Phase 2 Study of CT-868, a Novel Dual GLP-1/GIP Receptor Modulator, in Adults with Obesity or Overweight and Type 2 Diabetes

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INTRODUCTION

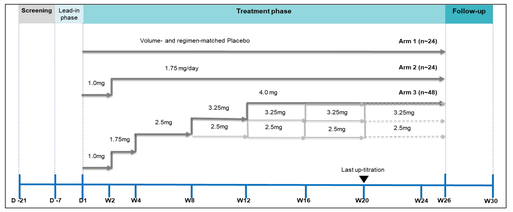
- CT-868 is a dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinogenic polypeptide (GIP) receptor modulator that exhibits no beta-arrestin coupling or receptor internalization at either receptor.
- A prior Phase 1 study demonstrated that CT-868 was generally well-tolerated.

Primary Objective: Assess the HbA1c-lowering effect of CT-868 in overweight/obese participants with T2D over 26 weeks

METHODS

- This was a Phase 2, randomized, placebo-controlled, double-blind, parallel group, multicenter study of CT-868 administered daily by subcutaneous injection for 26 weeks.
- Participants were aged 18-75, had a diagnosis of T2D for >6 mo, BMI ≥27 kg/m^2, HbA1c of 7–10%, and were on diet/exercise alone or metformin monotherapy at screening.
- A total of 103 participants were randomized 1:1:2 into one of three treatment arms: 1) volume-matched placebo (n~24), 2) CT-868 1.75 mg (n~24), or 3) CT-868 dosed up to 4.0 mg based on individual tolerability (n~48). Titration schemes are shown below.
  - Due to COVID-19-related drug supply issues, 18 of 51 participants received the 3.25 mg dose in Arm 3 (CT-868 group dosed up to 4.0 mg). To account for this, analyses were conducted on the final dose received by each participant (1.75 mg, 3.25 mg, 4 mg) instead of their initially randomized group.

Study design



- **Primary endpoint:** change from baseline in HbA1c at Week 26
- **Secondary endpoints**: change from baseline at Week 26 in body weight, fasting plasma glucose and lipids, and safety/tolerability.

RESULTS

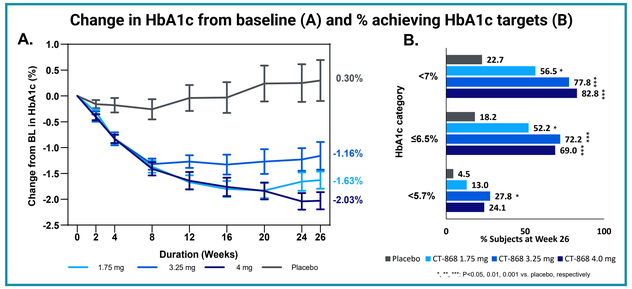
Demographics and baseline characteristics

Category	Placebo N=27	CT-868 1.75 mg N=26	CT-868 3.25 mg N=18	CT-868 4 mg N=32
Age, yrs	50.3 (11.7)	52.3 (7.8)	48.2 (9.9)	49 (12.1)
Female, n (%)	16 (59.3)	14 (53.8)	12 (66.7)	22 (68.8)
Ethnicity: Hispanic or Latino, n (%)	27 (100%)	26 (100%)	18 (100%)	32 (100%)
Weight, kg	94.6 (21.3)	92.3 (20.5)	90.1 (16.4)	90.6 (17.4)
BMI, kg/m^2	35.7 (6.3)	36.0 (6.6)	34.8 (4.5)	34.8 (5.5)
HbA1c, %	8.1 (1.0)	8.3 (0.8)	7.6 (1.0)	8.4 (0.7)
Fasting glucose, mg/dL	143.5 (46.6)	180.3 (42.2)	146.1 (40.2)	155.3 (37.8)
Metformin use, n (%)	27 (100)	24 (96.0)	18 (100)	32 (100)

Data presented as mean (SD) values unless otherwise specified

Glycemic control

- HbA1c improved significantly from baseline in CT-868 arms vs placebo at Week 26.
  - LS Mean difference in the change from baseline to Week 26 in HbA1c for CT-868 4.0 mg vs. placebo was **-2.3%** (95% CI -3.0 to -1.6, p<0.001).
- Significantly more participants achieved HbA1c ≤6.5% and HbA1c <7% in all three CT-868 arms compared with placebo.
- Fasting plasma glucose was significantly improved with CT-868 compared to placebo (treatment differences **-52.9 to -60.1 mg/dL**, p<0.001 for all arms).

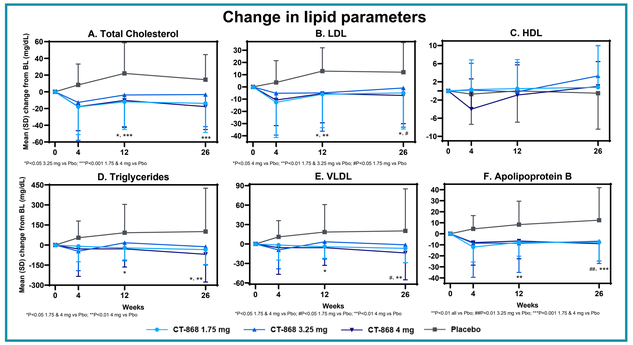


Body weight

- A dose-dependent %change from baseline to Week 26 in body weight (BW) was observed in CT-868 dose groups [Mean (SD): -2.3 (3.8)%, -3.0 (3.8)% and -5.7 (4.4)% for CT-868 1.75, 3.75 and 4 mg, respectively]; in the placebo group, %change in BW was -2.3 (4.4)%.
  - LS Mean difference in the change from baseline to Week 26 in BW for CT-868 4.0 mg vs. placebo was -2.6% (95% CI -4.8 to -0.3, p=0.025).
- 51.7% of participants on CT-868 4.0 mg achieved ≥5% weight loss at Week 26 compared to 22.7% on placebo (p=0.036).

Lipid parameters

- Total cholesterol, triglycerides, LDL-C, VLDL, and apolipoprotein B were all reduced in the CT-868 treated arms compared with placebo at Week 26.

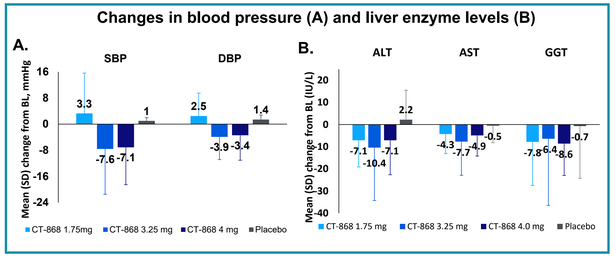


Vital signs

- CT-868 3.25mg and 4.0 mg decreased systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Week 26.
- Mean (SD) heart rate increased by 1.7 (8.8) to 2.3 (8.7) beats per minute (bpm) across CT-868 treatment arms, compared to a decrease of 4.5 (8.2) bpm for placebo.

Liver tests

- Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) were reduced by ~15% to 25% at Week 26 relative to baseline in all CT-868 treatment arms, while no meaningful change in placebo was observed. No clinically significant changes in bilirubin were noted.



Safety & tolerability

- CT-868 was well-tolerated with no treatment-related discontinuation.
- No clinically significant hypoglycemia was reported.
- The most frequent adverse events were gastrointestinal-related, with no dose dependence observed, and were mostly mild (Grade 1) in severity.

Overall summary of treatment-emergent adverse events (TEAEs)

Category, n (%)	Placebo N=27	CT-868 1.75 mg N=26	CT-868 3.25 mg N=18	CT-868 4 mg N=32
Subjects with ≥1 TEAE	23 (85.2)	22 (84.6)	16 (88.9)	28 (87.5)
Serious TEAEs, n	0	0	1 (5.6)	0
Subjects Discontinued due to TEAE	1 (3.7)	0	0	0
Fatal TEAEs, n	0	0	0	0
Drug-Related* TEAEs, n	16 (59.3)	15 (57.7)	9 (50.0)	20 (62.5)
Severity†:				
Grade 1	13 (48.1)	10 (38.5)	9 (50.0)	14 (43.8)
Grade 2	3 (11.1)	5 (19.2)	0	5 (15.6)
Grade 3	0	0	0	1 (3.1)

*Relationship to study drug is categorized as 'Possible' or 'Probable'; †Severity of drug-related TEAEs

Gastrointestinal TEAEs*

Preferred Term, n (%)	Placebo N=27	CT-868 1.75 mg N=26	CT-868 3.25 mg N=18	CT-868 4 mg N=32
Gastrointestinal Disorders	**15 (55.6)**	**16 (61.5)**	**7 (38.9)**	**22 (68.8)**
Abdominal distention	2 (7.4)	1 (3.8)	1 (5.6)	3 (9.4)
Constipation	5 (18.5)	2 (7.7)	0	10 (31.3)
Diarrhea	6 (22.2)	12 (46.2)	4 (22.2)	14 (43.8)
Dyspepsia	2 (7.4)	3 (11.5)	0	2 (6.3)
Flatulence	0	2 (7.7)	1 (5.6)	0
Nausea	7 (25.9)	5 (19.2)	2 (11.1)	11 (34.4)
Vomiting	1 (3.7)	3 (11.5)	2 (11.1)	2 (6.3)

*Occurring in at least 5% of participants

CONCLUSIONS

- CT-868 demonstrated robust glycemic control (–2.3% HbA1c lowering vs placebo) with ~70% of participants achieving HbA1c ≤6.5% at Week 26.
- CT-868 improved key cardiovascular risk factors (LDL-C, apoB, VLDL, TG, blood pressure) and liver enzymes, despite modest changes in body weight.
- CT-868 was well tolerated up to 4.0 mg without significant hypoglycemia, supporting investigation of CT-868 doses >4.0 mg in future studies to maximize its weight loss effects.

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