WEIGHT-INDEPENDENT EFFECTS OF CT-868, A SIGNALING BIASED DUAL GLP-1 AND GIP RECEPTOR MODULATOR, ON GLUCOSE HOMEOSTASIS IN OVERWEIGHT AND OBESE ADULTS WITH TYPE 2 DIABETES

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CARMOT THERAPEUTICS

BACKGROUND

- Multi-receptor agonism/ modulation of incretins are emerging as a therapeutic area of strong interest.
- CT-868 is a dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor modulator that exhibits no beta-arrestin coupling, does not cause internalization of the GLP-1 or GIP receptors, and thus enhances signaling efficacy.
- In a previous Phase 1 study, CT-868 was tested up to 11 mg as a single dose and up to 5 mg/day for 14-days without any up-titrations in healthy and overweight/obese participants and found to be safe and well tolerated.

STUDY OBJECTIVE

To assess the weight-independent effects of CT-868 on insulin secretion rate and glucose homeostasis compared to placebo and liraglutide (Lira) in overweight and obese adults with T2DM.

METHODS

- This was a Phase 1, double-blind, placebo-controlled, randomized, single-center, crossover trial of 20 adults (18–65 years of age) diagnosed with type 2 diabetes mellitus (T2DM):
  - On diet and exercise only or on stable therapy (≥ 3 months) with metformin monotherapy or metformin in combination with sulfonylurea (SUs) ≥ 3 months prior to screening. SUs were washed out ≥ 7 days prior to randomization.
  - Body Mass index (BMI) >27 and ≤ 45 kg/m^2
  - Baseline HbA1c ≤10.5%; and fasting plasma glucose < 250 mg/dL
- Group 1 (n = 13) - included a 3-way crossover design to assess CT-868, placebo and liraglutide as active comparator, assessed during 3 in-house periods.
- Group 2 (n = 7) - included a 2-way crossover design to assess CT-868 and placebo during 2 in-house periods.
- During each period, subjects received randomized study drug via subcutaneous injection (SC) on Days 1, 2, 3; pharmacokinetic (PK) and pharmacodynamic (PD) blood samples were collected.
- Assessments included a Graded Glucose Infusion (GGI) on Day 3; a Mixed Meal Tolerance Test (MMTT), Gastric Emptying (GE) and ad libitum food intake assessments on Day 4; appetite & satiety ratings via Visual Analogue Scales (VAS) on Days 1, 2, 3, 4.

STUDY ENDPOINTS

Primary Endpoint:

- To evaluate insulin secretory rate (ISR) relative to ambient glucose (ISR/G)

Secondary Endpoints:

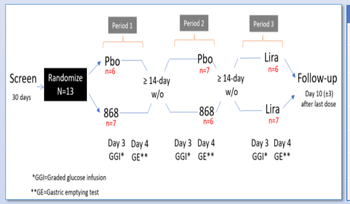
- To assess changes in glucose, insulin, C-peptide, and glucagon during a mixed meal tolerance test (MMTT)
- To assess gastric emptying via acetaminophen absorption
- To assess appetite, hunger, satiety by visual analog scales, and ad libitum food intake
- To assess plasma exposure of CT-868 [maximum plasma concentration (C_{max}); time to maximum plasma concentration (t_{max}); area under the concentration-time curve over a dosing interval ($AUC_{0\text{-}tau}$); terminal half-life ($t_{1/2}$)]

Safety Assessments:

- Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESI), vital signs, 12-lead electrocardiogram (ECG), clinical lab evaluations, and physical exam

STUDY DESIGN & DEMOGRAPHICS

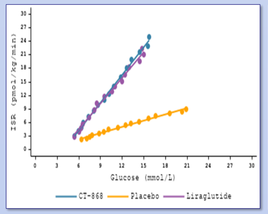
Cross-over design -- total of 20 participants with T2DM were randomized in the study conducted at a single-center, Clin Res Unit, ProSciento, USA



Baseline Characteristics	N=20
Gender – male [n (%)]	11 (55.0)
Mean age (years)	52.2
Ethnicity – Hispanic or Latino [n (%)]	16 (80.0)
Mean body weight (kg)	93.0
Mean BMI (kg/m^2)	32.7
Mean duration (years) of T2D	6.8
Mean HbA1c (%)	7.3

RESULTS

Robust insulin secretory responses are observed in T2DM patients with both Lira and CT-868 treatment compared to placebo treated participants

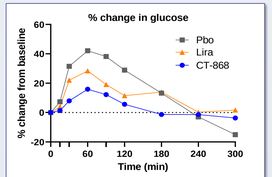


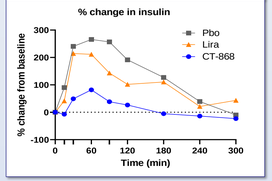
Parameter	Slope of the ISR / G		
	CT-868 (N=20)	PBO (N=18)	Lira (N=10)
LS Mean	2.43	0.47	2.4
LS Mean (Compared to CT-868)		**1.92***	0.02
95% Confidence Interval		[1.23, 2.61]	[-0.99, 1.03]

*Significant compared to CT-868; LS, least squares

RESULTS

CT-868 lowers glucose with significantly less insulin excursion vs. Lira during mixed meal tolerance test (MMTT) in T2DM patients





Incremental $AUC_{0\text{-}240min}$	CT-868 (N=20)	PBO (N=18)	Lira (N=10)
Glucose, mmol/L*min	72*	392	187
Insulin, mU/L*min	1178*‡	5832	4613
Ins x G	84,378	2,286,347	862,910
	27x lower vs Pbo		2.6x lower vs Pbo
	10x lower vs Lira		

*p <0.05 compared to placebo
‡p <0.05 compared to Lira

- During the MMTT, incremental $AUC_{0\text{-}240min}$ glucagon was suppressed by Lira but not by CT-868 treatment.
- Gastric emptying (GE) was delayed by both CT-868 and Lira compared to Pbo; however, the delay in GE was similar between Lira and CT-868.

Implications:

- Concomitantly reduced plasma glucose and insulin excursions could be due to enhanced glucose disposal, e.g., facilitated by insulin sensitizing mechanisms.
- Disposal of glucose with less/minimal suppression of glucagon could potentially lower hypoglycemic risk with CT-868 vs. Lira.

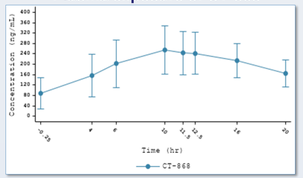
CT-868 tends to lower appetite and hunger scores which translates to a significant suppression of food intake (absolute amounts and calories consumed) during ad libitum meal

Parameters		CT-868 (N=20)	PBO (N=18)	Lira (N=10)
Body weight	(kg)			
	Pre-dose	93.3	94.3	94.6
	Day 4	93.4	94.3	94.2
	Change	0.09	0.00	-0.39
Appetite (0- 100)				
	Pre-dose	70.8	51.5	59.2
	Day 4	51.5	66.3	50.8
	Change	↓19 points	↑15 points	↓ 8 points
Hunger (0-100)				
	Pre-dose	61.5	37.9	54.5
	Day 4	53.0	51.1	52.0
	Change	↓9 points	↑13 points	↓ 3 points
Food Intake (g)		591.4*	745.7	680.2
Total Calories consumed (kcal)		733.7*	1078.1	959.3

*Significantly less food (total amount and calories) was consumed after CT-868 treatment vs Placebo (p<0.05), but Lira vs Placebo was not significant.

RESULTS

Plasma exposure of CT-868



PK parameters for CT-868

Key Parameters (mean)	T2DM (N=20)
Maximum Concentration of CT-868 (ng/mL)	273.9
Time of Maximum Concentration of CT-868 (minutes/hours)	655.8/10.9
Average Concentration of CT-868 (ng/mL)	211.9
AUC (0-tau) (ng/mL*min)	231699

- These data confirm that key PD assessments (i.e., GGI, MMTT, GE) were generally performed at time of max plasma concentration of CT-868.

CT-868 was well tolerated and most TEAEs were Grade 1 (mild) in severity

Reported AE	CT-868 (N=20), n (%)	PBO (N=18), n (%)	Lira (N=10), n (%)
At Least 1 TEAE	14 (70.0)	9 (50.0)	7 (70.0)
At Least 1 study drug related TEAE	9 (45.0)	7 (38.9)	3 (30.0)
Treatment Discontinuation	1 (5.0)*	1 (5.6)**	0
Injection Site Reaction	1 (5.0)	0	0
AEs of Special Interest (AESI)[ϕ] Total	10 (50.0)	2 (11.1)	4 (40.0)
Hypoglycemia[£]	7 (35.0)	2 (11.1)	3 (30.0)
Nausea	6 (30.0)	1 (5.6)	2 (20.0)
Vomiting	2 (10.0)	0	0
Constipation	1 (5.0)	0	0

*Anemia (mild); **Abnormal coagulation test (mild); [ϕ]All AESIs were Grade 1; [£] reported during GGI procedure

CONCLUSIONS

- Body weight was not significantly changed following any of the treatments consistent with the design and intent of the study.
- Gastric emptying was delayed by both CT-868 and Lira vs pbo consistent with the GLP-1 mechanism; however, delay was similar in CT-868 and Lira.
- CT-868 demonstrated a robust insulin secretory response from beta cells in T2DM relative to placebo; this response was similar between CT-868 and Lira.
- CT-868 lowered appetite and hunger scores with significantly decreased food intake relative to placebo; no significant changes between placebo and Lira.
- During MMTT, in T2DM patients CT-868 demonstrated lower blood glucose and significantly less insulin excursion compared to both placebo and Lira.
  - *This suggests enhanced insulin sensitivity and/or enhanced insulin independent glucose disposal induced by CT-868, independent of wt. loss.*
- CT-868 was well tolerated with no significant adverse effects in T2DM patients
- Further delineation of CT-868's longer term effects in overweight and obese patients with both T2D and T1D is underway.

ACKNOWLEDGEMENTS

We would like to thank Johan Enquist, Ray Fucini, Andrew Sawayama, David Lloyd, Jeff Iwig, Derek Bone, Dan Erlanson, Shyam Krishnan, Edgar Tenorio, Ruben Rodriguez, Anne Hergarden for their contributions to the discovery, development, and characterization of CT-868.

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