A Placebo-controlled Study of Repeated Subcutaneous Doses of COR-005 Alone or With Octreotide on GHRH-stimulated GH and Pharmacokinetics in Healthy Male Subjects

Klaus Kutz,[1,*] Manuel Haschke,[2] Christoph Beglinger,[2] Jiri Liska,[3] Carsten Dehning,[4] Fredric Cohen[5]

[1]AccelPharm, Basel, Switzerland; [2]University Hospital Basel, Basel, Switzerland; [3]CEPHA sro, Plzeň, Czech Republic; [4]Aspireo Pharmaceuticals Ltd., Tel Aviv, Israel; [5]Strongbridge Biopharma, Trevose, PA, USA.

*Presenting author.

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
- COR-005 inhibits growth hormone secretion in postnatal rats, isolated rat pituitary cells, and cell cultures from human adenomas

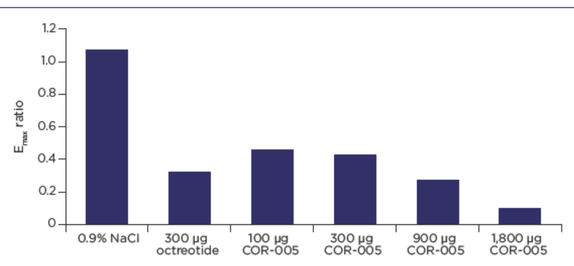
OBJECTIVES

- The objectives of the study were to investigate the following in healthy male subjects:
  - The effect of escalating doses of COR-005 on growth hormone–releasing hormone (GHRH)-stimulated human growth hormone (hGH) compared to octreotide and placebo
  - The pharmacokinetics of COR-005 under repeated-dose conditions
  - Safety and tolerability of repeated escalating doses of COR-005
  - To determine the effects of the different treatments on glucose and insulin plasma profiles after administration of a standard meal (data not shown)

METHODS

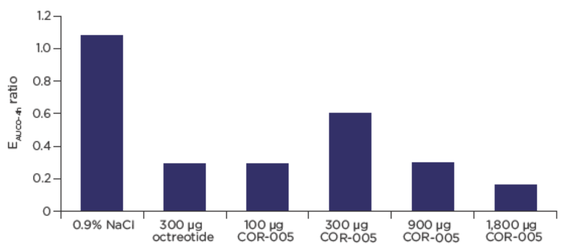
- Single-blind, placebo-controlled, safety and tolerability, pharmacokinetic and pharmacodynamic study in 4 parallel groups
- Healthy male subjects (18-45 years old; body mass index, 19-27 kg/m^2)
- Instead of placebo, isotonic saline (0.9% NaCl) was injected
- Four groups (n = 6 subjects per group)
- Treatments:
  - 100 µg COR-005 (n = 4), 0.9% NaCl (n = 1), 300 µg octreotide (n = 1)
  - 300 µg COR-005 (n = 4), 0.9% NaCl (n = 1), 300 µg octreotide (n = 1)
  - 900 µg COR-005 (n = 4), 0.9% NaCl (n = 1), 300 µg octreotide (n = 1)
  - 1,800 µg COR-005 (n = 4), 0.9% NaCl (n = 1), 300 µg octreotide (n = 1)
  - The subjects were treated 3 times daily (TID) in 8-hour intervals for 6.3 days
  - Note that 3 additional subjects received 0.9% NaCl and 3 additional subjects received 300 µg octreotide in other study arms; data from these subjects were included in this analysis, so a total of 30 subjects were analyzed
- GHRH (1 µg/kg body weight) was injected intravenously on the day before each study treatment and again, at the same time of day, 1 hour after the fourth administration of each treatment, and the hGH profiles were assessed
- hGH was measured by a validated, solid-phase, 2-site chemiluminescent immunometric assay
- Complete COR-005 profiles in plasma were determined after the first and last treatments
- COR-005 in plasma was determined by validated liquid chromatography–mass spectrometry/mass spectometry (LC-MS/MS)

RESULTS



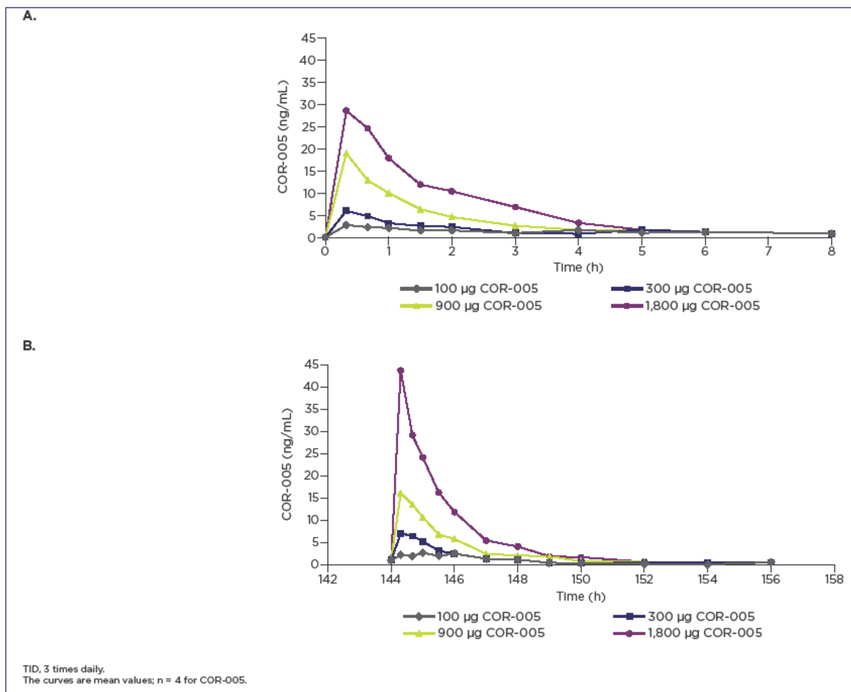
GHRH, growth hormone–releasing hormone; hGH, human growth hormone; TID, 3 times daily.

Figure 1. Median inhibition of maximum GHRH-stimulated hGH plasma concentrations (E_{max}) after 4 subcutaneous injections of different treatments TID.



GHRH, growth hormone-releasing hormone; hGH, human growth hormone; TID, 3 times daily.

Figure 2. Median inhibition of GHRH-stimulated hGH plasma exposure for 4 hours ($E_{AUC0-4h}$) after 4 subcutaneous injections of different treatments TID.



TID, 3 times daily.
The curves are mean values; n = 4 for COR-005.

Figure 3. Pharmacokinetic profile of COR-005 after single (A) and repeated (B) subcutaneous TID injections of 100, 300, 900, and 1,800 µg COR-005.

Table 1. Pharmacodynamic Parameters of hGH After IV Injection of GHRH (Before and After 4 Subcutaneous Injections of Different Treatments)*

Dose	Before treatment		After TID treatment		After versus before treatment	
	E_{max} (ng/mL)	$E_{AUC0-4h}$ (h·ng/mL)	E_{max} (ng/mL)	$E_{AUC0-4h}$ (h·ng/mL)	E_{max} ratio, median; range	$E_{AUC0-4h}$ ratio, median; range
0.9% NaCl	11.13 ± 7.79	13.61 ± 9.17	9.42 ± 4.38	13.27 ± 7.28	1.07; 0.51-2.44	1.08; 0.42-2.20
300 µg octreotide	9.34 ± 5.33	12.45 ± 10.03	2.28 ± 0.99	2.57 ± 0.93	0.32; 0.10-0.69	0.29; 0.09-0.53
100 µg COR-005	14.48 ± 7.75	23.30 ± 13.98	8.64 ± 4.89	10.91 ± 5.10	0.46; 0.36-1.33	0.29; 0.30-1.36
300 µg COR-005	7.07 ± 6.48	9.82 ± 8.08	4.29 ± 3.91	7.92 ± 8.25	0.43; 0.14-7.19	0.60; 0.14-3.82
900 µg COR-005	12.91 ± 9.11	16.24 ± 12.37	3.15 ± 1.77	4.24 ± 2.52	0.27; 0.29-0.42	0.30; 0.22-0.58
1,800 µg COR-005	8.59 ± 9.49	10.01 ± 11.24	0.98 ± 1.36	1.42 ± 1.48	0.10; 0.06-0.16	0.16; 0.12-0.19

hGH, human growth hormone; IV, intravenous; GHRH, growth hormone–releasing hormone; TID, 3 times daily; E_{max}, maximum effect; $E_{AUC0-4h}$, GHRH-stimulated hGH plasma exposure for 4 hours; SD, standard deviation.
*Data are mean ± SD values unless otherwise indicated; n = 7 for NaCl and octreotide groups and n = 4 for COR-005 groups.

Table 2. Pharmacokinetic Parameters of COR-005 During Different Treatments of COR-005*

Dose	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-8h} (h·ng/mL)	$t_{1/2}$ (h)
Day 1				
100 µg COR-005	3.28 ± 1.44	0.75 ± 0.28	6.42 ± 2.33	1.50 ± 0.65
300 µg COR-005	6.20 ± 1.84	0.42 ± 0.14	11.34 ± 2.67	1.70 ± 0.41
900 µg COR-005	19.06 ± 5.47	0.42 ± 0.14	28.28 ± 6.03	1.96 ± 0.33
1,800 µg COR-005	34.39 ± 12.43	0.42 ± 0.14	53.40 ± 13.57	1.58 ± 0.20
Day 7				
100 µg COR-005	3.11 ± 1.66	1.00 ± 0.62	8.77 ± 4.78	3.30 ± 1.33
300 µg COR-005	8.29 ± 1.91	0.58 ± 0.27	14.35 ± 3.48	2.02 ± 0.58
900 µg COR-005	17.10 ± 2.99	0.42 ± 0.14	31.00 ± 2.52	2.07 ± 0.18
1,800 µg COR-005	43.88 ± 13.01	0.33 ± 0	68.82 ± 14.22	1.69 ± 0.50

C_{max}, maximum concentration; t_{max}, time to reach maximum concentration; AUC_{0-8h}, area under the plasma concentration versus time curve of COR-005 from time 0 to 8 hours post-dose; $t_{1/2}$, half-life; SD, standard deviation.
*Data are mean ± SD values; n = 4.

SAFETY AND TOLERABILITY

Drug-related Adverse Events

- Among the 286 drug-related adverse events that were experienced by 23 subjects, 49.7% were general disorders or administration-site conditions, 35.0% were gastrointestinal disorders, and 15.3% were from different organ classes

Table 3. General Disorders and Administration-site Conditions

			COR-005				
	0.9% NaCl	300 µg octreotide	100 µg	300 µg	900 µg	1,800 µg	All
Subjects, n	7	7	4	4	4	4	30
MedDRA SOC, F/N							
Preferred term, F/N							
General disorders and administration-site conditions	1/1	42/6	1/1	2/2	49/4	47/4	142/18
Injection-site erythema	–	31/5	–	1/1	24/4	36/4	92/14
Injection-site hematoma	1/1	–	–	–	–	–	1/1
Injection-site pain	–	2/2	–	1/1	10/3	–	13/6
Injection-site pruritus	–	1/1	–	–	1/1	1/1	3/3
Injection-site swelling	–	2/1	–	–	–	–	2/1
Injection-site urticaria	–	4/2	–	–	12/3	6/2	22/7
Other general disorders	–	2/2	1/1	–	2/2	4/2	9/7

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.

Table 4. Gastrointestinal Disorders

			COR-005				
	0.9% NaCl	300 µg octreotide	100 µg	300 µg	900 µg	1,800 µg	All
Subjects, n	7	7	4	4	4	4	30
MedDRA SOC, F/N							
Preferred term, F/N							
Gastrointestinal disorders	4/2	36/5	1/1	–	23/4	36/4	100/16
Abdominal discomfort	–	3/1	–	–	1/1	1/1	5/3
Abdominal pain	1/1	4/2	–	–	1/1	1/1	7/5
Diarrhea	1/1	9/4	–	–	3/3	3/2	16/10
Flatulence	2/1	4/4	–	–	–	2/2	8/7
Nausea	–	9/3	1/1	–	12/3	23/3	45/10
Miscellaneous	–	7/3	–	–	6/2	6/2	19/7

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.

Table 5. Laboratory Investigations

			COR-005				
	0.9% NaCl	300 µg octreotide	100 µg	300 µg	900 µg	1,800 µg	All
Subjects, n	7	7	4	4	4	4	30
MedDRA SOC, F/N							
Preferred term, F/N							
Investigations	–	3/2	–	–	–	–	3/2
ALAT increased	–	2/2	–	–	–	–	2/2
ASAT increased	–	1/1	–	–	–	–	1/1

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; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase.

Severity of Adverse Events

- There were no serious adverse events
- There were 5 severe adverse events
- No clinically relevant effects on vital signs, electrocardiogram, or physical findings were observed
- Transient increases in liver enzyme activities were seen with octreotide treatment

CONCLUSIONS

Pharmacodynamics

- Both COR-005 and octreotide have the same efficiency to suppress GHRH-induced hGH secretion in healthy subjects
- The potencies of COR-005 and octreotide differ substantially

Pharmacokinetics

- COR-005, given as single and repeated subcutaneous doses up to 1,800 µg, reached maximum plasma concentrations within 1 hour, on average, after administration
- Maximum concentration and area under the curve values increased approximately dose proportionally
- The terminal disposition half-life was around 2 hours after single and repeated subcutaneous administration

Safety and Tolerability

- Repeated subcutaneous doses of COR-005 (up to 1,800 µg) and 300 µg octreotide given TID were well tolerated by healthy male subjects
- No serious adverse events were observed
- The majority of reported adverse events were mild; the observed local intolerance to the study medication and the gastrointestinal symptoms are consistent with the known adverse events for the substance class of somatostatin analogues

Acknowledgements

These studies were supported by Strongbridge Biopharma. Medical writing support was provided by Erica Chevalier-Larsen, PhD, of MedErgy, and was funded by Strongbridge Biopharma.

POSTER PRESENTED AT THE 18TH EUROPEAN CONGRESS OF ENDOCRINOLOGY (ECE); 28-31 MAY 2016; MUNICH, GERMANY.