Clinical Study Report Synopsis	
Drug Substance	Cotadutide (MEDI0382)
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A Phase 1 Randomized, Double-blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Cotadutide in Chinese Overweight/Obese Subjects with Type 2 Diabetes Mellitus

Study dates: First subject enrolled: 25 February 2022
Last subject last visit: 12 December 2022
The analyses presented in this report are based on a clinical data lock date of 14 February 2023

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator: PPD
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Sponsor's Responsible Medical Officer: PPD MD PhD
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This was a Phase 1 study conducted at 2 study centres in China.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of cotadutide titrated up to the dose of 600 µg	• Incidence of TEAEs and TESAEs till the end of the Up-titration Period (up to 7 weeks) and through the end of the Follow-up Period • Clinically important changes in 12-lead ECG, vital signs (including pulse rate and blood pressure), physical examination, and clinical laboratory evaluations through the end of Up-titration Period (up to 7 weeks) and through the end of the Follow-up Period
• To characterize the PK profile of cotadutide titrated up to the dose of 600 µg	• AUC_{τ}, C_{max}, t_{max}, C_{trough} based on NCA
Secondary	
• To characterize the immunogenicity of cotadutide titrated up to the dose of 600 µg	• ADAs to cotadutide at baseline through end of study
• To assess the effects of cotadutide, titrated up to the dose of 600 µg, on various measures of glucose control as measured by CGM	• Change in daily average glucose levels as measured by CGM from baseline to the end of the Up-titration Period, end of the Treatment Extension Period, and during 14 days of the Follow-up Period • Change in 7-day average glucose levels as measured by CGM from baseline versus each week of the Up-titration Period and end of the Treatment Extension Period • Change in coefficient of variation as measured by CGM over 7 days from baseline versus each week of the Up-titration Period and end of the Treatment Extension Period • Change in percentage time spent in hyperglycaemia >7.8 mmol/L (140 mg/dL), target range 3.9-7.8 mmol/L (70–140 mg/dL), and the range <3.0 mmol/L (54 mg/dL) as measured by CGM over 24 hours from baseline versus each week of the Up-titration Period and end of the Treatment Extension Period • Change in percentage time spent in hyperglycaemia >7.8 mmol/L (140 mg/dL), target range 3.9-7.8 mmol/L (70–140 mg/dL),

Objectives	Endpoints
	and the range <3.0 mmol/L (54 mg/dL) as measured by CGM over 7 days from baseline versus each week of the Up-titration Period and end of the Treatment Extension Period • Change in estimated HbA1c from baseline to the end of each week of the Up-titration Period and the end of the Treatment Extension Period
• To assess the effects of cotadutide, titrated up to the dose of 600 µg, on additional measures of glucose control	• Change in fasting plasma glucose from baseline versus each week of the Up-titration Period, the end of the Up-titration Period, and the end of the Treatment Extension Period • Change in HbA1c from baseline to the end of the Treatment Extension Period
• To assess the effects of cotadutide, titrated up to the dose of 600 µg, on body weight	• Percentage and absolute change in body weight from baseline to the end of the Up-titration Period and the end of the Treatment Extension Period • Percentage and absolute change in body weight from baseline to the end of each week of the Up-titration Period • Proportion of subjects achieving >5% body weight loss from baseline to the end of the Treatment Extension Period.

ADA = anti-drug antibody, AUC_τ = area under plasma concentration-time curve in the dose interval, CGM = continuous glucose monitoring, C_{max} = maximum observed plasma drug concentration, C_{trough} = observed lowest drug concentration reached before the next dose, ECG = electrocardiogram, HbA1c = haemoglobin A1c, NCA = non-compartmental analysis, PK = pharmacokinetics, TEAE = treatment-emergent adverse event, TESAE = treatment-emergent serious adverse event, t_{max} = time to reach maximum observed concentration.

Note: Exploratory objectives and endpoints are described in the main report body.

Study design

This was a randomized, double-blinded, placebo-controlled study designed to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of ascending doses of cotadutide in overweight or obese Chinese subjects with type 2 diabetes mellitus (T2DM). Subjects aged 18 to 74 years, with a body mass index (BMI) ≥ 25 and ≤ 35 kg/m^2 were enrolled. Subjects were required to have a diagnosis of T2DM and inadequate blood glucose control as defined by a haemoglobin A1c (HbA1c) of 7% to 8.5% and were required to have been on metformin monotherapy in the 3 months prior to screening. A total of 16 Chinese subjects were planned to be randomized to cotadutide or placebo in a 3:1 ratio (cotadutide [n=12] and placebo [n=4]) at two study centres in mainland China. Those subjects who received cotadutide once daily subcutaneously (SC) were titrated to a maximum of 600 µg once daily SC, beginning at 50 µg once daily SC. The study included a screening period of approximately 2 weeks, a run-in period of 10 days, an Up-titration Treatment Period of up to 7 weeks, a Treatment Extension Period of 3 weeks at the dose of 600 µg, and a Follow-up Period of 28 days.

The first up-titration was from 50 to 100 µg once daily, and thereafter the weekly titration included increments by 100 µg once daily, up to 600 µg once daily. The 3-week treatment extension was triggered from the end of the initial 7-day treatment administration titration period at the dose of 600 µg once daily.

Subjects were asked to provide informed consent before undergoing screening assessments to determine their eligibility to participate in the study. Consent was collected at a visit prior to performing the assessments. Screening was performed within 14 days before subjects starting the 10-day run-in period. During the run-in period, subjects refrained from taking prohibited medications but continued to take their prescribed stable dose of metformin as they did for the duration of their participation in the study. They were required to wear a continuous glucose monitoring (CGM) device for at least 7 days during the run-in period and received further training in self-injection technique, as determined at the screening visit. An ambulatory blood pressure monitoring (ABPM) device was fitted and worn for 24 hours. Following an overnight fast, blood tests and a series of electrocardiograms (ECGs) were performed during run-in period for eligibility verification.

After the run-in period, subjects were admitted to the clinical unit on Day -1 and initial safety assessments were performed. Eligibility criteria were also reverified prior to treatment administration. Following an overnight fast, subject weight was measured on the morning of Day -1, and a series of ECGs were conducted. Subjects were randomized at any time from Day -1 to prior to receiving a cotadutide or placebo dose on Day 1.

On Day 1, a replacement CGM sensor was fitted before treatment administration. Subjects were expected to wear the sensor continuously until the end of the study, which required periodic replacement. Each treatment administration period consisted of 7 days of treatment daily and began on Day 1, after pre-dose PK blood sample collection and after performing safety assessments including vital signs, and an ECG etc. On Days 1 and 2, for the dose of 50 µg, subjects had the option to remain as inpatient or attend the clinical unit daily for treatment administration and other assessments, as applicable. During this time, subjects were supervised while self-administering the investigational product (IP). If the subject returned on a daily basis, the visits were at approximately the same time each day. The IP was to be administered at a time close to that of the first dose, not exceeding 4 hours at the most. On Day 2, pre-dose blood samples were collected for PK assessment and safety assessment were performed. On Day 7, PK and safety assessments were performed, and the ABPM device was fitted, to be worn for 24 hours.

On Days 8, 15, and 22, PK and safety assessments, and an up-titration step were performed as per the randomization schedule. On Days 9, 14, and 23, blood samples were collected for PK assessment. On Day 28, subjects were admitted to the centre for PK and safety assessments prior to up-titration to 400 µg the following day (Day 29), then remained in-house for

approximately 24 hours for safety, PK, and efficacy assessments. Subjects could be discharged from the centre after completing all required sample collection and assessments on Day 30. The inpatient period was repeated on Days 35 to 37 as well as Days 42 to 44, and included up-titration to 500 µg and 600 µg, respectively. Subjects returned to the centre following an overnight fast as inpatients for PK sampling and fitting of the ABPM device in the morning on Day 49, after which, the subjects were discharged on the first day of the treatment extension period.

After titration to 600 µg dose, subjects continued at the dose of 600 µg for 3 weeks, returning to the clinical unit at Days 7 (for an outpatient visit) and Days 20 to 21 (for an inpatient visit) of the treatment extension period, for safety and efficacy assessments as well as dispensing IP, as required. On Days 1, 7, and 21 of the treatment extension period and Days 1, 2, and 3 of follow-up, blood samples were collected for PK assessment. A follow-up visit was performed for final safety assessments at 28 days after the last dose of IP or as convenient, in the event of discontinuation.

Target subject population and sample size

Approximately 16 subjects were to be randomized to cotadutide or placebo group to ensure approximately 12 evaluable subjects.

Subjects aged 18 to 74 years, with a BMI ≥ 25 and ≤ 35 kg/m^2 were enrolled. Subjects were required to have a diagnosis of T2DM and inadequate blood glucose control as defined by a HbA1c of 7% to 8.5% and were required to have been on metformin monotherapy, where no significant dose changes (increase or decrease ≥500 mg/day) had occurred in the 3 months prior to screening.

Investigational product and comparator: dosage, mode of administration and batch numbers

Table S2 Study Treatments

Arm name	**Treatment**	**Placebo**
Intervention name	**Cotadutide**	**Placebo**
Type	Combination	Combination
Dose formulation	Liquid drug product [a]	Liquid drug product [a]
Unit dose strength(s)	Multidose prefilled pen device containing 2.7 mL at a concentration of 1 mg/mL. Each pen can deliver doses of 50-600 µg in increments of 50 µg	Multidose prefilled pen device containing 2.7 mL. Each pen can deliver doses of 50-600 µg in increments of 50 µg
Dosage level(s)	50, 100, 200, 300, 400, 500 or 600 µg daily	Matched to 50, 100, 200, 300, 400, 500 or 600 µg cotadutide daily

Table S2 Study Treatments

Arm name	Treatment	Placebo
Intervention name	**Cotadutide**	**Placebo**
Route of administration	Subcutaneous Injection	Subcutaneous Injection
Use	experimental	placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor
Packaging and labelling	Study intervention will be provided in a carton containing 1 prefilled pen. Each carton and prefilled pen will be labelled as required per country requirement.	Study intervention will be provided in a carton containing 1 prefilled pen. Each carton and prefilled pen will be labelled as required per country requirement.
Current/former name(s) or alias(es)	Cotadutide/MEDI0382	Not applicable
Batch Numbers	361845/00007	361844/00008

CSP = clinical study protocol; IMP = Investigational medicinal product; NIMP = non-investigational medicinal product; SAE = serious adverse event.

[a] Both the liquid drug product and prefilled pen constituted the investigational product. Adverse events and SAEs that occurred with the investigational product were to be reported per the processes outlined in Section 8.3 of the CSP.

Other medical devices (not manufactured by or for AstraZeneca) provided for use in this study were:

- Glucometer
- CGM device
- 24-hour ABPM
- Telemetry ECG
- Digital ECG

Duration of treatment

Following randomization, eligible subjects were to receive either cotadutide or placebo (3:1 ratio) once daily in the morning via SC injection.

Cotadutide was administered for up to 7 weeks during the up-titration period as follows:

- 50 µg for 7 days
- 100 µg for 7 days
- 200 µg for 7 days
- 300 µg for 7 days

- 400 µg for 7 days
- 500 µg for 7 days
- 600 µg for 7 days

The up-titration period was followed by cotadutide at 600 µg for a 3-week treatment extension. Subjects randomized to the placebo group received matched placebo SC once daily for up to 10 weeks.

Statistical methods

Analysis Data Sets

The Full Analysis Set (FAS) included all subjects that were assigned a randomization number and received at least one dose of IP. Subjects in the FAS were analysed according to the randomized treatment. The Safety Analysis Set included all subjects who received at least one dose of IP. Subjects in the Safety Analysis Set were analysed according to the actual treatment they received. The PK Analysis Set included all subjects who received at least one dose of cotadutide and had at least one post-baseline cotadutide PK concentration that was above the lower limit of quantification and without pre-defined important protocol deviations (IPDs) or violations that significantly affect the PK. The Immunogenicity Analysis Set included all subjects in FAS who received at least one dose of IP with at least one reportable immunogenicity data. Subjects in the Immunogenicity Analysis Set were analysed according to the actual treatment they received.

Statistical Analysis of Endpoints

Two analyses were planned for this study as follows:

- An interim analysis may be conducted after a certain number of subjects completed the Up-titration Period, and

1 A final analysis after the last subject completed the safety Follow-up Period.

However, no interim analysis was performed.

The FAS was used for efficacy evaluations, the Safety Analysis Set was used for safety evaluations, PK evaluations were based on the PK Analysis Set, and Immunogenicity evaluations were based on the Immunogenicity Analysis Set.

Efficacy data were summarized descriptively by treatment group, and further by dose level and time point, as appropriate.

Safety data were summarized descriptively, by treatment group and also by dose level if appropriate.

Pharmacokinetics parameters such as cotadutide maximum observed plasma concentration (C_{max}), time at which C_{max} is observed (t_{max}), area under the plasma concentration-time curve (AUC) for a treatment administration interval at steady-state (AUC_{τ}), and trough

concentrations from the plasma concentration-time data defined as pre-dose samples (C_{trough}) were evaluated from plasma concentration-time data for cotadutide at dose levels of 100, 300, 400, 500, and 600 µg. Descriptive statistics including mean, standard deviation (SD), median, minimum, and maximum were generated for plasma concentrations of cotadutide at each time point and dose level separately, and for all PK parameters including C_{trough}. Samples confirmed positive for anti-drug antibodies (ADAs) were tested and analysed for antibody titre and reported. The ADA incidence rate and titre were tabulated for each treatment group.

A total of 16 subjects were to be randomized at 3:1 ratio to the cotadutide arm or the placebo arm (cotadutide [n=12] and placebo [n=4]).

Study population

- Total of 16 subjects were randomized and all subjects completed the treatment and study. A total of 7 IPDs were identified, no subject was excluded from any analysis set.
- Overall, demographic and subject characteristics were representative of the intended target population of this study and were generally well balanced across treatment groups.
- There was a slightly higher proportion of subjects with hypertension in the cotadutide group (5/12, 41.7% subjects) compared with the placebo group (1/4, 25.0% subjects), and the use of anti-hypertensive medication was in line with medical history which had no obvious impact on the study conclusions.

Summary of efficacy results

- The cotadutide group showed a larger decrease in average daily and 7-day average glucose levels (measured by CGM) from baseline compared with placebo group to the end of Up-titration and Treatment Extension Periods.
- The cotadutide group generally showed a larger change from baseline compared with placebo group for decrease in time spent in hyperglycaemia (>7.8 mmol/L) and increase in time spent in target range (3.9 to 7.8 mmol/L) and hypoglycaemia (<3.0 mmol/L). The cotadutide group generally showed a larger reduction in percentage of time spent in hyperglycaemia (>7.8 mmol/L), and a larger increase in percentage of time spent in target range (3.9 to 7.8 mmol/L) throughout the study compared with the placebo group.
- The cotadutide group showed a consistent decrease in estimated HbA1c (derived from the average CGM glucose) throughout the study, with a substantial decrease in HbA1c values at Day 21 of Treatment Extension Period.
- Decrease in fasting plasma glucose and HbA1c were seen across both treatment groups, with a slightly larger decrease seen in the cotadutide group at all timepoints.
- The cotadutide group showed a gradual (consistent) decrease in body weight at each time point (up to -7.3% at Day 21 of Treatment Extension Period from baseline), with >5% weight loss achieved by 9 out of 12 (75.0%) subjects in the cotadutide group compared with none (0% subjects) in the placebo group at Day 49, as well as 9 out of 12 (75.0%) subjects in the cotadutide group compared with 1 (25.0%) subjects in the placebo group at Day 21 of the Treatment Extension Period.

- Reductions in waist circumference were numerically larger in the placebo group, which is not consistent with the larger weight reduction in the cotadutide group.
- The cotadutide group showed numerically larger decreases in total cholesterol (TC) , triglycerides, low-density lipoprotein (LDL) and TC/ high-density lipoprotein (HDL) ratio) from baseline compared with placebo group throughout the study, and numerically larger decrease in HDL up to the end of Up-titration Period.
- The cotadutide group showed a larger decrease in hepatic fat fraction (50.6% decrease) compared with placebo group (37.5% decrease from baseline) at Day 21 of Treatment Extension Period.

Summary of pharmacokinetic results

- In Chinese subjects after SC administration of 100, 300, 400, 500 and 600 μg of cotadutide, cotadutide showed moderate absorption rate, with median tmax ranging from 3.98 to 6.06 hours.
- The geometric mean half-life of cotadutide ranged from 11.03 to 16.84 hours with no consistent trend across the doses.
- Exposures to cotadutide obtained in this study suggested dose proportionality following SC administration of cotadutide doses ranging from 50 to 600 μg.

Immunogenicity

- Cotadutide ADA positivity was reported in 4 subjects treated with cotadutide at dose levels of 300 and 600 μg, which were all treatment-emergent ADAs, but no effect of ADA on cotadutide exposures was suggested.

Summary of safety results

- The study met its primary endpoint and demonstrated that cotadutide given once daily at doses titrated from 50 μg up to 600 μg (highest clinically tolerated dose), was generally well tolerated in terms of treatment-emergent adverse events (TEAEs) and laboratory parameters.
- There were no reported deaths, serious adverse events, or adverse events (AEs) leading to discontinuation of the study drug or discontinuation from the study.
- Most commonly reported AEs (by preferred term [PT]) in the cotadutide group were injection site bruising (6/12 [50%] subjects), followed by decreased appetite, nausea, and vomiting (5/12 [41.7%] subjects, each). In the placebo group, diarrhoea was reported by 2 (50.0% subjects), while all other PTs were reported by 1 subject, each.
- The most commonly (≥20% subjects) reported AEs (PT level) in the cotadutide group that were assessed by the Investigator as possibly related to the study drug were nausea and vomiting (5/12, 41.7% subjects, each), followed by diarrhoea and decreased appetite (4/12, 33.3% subjects, each), and eructation and abdominal pain upper (3/12, 25.0% subjects, each).
- Most of the reported AEs across both treatment groups were mild. Moderate AEs were reported for 3/12 (25.0%) subjects in the cotadutide group, and the PTs reported were hypertension, abdominal pain, abdominal pain upper, diarrhoea, nausea, and acute kidney

injury, while none were reported in the placebo group. No severe AEs were reported in any treatment group.

- Among the 5 (41.7%) subjects who reported nausea or vomiting in the cotadutide group, all 5 (41.7%) subjects had mild vomiting, 4 (33.3%) subjects had mild nausea, and 1 (8.3%) subject had moderate nausea. No conclusion could be made on the dose-dependent relationship between cotadutide and the incidence of nausea and vomiting.
- No clinically meaningful trends were noted for laboratory tests during the study within each treatment group as well as across treatment groups. Increase in heart rate and pulse rate were observed in cotadutide group compared with placebo group.
- Overall, clinical laboratory, and other safety assessments were in line with the reported safety profile of cotadutide.

Conclusion(s)

- The study met its primary endpoints and demonstrated that cotadutide given once daily at doses titrated from 50 μg up to 600 μg (highest clinically tolerated dose), was generally well tolerated in terms of TEAEs and laboratory parameters.
- Overall, clinical laboratory, and other safety assessments were in line with the reported safety profile of cotadutide. No new safety concerns were raised.
- Cotadutide PK exposure in Chinese participants was generally within expectation and increased proportionally to dose after continuous titration doses from 50 μg to 600 μg. Four out of 12 subjects in Cota group developed treatment-emergent ADAs. No clear trend of ADA impact on Cota PK was indicated.
- Effects of cotadutide, titrated up to the dose of 600 μg, on glucose control, body weight, and lipid profile showed results in favour of the cotadutide group in this study.