Cotadutide (MEDI0382) is well tolerated at doses up to 600 µg with hypoglycemic effect/body weight reduction in Japanese patients with T2DM

Poster xxx

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Introduction

- Cotadutide (MEDI0382), a dual receptor agonist with activity on receptors for glucagon-like peptide-1 (GLP-1) and glucagon, is under development for the treatment of nonalcoholic steatohepatitis and chronic kidney disease in patients with type 2 diabetes mellitus (T2DM).[1,2]
- In many patients with T2DM, significant weight loss (typically 5% or more of body weight) can improve glycemic control, cardiovascular risk, and mortality, and may even slow or reverse disease progression.[3,4]
- In a randomized, placebo-controlled, phase 2a, clinical trial in obese or overweight patients with T2DM, once-daily cotadutide (300 µg) for 41 days provided robust improvements in glycemic control and significant weight loss, and was generally well tolerated in a Caucasian population.[1]
  - In a subsequent phase 2a clinical trial, cotadutide titrated up to 300 µg showed similar efficacy and safety in overweight or obese Japanese participants with or without T2DM, to that demonstrated in the Caucasian population.[5]
- We explored the safety and tolerability of cotadutide up to a maximum of 600 µg to determine the highest clinically tolerated dose (HCTD), which can then be studied in future long-term efficacy studies as a potential maintenance dose.
  - It is known from studies of currently available GLP-1 receptor monoagonists that a controlled up-titration regimen is associated with improved tolerability.[6]
  - This study therefore started cotadutide at a low dose (e.g. 50 µg), for which improved tolerability has previously been confirmed.

Objective

- This phase 1b study examined the safety and efficacy of cotadutide at doses up to and including 600 µg in obese Japanese patients with T2DM (NCT04208620).

Methods

- During this double-blind, phase 1b study, adults (aged 20–74 years) with T2DM (glycated hemoglobin [HbA_{1c}], 6.5–8.5% [48–69 mmol/mol]) and obesity (body mass index [BMI], 25–35 kg/m^2) were randomized 3:1 to either of two cohorts of once-daily cotadutide (n = 6 each) or placebo (n = 2 each) for 70 days (**Figure 1**).
  - The dose-escalation committee used Cohort 1 to determine the HCTD, and dosing in Cohort 2 occurred 7 days or more after the initiation of Cohort 1. Participants in the cotadutide group received doses titrated to a maximum of 600 µg (starting at 50 µg).
  - The study comprised an approximately 2-week screening period, a run-in period of 10 days and an up to 7-week up-titration treatment period, followed by a 3-week treatment extension period at the dose level of 600 µg, followed by a 28-day follow-up period, if the HCTD reached 600 µg.

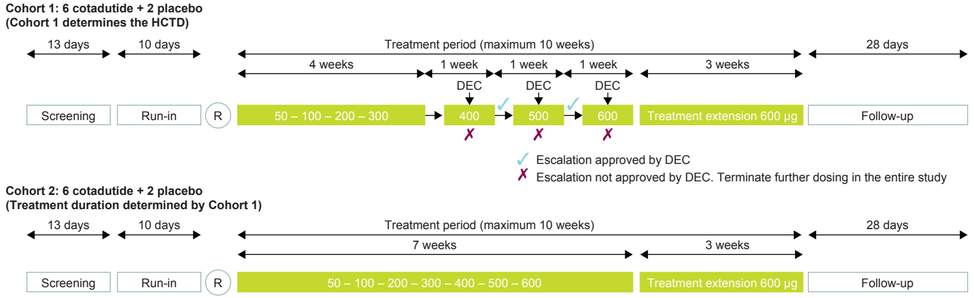
Endpoints

- The primary objective was to assess the safety and tolerability of cotadutide titrated up to the HCTD. Secondary objectives, assessing cotadutide titrated up to the HCTD, included characterization of the pharmacokinetic profile of cotadutide, effects on measures of glucose control, and effects of cotadutide on body weight.

Statistical analyses

- Cohort 1 and Cohort 2 were pooled for statistical analyses.
- Change from baseline and percentage change from baseline were derived for selected study endpoints.
- Study endpoints were summarized descriptively by treatment group for comparing cotadutide against placebo.

Figure 1. Study design.



DEC, dose-escalation committee; HCTD, highest clinically tolerated dose; R, randomization.

Results

- Of 40 participants screened, 4 were randomized to placebo and 12 to cotadutide, all of whom received study treatment and were included in the full analysis set, the safety analysis set, and the immunogenicity analysis set. Twelve participants randomized to and treated with cotadutide were included in the pharmacokinetic analysis set.
- Participant demographics and characteristics were relevant to the disease under study and balanced across treatment groups (**Table 1**).
  - The median age of participants was 60 years, the majority were male (10 [62.5%]), the median BMI was 27.2 kg/m^2, and the mean (standard deviation [SD]) HbA_{1c} was 7.41% (0.67) (57 mmol/mol [5.0]) in the cotadutide group and 7.95% (0.45) (63 mmol/mol [2.6]) in the placebo group.
  - Based on medical history, in total, 12 participants (75%) had metabolism and nutrition disorders (dyslipidemia in 10 participants) and 6 (37.5%) had hepatic steatosis.
  - One participant discontinued treatment in the placebo group (subject decision), and four participants discontinued treatment in the cotadutide group (one owing to meeting a study-specific discontinuation criterion that was transient and not reported as an adverse event (AE), one was a subject decision, and two owing to COVID-19 logistics).
- Compliance with treatment was 100% for both treatment groups.
- The dose-escalation committee approved titrations up to 600 µg following data reviews.

Table 1. Participant demographic and characteristics (safety analysis set).

Demographic characteristic	Placebo (n = 4)	Cotadutide (n = 12)	Total (N = 16)
Age, years, mean (SD)	57.3 (7.8)	58.2 (11.2)	57.9 (10.2)
Sex, n (%)			
Male	3 (75.0)	7 (58.3)	10 (62.5)
Female	1 (25.0)	5 (41.7)	6 (37.5)
Race, n (%)			
Asian	4 (100)	12 (100)	16 (100)
Height, cm, mean (SD)	165.00 (5.78)	163.22 (6.55)	163.66 (6.23)
Weight, kg, mean (SD)	77.33 (5.07)	75.66 (6.77)	76.08 (6.27)
BMI, kg/m^2, mean (SD)	28.60 (2.81)	28.59 (2.88)	28.59 (2.77)
BMI group, n (%)			
< 25 kg/m^2	0	0	0
≥ 25 and < 30 kg/m^2	3 (75.0)	9 (75.0)	12 (75.0)
≥ 30 and < 35 kg/m^2	1 (25.0)	3 (25.0)	4 (25.0)
Mean HbA_{1c}, % (SD) [mmol/mol (SD)]	7.95 (0.45) [63 (2.6)]	7.41 (0.67) [57 (5.0)]	–

BMI, body mass index; HbA_{1c}, glycated hemoglobin; SD, standard deviation.

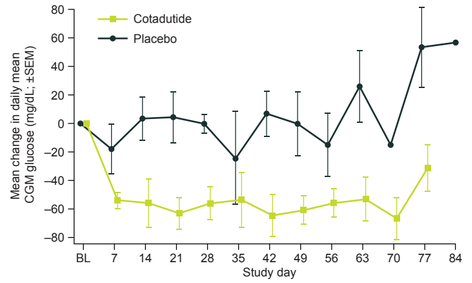
Primary objective

- Overall, 12 participants (75.0%) reported any AE, 1 participant (25.0%) in the placebo group and 11 participants (91.7%) in the cotadutide group.
- Gastrointestinal disorders were the most frequently reported AE, with nine patients on cotadutide (75%) reporting at least one event. The most prevalent AEs assessed as related to treatment with cotadutide were nausea in eight participants (66.7%), constipation in four participants (33.3%), and abdominal discomfort in three participants (25.0%).
  - No AEs of nausea or vomiting were reported within the first 3 days of the start of each of cotadutide 100, 200, or 500 µg dosing periods, or during the 600 µg treatment extension period.
  - All AEs in the cotadutide groups were of grade 1 (six participants [50.0%]) or grade 2 (five participants [41.7%]) severity according to the Common Terminology Criteria for Adverse Events.
- There were no reported deaths, no serious AEs, and no discontinuations due to AEs. Clinical laboratory and other safety assessments were in line with the reported safety profile of cotadutide.

Secondary objectives

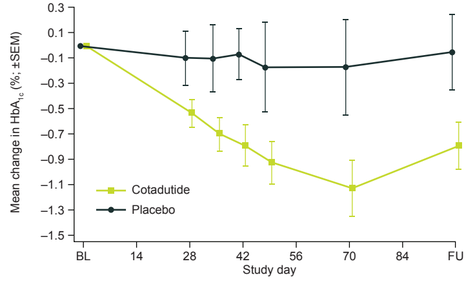
- There was a significant reduction from baseline in 7-day mean glucose levels measured by continuous glucose monitoring (CGM) with cotadutide (**Figure 2**). The mean (SD) change to final week of treatment with cotadutide was –62.79 mg/dL (35.66) versus an increase of 28.52 mg/dL (9.16) with placebo.
- Cotadutide treatment reduced HbA_{1c} by 1.13% (0.64) at the end of treatment from a baseline of 7.41% (0.67) (**Figure 3**). In the placebo group, HbA_{1c} was reduced by 0.17% (0.65) at the end of treatment from a baseline of 7.95% (0.45).
- Cotadutide treatment was associated with a –6.93% (3.44) reduction from baseline in body weight on day 70 compared with –1.23% (1.20) reduction in the placebo group (**Figure 4**).
  - At the follow-up visit (day 98), body weight reduction was 3.93% (3.21) in the cotadutide group compared with an increase of 0.32% (0.81) in the placebo group.
  - A total of 62.5% participants in the cotadutide group, compared with 0% of participants in the placebo group, achieved more than 5% body weight loss from baseline to the end of the treatment extension period.

Figure 2. Change in daily mean CGM glucose levels at the end of each week during the treatment period (full analysis set).



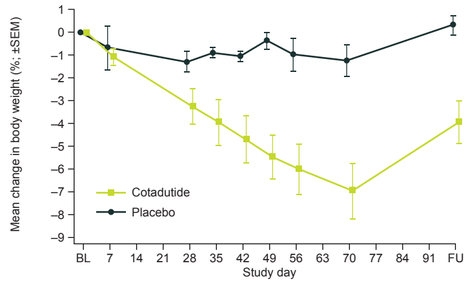
Data are mean ± SEM.
BL, baseline; CGM, continuous glucose monitoring; SEM, standard error of the mean.

Figure 3. Percentage change in HbA_{1c} with cotadutide versus placebo (full analysis set).



Data are mean ± SEM.
BL, baseline; FU, follow-up; HbA_{1c}, glycated hemoglobin; SEM, standard error of the mean.

Figure 4. Percentage change in body weight with cotadutide versus placebo (full analysis set).

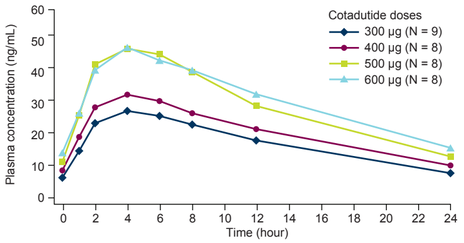


Data are mean ± SEM.
BL, baseline; FU, follow-up; SEM, standard error of the mean.

Pharmacokinetics

- Pharmacokinetics data suggested linear pharmacokinetics of cotadutide following once-daily subcutaneous administration of cotadutide across the investigated dose range.
  - **Figure 5** shows geometric mean plasma concentration–time curves of cotadutide at 300, 400, 500, and 600 µg.
  - Peak plasma concentrations were generally observed at 4–6 hours post dose.
  - The half-life of cotadutide was 10.9–14.3 hours at dose levels of 300–600 µg.
  - Consistent with the half-life, minimal trough concentration accumulation was observed during the first week of 50 µg daily dosing.
  - Cotadutide antidrug antibody positivity was reported in two participants treated with cotadutide, but no effect on cotadutide exposure was suggested.

Figure 5. Geometric mean plasma concentration time-course at different cotadutide doses (pharmacokinetics analysis set).



Conclusions

- Cotadutide treatment for 70 days was well tolerated at doses up to 600 µg in Japanese patients with T2DM.
- Cotadutide safety did not generally differ from that previously reported and no new safety concerns were raised during the study.
- Participants treated with cotadutide showed a greater impact in most of the efficacy objectives and outcomes than participants treated with placebo.
- Cotadutide treatment was associated with greater reductions from baseline in 7-day mean glucose measured by CGM, HbA_{1c}, and body weight.
- Cotadutide lowers blood glucose levels and reduces body weight, and has the potential to improve clinical outcomes in patients with T2DM.
- This study in a Japanese population is part of the ongoing global clinical development of cotadutide.

References

1. Ambery P *et al. Lancet* 2018;391:2607–18.
2. Ambery PD *et al. Br J Clin Pharmacol* 2018;84:2325–35.
3. Henderson SJ *et al. Diabetes Obes Metab* 2016;18:1176–90.
4. Inzucchi SE *et al. Diabetes Care* 2012;35:1364–79.
5. Asano M *et al. Diabetes Obes Metab* 2021 Apr 28. doi:10.1111/dom.14412. Epub ahead of print.
6. Perreault L *et al. Adv Ther* 2019;36:265–77.

Conflicts of interest

MA, AS, MS, and HS are employees of AstraZeneca K.K. DR and LH are employees of AstraZeneca. All hold AstraZeneca stocks.

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