CT-388, a Novel GLP-1/GIP Receptor Modulator, Improved Insulin Sensitivity in Overweight/Obese Adults

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INTRODUCTION

- CT-388 is a biased dual GLP-1 and GIP receptor modulator that exhibits minimal to no beta-arrestin coupling at either receptor, designed for once-weekly subcutaneous administration.
- A Phase 1 study (NCT04838405) was designed to investigate safety/tolerability, pharmacokinetic and pharmacodynamic activity of CT-388 in adults with overweight/obesity.
- Here we report CT-388's effect on glucose homeostasis and insulin sensitivity from the multiple ascending dose (MAD) portion of the study.

METHODS

- This was a double blind, placebo-controlled, single center, Phase 1, MAD study consisting of 3 cohorts for 4 weeks.
- Participants (n=24) had BMI ≥25 kg/m^2 (Cohort 6) or BMI ≥30 kg/m^2 (Cohorts 7 & 8) and were without type 2 diabetes.
- Participants were randomized 3:1 (6 to CT-388, 2 to placebo, n=8 per cohort). CT-388 was administered once weekly at a dose of 5mg at baseline in all cohorts and up-titrated up to 12mg in Cohorts 7 & 8.
- Oral Glucose Tolerance Test (OGTT) with 75 g glucose solution was performed at baseline (Day -1) and on Day 23.
- Blood was collected at 15 min prior to OGTT, at OGTT start, and in 30 minute intervals until 120 minutes.
- Fasting glucose, insulin, C-peptide, and HOMA-IR were measured/calculated at baseline and on Day 23.

Study design

Population: overweight/ obesity without T2D			CT-388 or Placebo SC QW				EOT
			Day 1	Day 8	Day 15	Day 22	Day 29
Cohort 6	Overweight (BMI ≥ 25)	N=8 (6:2)	5mg	5 mg	5 mg	7.5 mg	X
Cohort 7	Obesity (BMI ≥ 30)	N=8 (6:2)	5mg	5 mg	8 mg	12 mg	X
Cohort 8	Obesity (BMI ≥ 30)	N=8 (6:2)	5 mg	8 mg	12 mg	12 mg	X

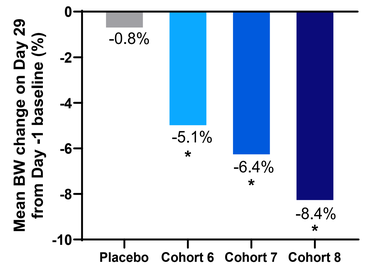
RESULTS

Demographics and baseline characteristics

Parameter	Pooled Placebo (N=6)	BMI ≥25 Cohort 6 5/5/5/7.5 mg (N=6)	BMI ≥30 Cohort 7 5/5/8/12 mg (N=6)	BMI ≥30 Cohort 8 5/8/12/12 mg (N=6)
Age, yrs	41.5 (10.7)	34.0 (10.9)	34.3 (14.0)	26.3 (7.9)
Female, n (%)	4 (66.7)	5 (83.3)	1 (16.7)	2 (33.3)
Weight, kg	90.1 (14.1)	81.8 (16.7)	107.2 (19.3)	97.1 (18.9)
BMI, kg/m^2	34.0 (1.1)	31.3 (3.8)	35.6 (2.8)	34.8 (4.0)
HbA1c, %	5.5	5.2	5.3	5.4
Fasting glucose, mg/dL	95.5	95.0	101.0	91.5
Fasting insulin, mIU/L	11.7	8.9	18.9	12.7
Fasting C-peptide, ng/mL	2.7	2.5	3.7	2.7
HOMA-IR	2.8	2.0	4.9	2.8

Mean (SD) values are presented for age, weight and BMI; medians are presented for fasting glucose, insulin, C-peptide, HOMA-IR and HbA1c.

Body weight change after 4 weeks of CT-388 dosing



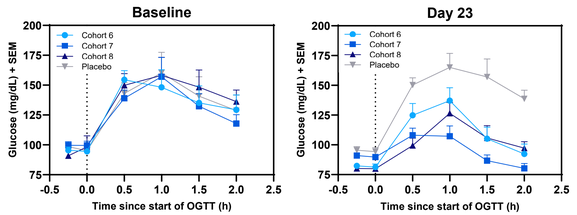
- Robust dose response in body weight following 4 wks of CT-388 dosing
- All arms yielded clinically and statistically significant weight loss compared to placebo
- Weight loss effects persists for up to 2 weeks following CT-388 discontinuation

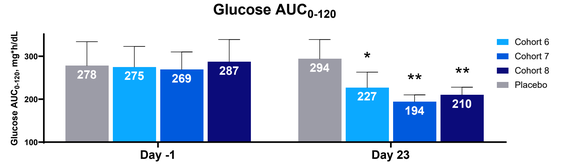
*P<0.001 vs. placebo

Oral glucose tolerance test

- At Day 23, glucose AUC$_{0\text{-}120}$ was significantly reduced in all CT-388 cohorts compared to placebo (P<0.001 for all).
- Insulin AUC$_{0\text{-}120}$ and C-peptide AUC$_{0\text{-}120}$ were lower in participants with baseline BMI ≥30 (C7 & C8).
- Peak glucose excursion (C$_{max}$) was reduced by 16-31% across all CT-388 cohorts vs placebo (P<0.05) accompanied by decreases in C$_{max}$ of insulin (20-55% in C7 & C8) and C-peptide (17-39% in C7 & C8).

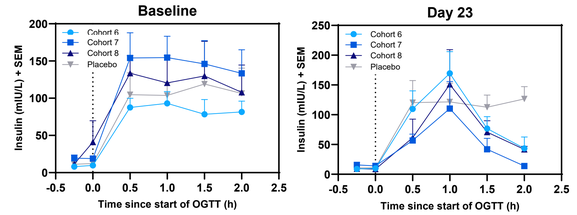
Glucose response

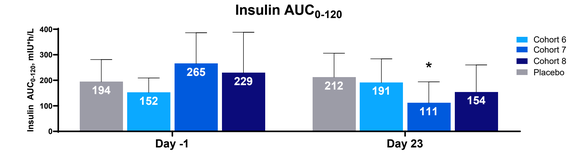




*P<0.01 vs. placebo for Glucose AUC$_{0\text{-}120}$ on Day 23; **P<0.001

Insulin response





*P=0.01 vs. placebo for Insulin AUC$_{0\text{-}120}$ on Day 23

Fasting glycemic parameters

- At Day 23, improvements were observed in fasting glucose in all CT-388 cohorts compared to placebo (P=0.001 for C6 & C8).
- Fasting insulin, C-peptide, and HOMA-IR were also significantly lower for Cohort 8 compared to placebo on Day 23 (P<0.05).

HOMA-IR

	HOMA-IR* (Day 23)	Ratio (vs. placebo)	95% CI
Cohort 6	1.75	0.65	0.33, 1.31
Cohort 7	2.37	0.89	0.44, 1.80
Cohort 8	1.15	0.43**	0.21, 0.87
Placebo	2.67		

*Values represent geometric mean; **P=0.02 vs. placebo for HOMA-IR on Day 23

Safety & tolerability

- No serious adverse events or discontinuations due to adverse events were reported. Most common adverse events were gastrointestinal-related, consistent with the incretin class.

CONCLUSIONS

- CT-388, a biased dual GLP-1/GIP receptor modulator, at a starting dose of 5 mg and up-titrated up to 12 mg within 4 weeks, showed a favorable profile among insulin-resistant participants with overweight/obesity.
- CT-388 resulted in clinically meaningful weight loss, improved insulin sensitivity, and glucose homeostasis.
- These findings suggest that CT-388 has the potential to both reduce the risk of T2D in individuals with obesity and have a beneficial effect on glucose metabolism in people with T2D.
- These data warrant further clinical evaluation of CT-388 for the treatment of obesity, type 2 diabetes, and other weight-related comorbidities.

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