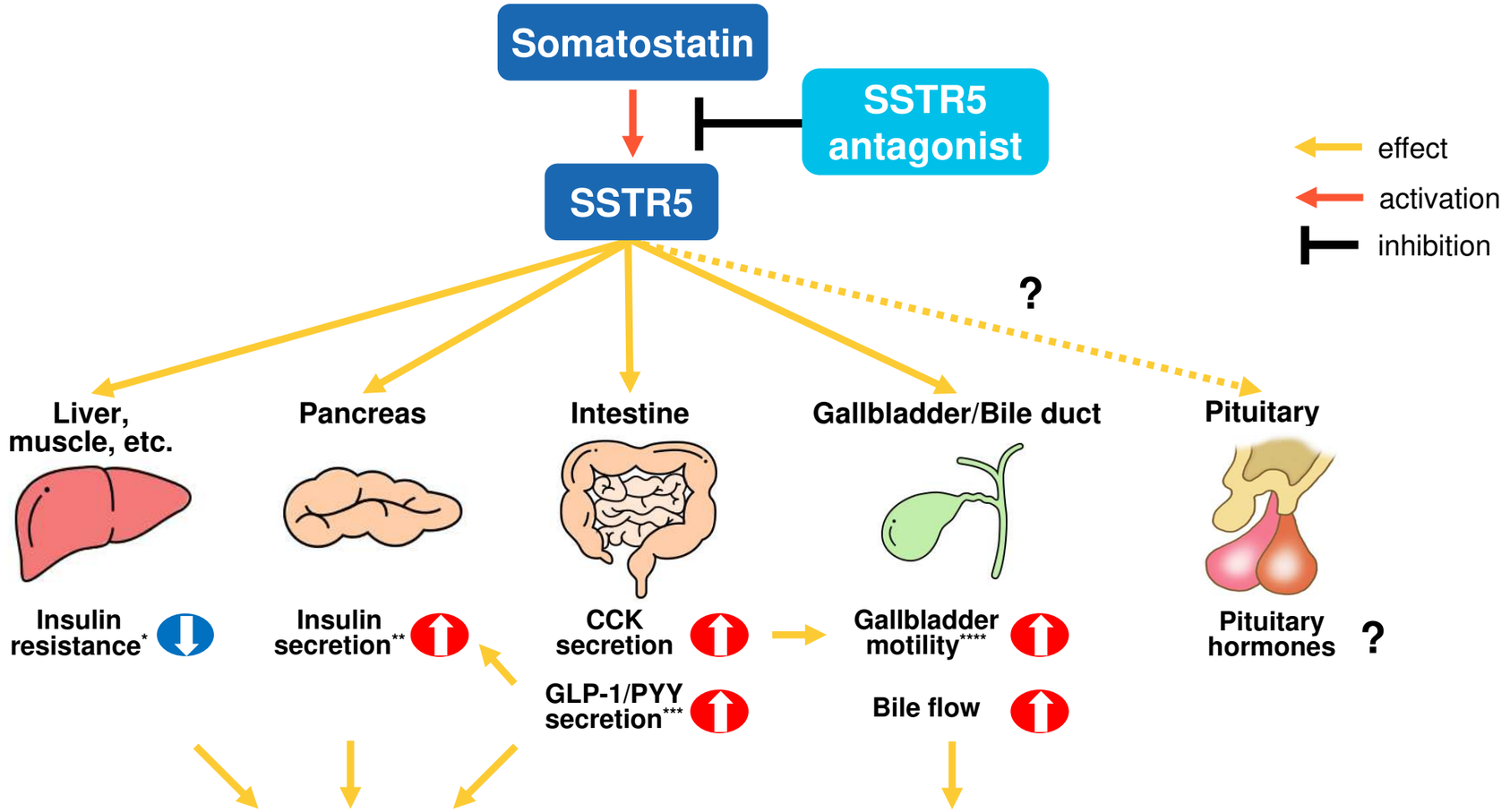
Accumulated Evidence Indicated That SSTR5 Antagonism May be Therapeutically Effective in Following Diseases



Pharmacol Res Perspect. 2023, 11(1):e01043
**ACS Med Chem Lett.* 2018, 9(11):1082-1087
***Endocrinology.* 2017, 158(11):3859-3873
****Neurogastroenterol Motil.* 2010, 22(2):204-209

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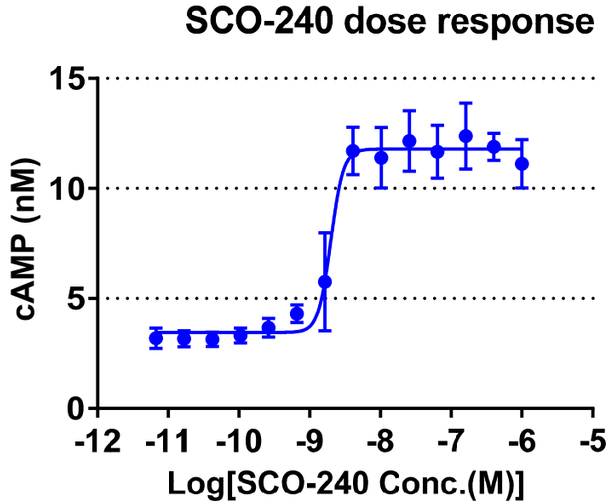
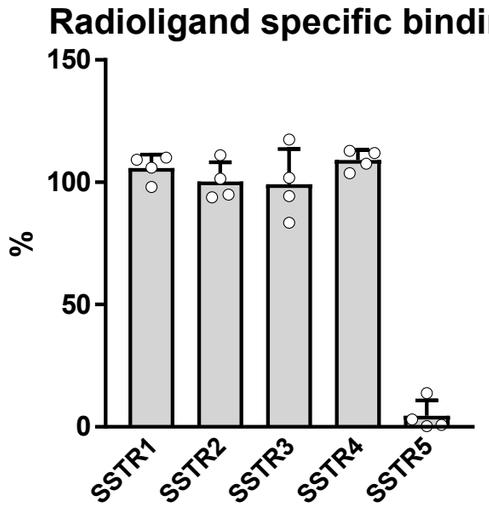
SCO-240 is the Only Clinical Stage Selective SSTR5 Antagonist

- An orally available small molecule
- Human SSTR5 IC_{50}: 2.0 nmol/L
- Highly selective to SSTR5 among SSTR1-5



Means + SD (hexaplicate)



Means + SD (quadruplicate)

Antagonist activity (cyclic AMP assay)
Cell:
Chinese hamster ovary (CHO) cells stably expressing human SSTR5
Treatment:
The cells were stimulated with 0.1 nM SST-28 and 0.5 μM forskolin w/wo various concentrations of SCO-240.

Selectivity (competitive radioligand binding assay)
Material:
The membrane fraction of CHO-K1 cells expressing each human SSTR
Treatment:
The membrane was incubated with 1 μM SCO-240 and [^{125}I]SST-14.

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SCO-240 Phase 1 Single Ascending Dose Study

Study design

A Randomized, Single-Center, Double-Blind, Placebo-Controlled, Phase 1 Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Single Dose of SCO-240 in Healthy Adult Subjects

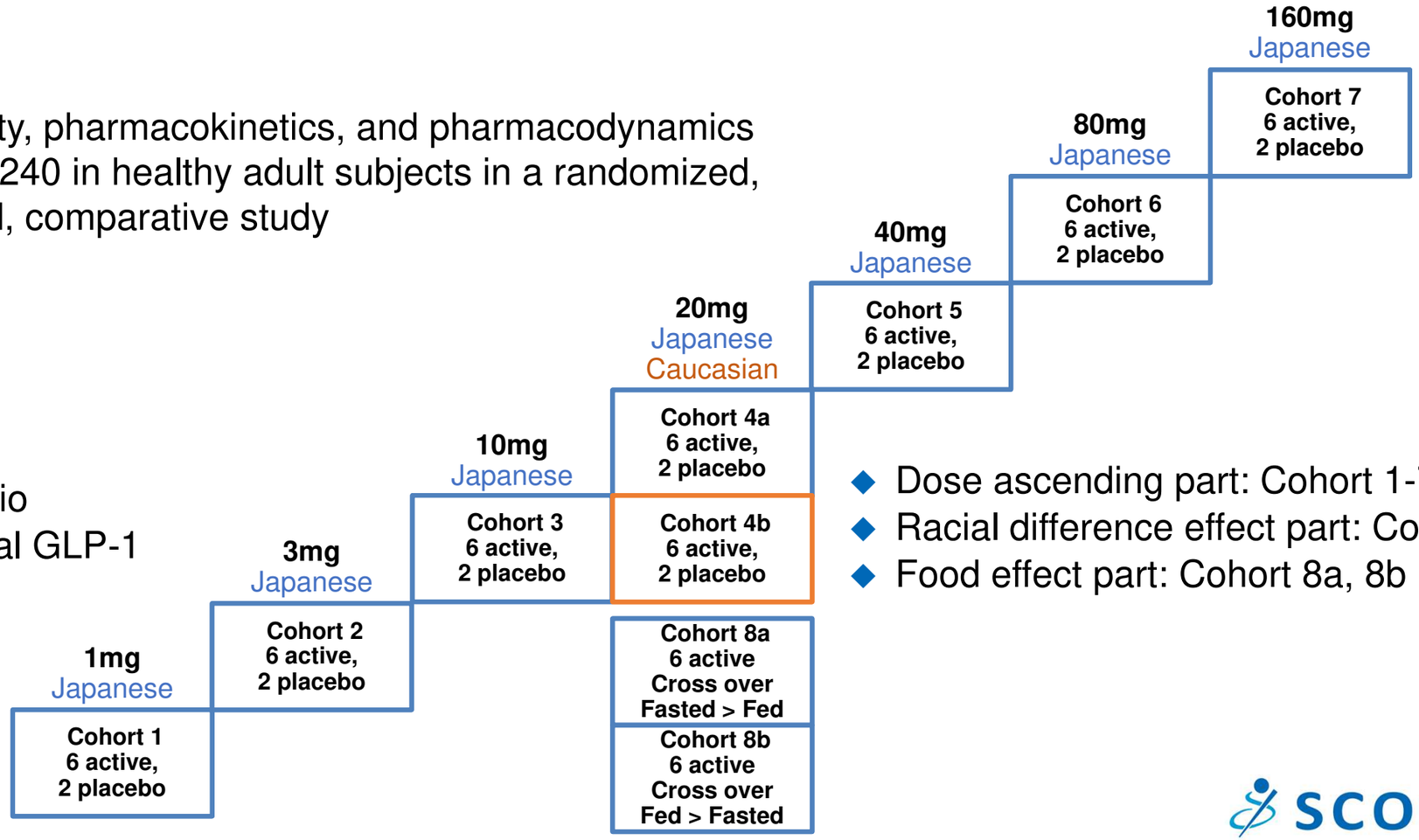
Registration No. jRCT2051210027

Primary Objective

To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics after a single oral dose of SCO-240 in healthy adult subjects in a randomized, double-blind, placebo-controlled, comparative study

Endpoints

- Pharmacokinetics
- Safety
- Pharmacodynamics*
  - Gallbladder contractile ratio
  - Serum insulin, plasma total GLP-1

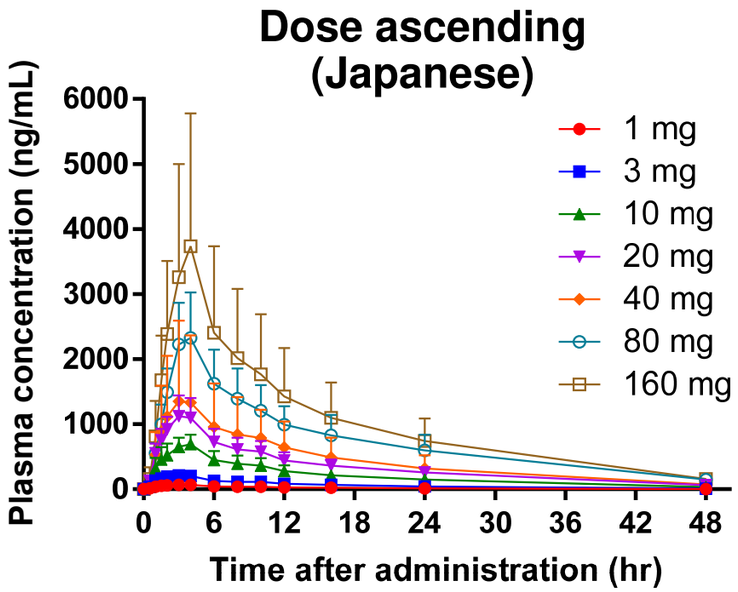


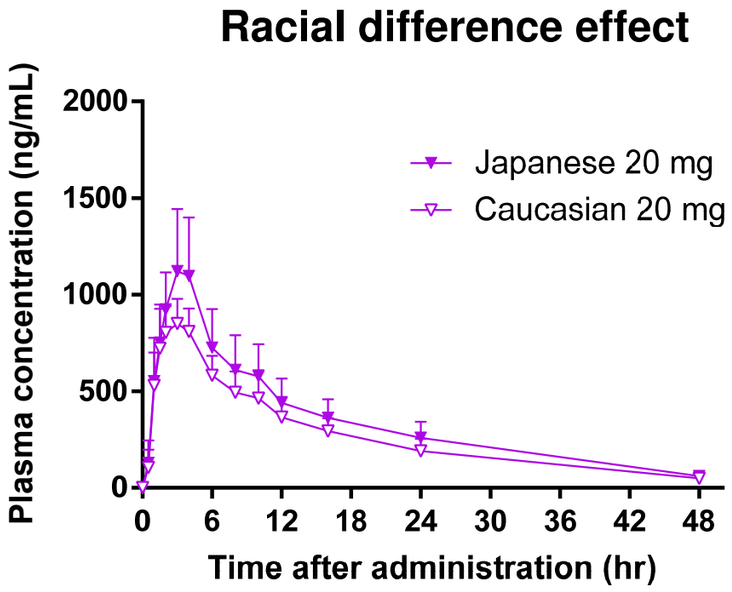
- Dose ascending part: Cohort 1-7
- Racial difference effect part: Cohort 4a, 4b
- Food effect part: Cohort 8a, 8b

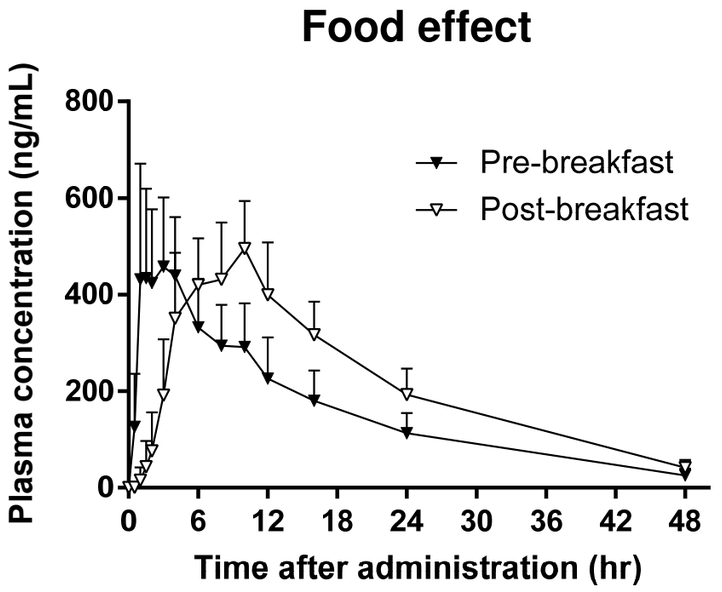
*Additional exploratory analyses using the remaining blood sample were allowed by informed consent

SCO-240 Phase 1 Single Ascending Dose Study

Excellent pharmacokinetic profiles allowing once-daily oral dosing in humans







Means + SD (n=5-12)

			$AUC_{(0\text{-inf})}$ (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
Dose ascending part	**Japanese**	1 mg (N=6)	990.1	69.6	3.5	10.2
		3 mg (N=5)	3176.8	220.6	3.0	10.7
		10 mg (N=6)	10240.9	696.7	4.0	11.0
		20 mg (N=6)	17477.8	1144.2	3.0	12.2
		40 mg (N=6)	22033.5	1436.5	4.0	11.4
		80 mg (N=6)	38187.2	2351.7	4.0	12.6
		160 mg (N=6)	51622.8	3820.0	3.0	11.7
Racial difference effect part	**Caucasian**	20 mg (N=6)	13790.1	873.5	3.0	11.9
Food effect part	**Pre-breakfast**	20 mg (N=12)	8084.1	519.3	2.3	11.3
	Post-breakfast	20 mg (N=12)	10831.3	517.3	10.0	10.7

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SCO-240 Phase 1 Single Ascending Dose Study

Safe and well tolerated in single doses

	Dose Ascending Part									Racial Difference Effect Part		
	Placebo	1 mg	3 mg	10 mg	20 mg	40 mg	80 mg	160 mg	Total	Placebo	20 mg	Total
N	14	6	6	6	6	6	6	6	56	2	6	8
TEAEs	0 (0.0)	2 (33.3)	1 (16.7)	0 (0.0)	1 (16.7)	2 (33.3)	1 (16.7)	0 (0.0)	7 (12.5)	1 (50.0)	0 (0.0)	1 (12.5)
Abdominal discomfort	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain lower	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Tonsillitis	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Blood corticotrophin increased	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Blood triglycerides increased	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0.0)	4 (7.1)	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)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (12.5)
Hypoaesthesia	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)

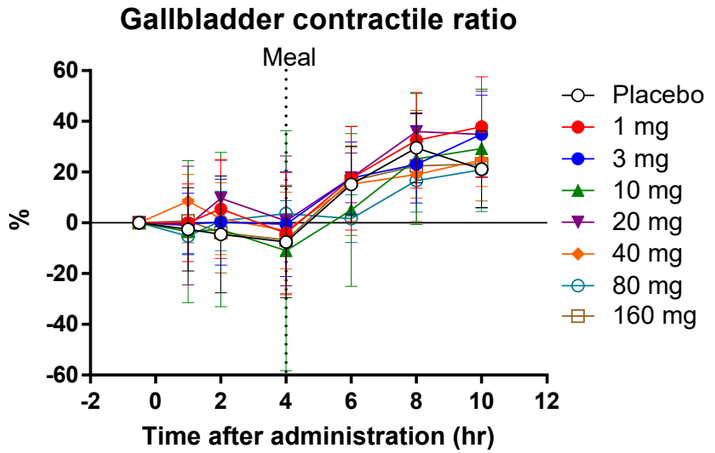
Number of Subjects (%)
TEAE: Treatment-Emergent Adverse Events
TEAEs related to the Drug

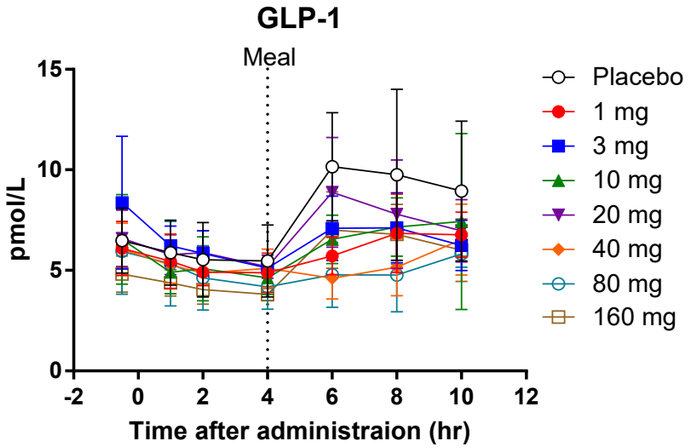
- No serious adverse events were observed, and all TEAEs were mild in intensity.

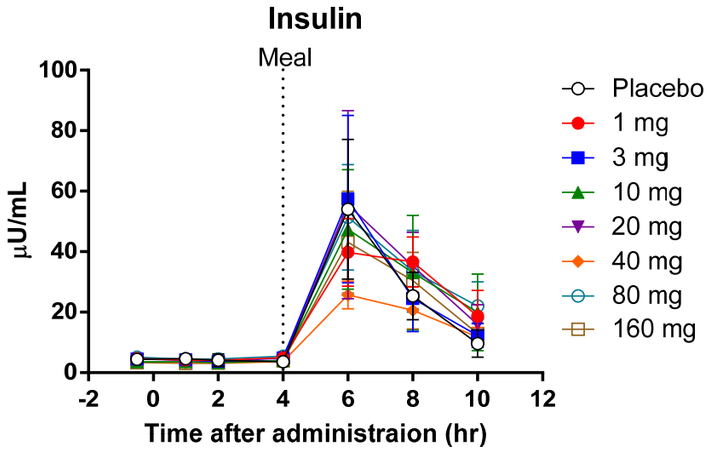
SCO-240 Phase 1 Single Ascending Dose Study

GLP-1, insulin, and gallbladder contraction were unchanged

	Day -1	Day 1						
Time	19:00	8:30	9:00	10:00	11:00	13:00	15:00	17:00	19:00
Hour after dose	-14	-0.5	0	1	2	4	6	8	10
Blood sampling		X		X	X	X	X	X	X
Echography		X		X	X	X	X	X	X
Meal	X					X			X





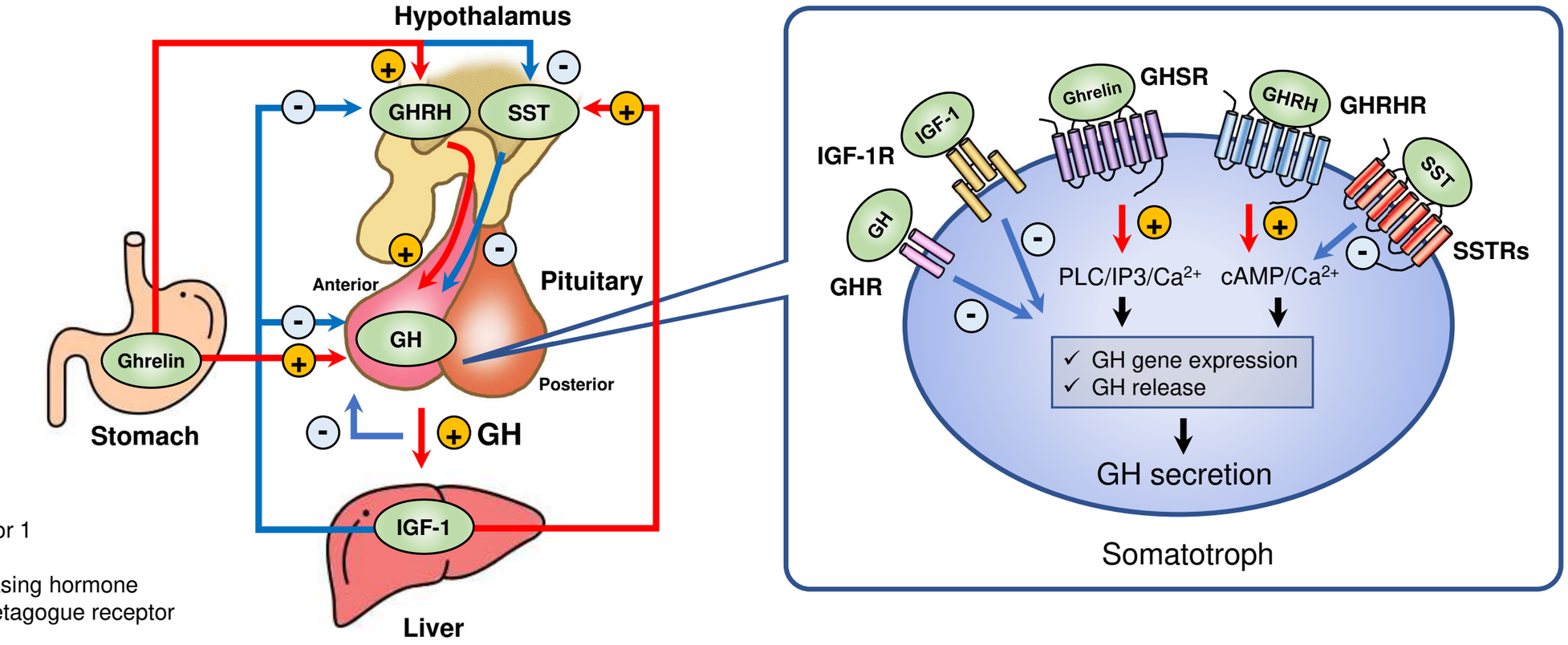


- These parameters, regulated by SSTR5 in mice, were unexpectedly unchanged in humans
- Additional exploratory analyses were conducted to determine the physiological role of SSTR5 in humans

Means + SD (n=14 for placebo group, and 6 for SCO-240 groups)

Somatostatin Negatively Regulates Growth Hormone Secretion from Somatotroph in the Anterior Pituitary

A key SSTR subtype that regulates GH release was largely unknown in humans

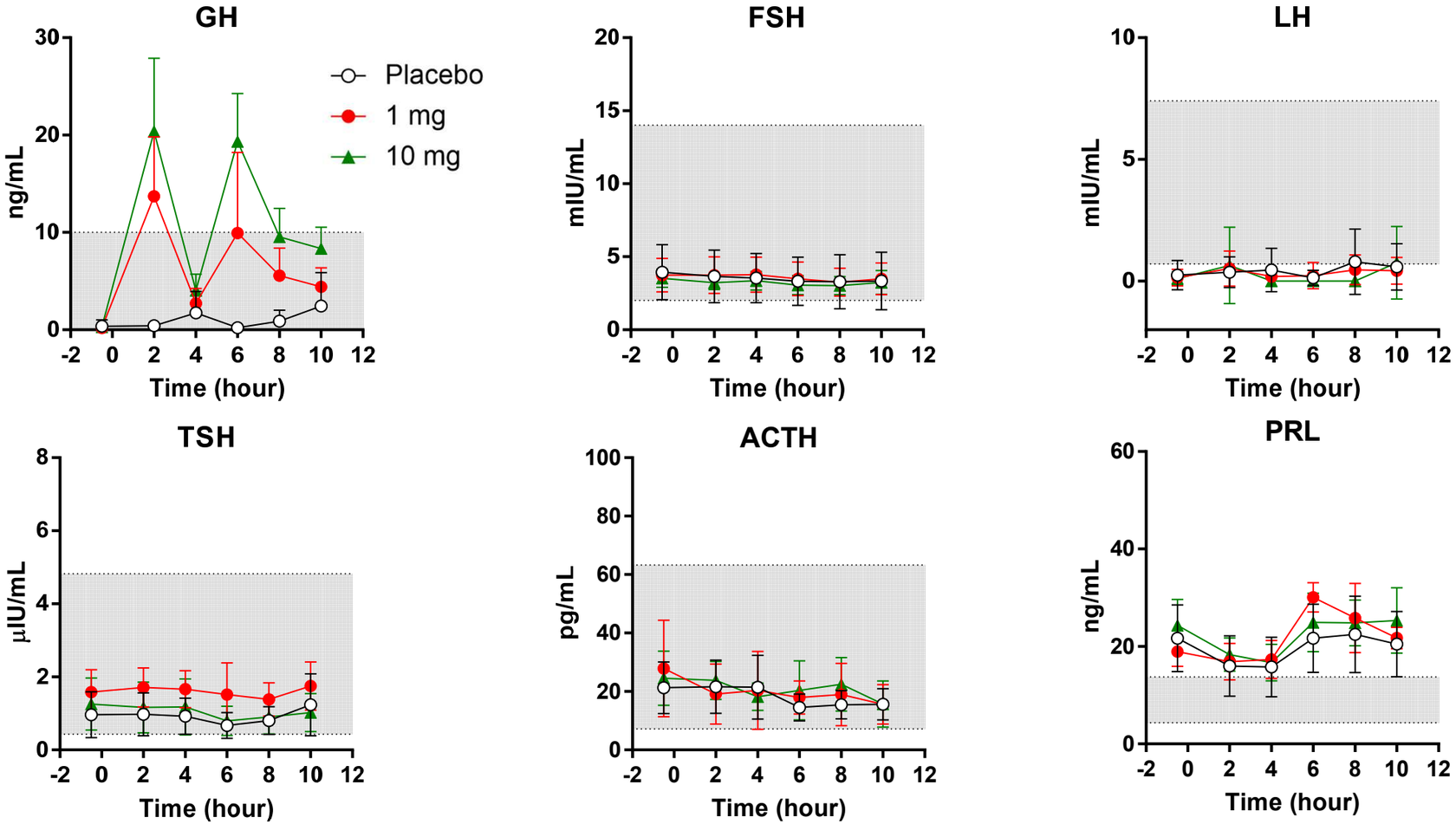


GH: growth hormone
IGF-1: insulin-like growth factor 1
SST: somatostatin
GHRH: growth hormone-releasing hormone
GHSR: growth hormone secretagogue receptor

- Growth hormone is secreted from anterior pituitary somatotrophs in a pulsatile fashion under the control of multiple stimulatory (GHRH, ghrelin) and inhibitory (**somatostatin**) factors

Additional Analysis in the Phase 1 Study

Significant stimulation on GH release and neutral effects on other pituitary hormones in humans

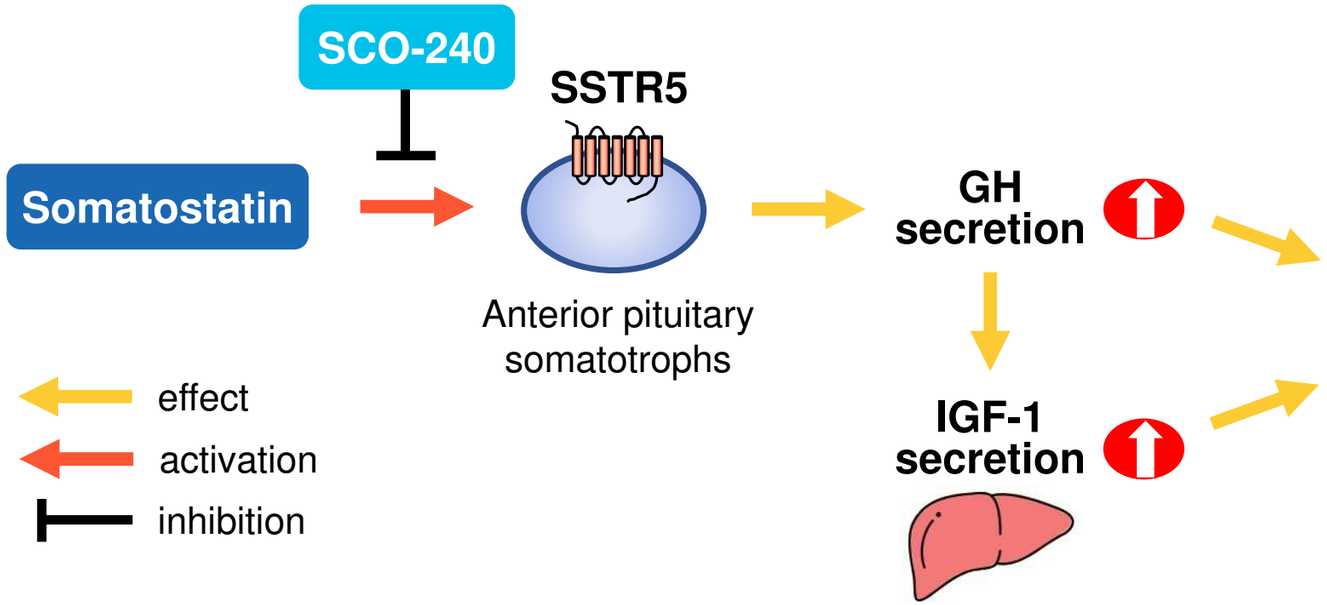


GH: growth hormone
FSH: follicle-stimulating hormone
LH: luteinizing hormone
TSH: thyroid-stimulating hormone
ACTH: adrenocorticotropic hormone
PRL: prolactin

Means + SD (n=14 for placebo group, and 6 for SCO-240 groups)
Gray area indicates the normal range for each hormone

- Increased GH levels by SCO-240 are comparable to those after the injection of therapeutic dose of recombinant human GH

Summary



- Oral alternative to injectable rhGH for growth failure, short stature, and GH deficiency
- New drug opportunity for rhGH-treatable indications that have not been addressed due to its high drug cost and administration route

GH: growth hormone
IGF-1: insulin-like growth factor 1
rhGH: recombinant human GH

- SCO-240 was safe and well tolerated and exhibited once-daily oral dosing potential
- Robust GH secretion was demonstrated with SCO-240-mediated SSTR5 antagonism in humans
- These results support the further clinical development of SCO-240 as an oral treatment option for GH-related disorders