Poster #GP123

A Placebo-controlled Study to Assess the Dose Effect of COR-005, a Novel Somatostatin Analogue, on Plasma Glucose Regulation Compared to Octreotide in Healthy Male Subjects

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INTRODUCTION

- COR-005 (veldotide; formerly known as somatoprim or DG3173) is a synthetic, cyclic, 8 amino acid somatostatin analogue
- COR-005 has high affinity for human somatostatin receptor subtypes 2, 4, and 5, and is a full agonist of subtypes 2 and 5
- COR-005 does not bind to opiate receptors

OBJECTIVES

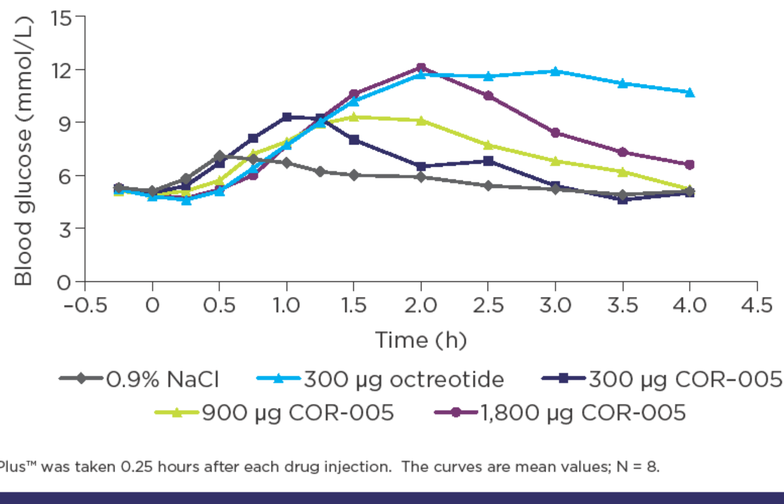
- To study the effect of escalating doses of COR-005 compared to 300 µg octreotide and placebo on glucose, insulin, and glucagon profiles after intake of a mixed meal (400 mL Ensure Plus™ [Abbott Laboratories, Alameda, CA, USA]) in healthy male subjects
- To assess the safety and tolerability of COR-005

METHODS

- Single-blind, placebo-controlled, 5-period, crossover, single-group study
- Healthy male subjects (18-45 years of age; body mass index 19-27 kg/m²; N = 8)
- Single subcutaneous injections of the following:
  - 300 µg COR-005, 900 µg COR-005, 1,800 µg COR-005, placebo, and 300 µg octreotide
  - The subjects received single administrations with a washout of 4 to 5 days between treatments
  - Overnight fast of ≥10 hours before drug injections
- 400 mL Ensure Plus™ (25 g proteins, 80.8 g carbohydrates, 19.68 g lipids, 600 kcal) taken 0.25 hours after each drug injection
- Mixed meal–stimulated glucose, insulin, and glucagon 4-hour profiles were assessed after each treatment
- Blood glucose concentrations were determined by using a validated enzymatic (hexokinase) in vitro test
- Plasma insulin and plasma glucagon concentrations were determined by using validated, commercially available, enzyme-linked immunosorbent assay (ELISA) kits

RESULTS

Pharmacodynamics



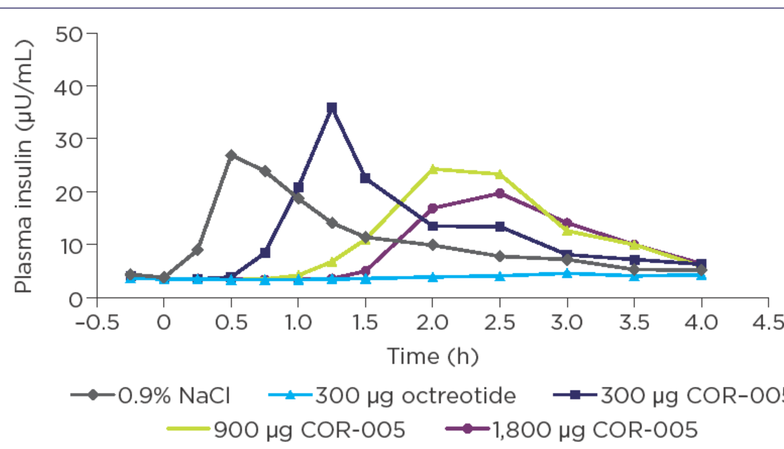
400 mL Ensure Plus™ was taken 0.25 hours after each drug injection. The curves are mean values; N = 8.

Figure 1. Mean mixed meal–stimulated blood glucose profiles after a single subcutaneous injection of different treatments.

Table 1. Pharmacodynamic Parameters of Mixed Meal–stimulated Blood Glucose After a Single Subcutaneous Injection of Different Treatments

Dose	E_{max} (mmol/L)	t_{Emax}* (h)	$E_{AUC0-4h}$ (h·mmol/L)	E_{max}/C_{pre}
0.9% NaCl	7.56 ± 0.93	0.75 (0.50-1.50)	23.02 ± 1.83	1.47 ± 0.24
300 µg octreotide	12.39 ± 1.56	2.25 (1.50-4.00)	38.69 ± 5.79	2.49 ± 0.34
300 µg COR-005	9.76 ± 1.00	1.25 (1.00-1.50)	26.13 ± 2.18	1.94 ± 0.22
900 µg COR-005	9.73 ± 1.31	1.50 (1.25-2.00)	28.86 ± 3.82	1.95 ± 0.27
1,800 µg COR-005	12.15 ± 1.06	2.00 (2.00-2.50)	33.56 ± 4.71	2.42 ± 0.48

E_{max}, maximum effect; t_{Emax}, time to maximum effect; $E_{AUC0-4h}$, area under the plasma concentration versus time curve for the effect from time 0 to 4 hours post-dose; C_{pre}, arithmetic mean of $C_{(-0.25)}$ and C_0; SD, standard deviation.
The data are mean ± SD values.
*Median and range; N = 8.



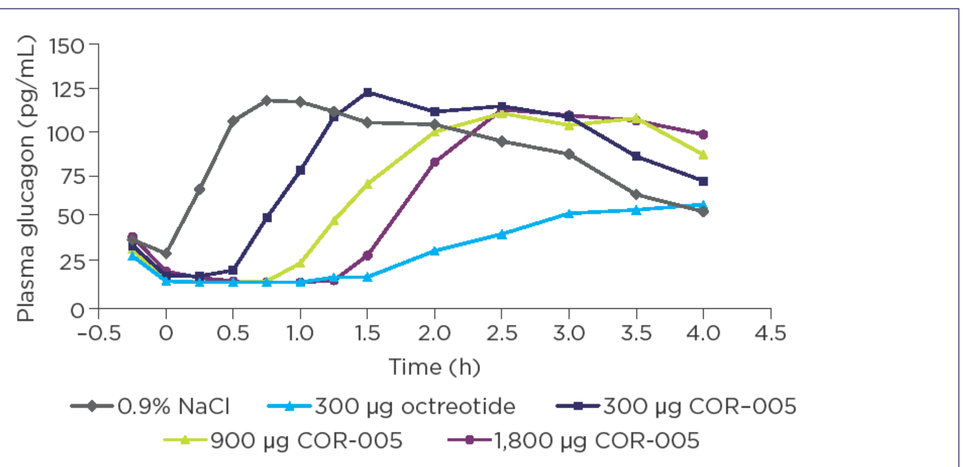
400 mL Ensure Plus™ was taken 0.25 hours after each drug injection. The curves are mean values; N = 8.

Figure 2. Mean mixed meal–stimulated plasma insulin profiles after a single subcutaneous injection of different treatments.

Table 2. Pharmacodynamic Parameters of Mixed Meal–stimulated Plasma Insulin After a Single Subcutaneous Injection of Different Treatments

Dose	E_{max} (mmol/L)	t_{Emax}* (h)	$E_{AUC0-4h}$ (h·mmol/L)	E_{max}/C_{pre}
0.9% NaCl	31.8 ± 17.8	0.75 (0.50-1.50)	44.29 ± 10.65	7.84 ± 4.48
300 µg octreotide	4.9 ± 1.3	3.00 (0.25-4.00)	15.56 ± 2.02	1.36 ± 0.41
300 µg COR-005	41.1 ± 30.6	1.38 (1.00-3.50)	49.73 ± 21.23	10.46 ± 6.92
900 µg COR-005	36.7 ± 30.3	2.50 (1.50-3.00)	46.52 ± 21.62	9.95 ± 8.19
1,800 µg COR-005	26.8 ± 22.5	2.50 (2.00-3.50)	38.70 ± 22.78	6.96 ± 5.76

E_{max}, maximum effect; t_{Emax}, time to maximum effect; $E_{AUC0-4h}$, area under the plasma concentration versus time curve for the effect from time 0 to 4 hours post-dose; C_{pre}, arithmetic mean of $C_{(-0.25)}$ and C_0; SD, standard deviation.
The data are mean ± SD values.
*Median and range; N = 8.



400 mL Ensure Plus™ was taken 0.25 hours after each drug injection. The curves are mean values; N = 8.

Figure 3. Mean mixed meal–stimulated plasma glucagon profiles after a single subcutaneous injection of different treatments.

Table 3. Pharmacodynamic Parameters of Mixed Meal–stimulated Plasma Glucagon After a Single Subcutaneous Injection of Different Treatments

Dose	E_{max} (mmol/L)	t_{Emax}* (h)	$E_{AUC0-4h}$ (h·mmol/L)	E_{max}/C_{pre}
0.9% NaCl	129.9 ± 15.6	1.00 (0.50-3.00)	363.2 ± 40.9	4.67 ± 2.41
300 µg octreotide	61.5 ± 28.6	3.50 (0.25-4.00)	135.5 ± 55.1	2.82 ± 1.32
300 µg COR-005	136.9 ± 21.1	1.75 (1.50-3.00)	346.8 ± 57.4	5.93 ± 1.90
900 µg COR-005	128.9 ± 26.7	2.75 (2.00-4.00)	292.0 ± 60.2	5.35 ± 1.33
1,800 µg COR-005	128.4 ± 27.7	3.25 (2.50-4.00)	264.5 ± 55.4	4.83 ± 1.84

E_{max}, maximum effect; t_{Emax}, time to maximum effect; $E_{AUC0-4h}$, area under the plasma concentration versus time curve for the effect from time 0 to 4 hours post-dose; C_{pre}, arithmetic mean of $C_{(-0.25)}$ and C_0; SD, standard deviation.
The data are mean ± SD values.
*Median and range; N = 8.

Treatment-emergent Adverse Events

- Of the 18 reported treatment-emergent adverse events, 8 (44.4%) were gastrointestinal disorders, 5 (27.8%) were administration-site disorders, and 5 (27.8%) were adverse events from different organ classes
- No clinically relevant effects on vital signs, electrocardiogram (ECG), physical findings, or laboratory parameters were observed

Table 4. Summary of the Most Common Treatment-emergent Adverse Events

	0.9% NaCl	300 µg octreotide	300 µg COR-005	900 µg COR-005	1,800 µg COR-005	All
Subjects, N	8	8	8	8	8	8
Total number of adverse events/subjects	2/2	8/5	2/1	4/3	2/2	18/6
MedDRA SOC, F/N Preferred term, F/N						
Gastrointestinal disorders	1/1	5/3	–	–	2/2	8/3
Abdominal distension	–	1/1	–	–	–	1/1
Diarrhea	1/1	1/1	–	–	–	2/1
Flatulence	–	1/1	–	–	–	1/1
Nausea	–	2/2	–	–	2/2	4/2
General disorders and administration-site conditions	–	2/1	1/1	2/1	–	5/3
Injection-site erythema	–	1/1	–	1/1	–	2/2
Injection-site pain	–	1/1	–	1/1	–	2/2
Injection-site pruritus	–	–	1/1	–	–	1/1
Miscellaneous	1/1	1/1	1/1	2/2	–	5/3

MedDRA, *Medical Dictionary for Regulatory Activities*; SOC, system organ class; F, incidence of the adverse event; N, number of subjects with a given adverse event.
All adverse events were of mild intensity.

CONCLUSIONS

Pharmacodynamics

- **COR-005 slightly and dose dependently inhibits mixed meal–stimulated plasma insulin concentrations in contrast to complete inhibition by octreotide**
- **COR-005 only marginally inhibits mixed meal–stimulated plasma glucagon concentrations in contrast to strong inhibition by octreotide**
- **COR-005 dose dependently delays but does not reduce the maximum mixed meal–stimulated plasma concentrations of insulin and glucagon**
- **There was no clinically relevant effect on mixed meal–stimulated blood glucose by COR-005 except for 1,800 µg COR-005, and the effect was less pronounced than the effect of octreotide**

Safety and Tolerability

- **Single subcutaneous doses of COR-005 up to 1,800 µg, isotonic saline, and 300 µg octreotide were well tolerated by the healthy male subjects**
- **No serious adverse events were observed**
- **All adverse events reported were mild. The observed gastrointestinal symptoms are consistent with the known adverse events for the substance class of somatostatin analogues**
- **No clinically relevant effects on vital signs, ECG, physical findings, or laboratory parameters were observed**

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