SYNOPSIS

Study centre(s)

This was a Phase II study conducted at a total of 2 sites in 2 countries. Part A was conducted at one site (Sweden) and Part B was conducted at 2 sites (Netherlands and Sweden, one site each).

Publications

Parker VE, Robertson D, Hansen L, Ambery PD, Esterline R, Jermutus L, et al. Cotadutide (MEDI0382), a dual receptor agonist with balanced glucagon-like peptide-1 and glucagon activity, modulates hepatic glycogen stores. European Association for the Study of Diabetes 2019 Virtual Meeting 17-20 Sept 2019; Barcelona, Abstract 113.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary	
• To assess the effect of cotadutide on hepatic glycogen levels versus placebo after 28 days (Part A) and 35 days (Part B) of treatment	• Change in hepatic glycogen concentration adjusted for liver volume as measured by MRS at T = 4 hours post standardised morning meal from baseline (Day -1) to the end of 28 days of treatment (Part A only) • Percentage change in fasting hepatic glycogen concentration adjusted for liver volume as measured by MRS at T = 24 hours post standardised morning meal from baseline (Day 1) to the end of 35 days of treatment (Day 36) (Part B) (Note that the primary endpoint was updated in CSP Amendment 5 [03 May 2019]).
Secondary	
• To assess the effect of cotadutide on hepatic glycogen levels versus liraglutide after 35 days of treatment (Part B only)	• Percentage change in fasting hepatic glycogen concentration adjusted for liver volume as measured by MRS at T = 24 hours post standardised morning meal from baseline (Day 1) to the end of 35 days of treatment (Day 36, Part B only)
• To assess the effect of cotadutide on hepatic fat fraction versus placebo after 35 days of treatment (Part B only)	• Change in hepatic fat fraction from baseline as measured by MRI (Day -1) to the end of 35 days of treatment (Part B only)
• To characterise the immunogenicity profile of cotadutide titrated up to a dose level of 300 µg	• Development of ADA and titre (if confirmed positive)
Safety	

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Primary	
• To assess the effect of cotadutide on hepatic glycogen levels versus placebo after 28 days (Part A) and 35 days (Part B) of treatment	• Change in hepatic glycogen concentration adjusted for liver volume as measured by MRS at T = 4 hours post standardised morning meal from baseline (Day -1) to the end of 28 days of treatment (Part A only) • Percentage change in fasting hepatic glycogen concentration adjusted for liver volume as measured by MRS at T = 24 hours post standardised morning meal from baseline (Day 1) to the end of 35 days of treatment (Day 36) (Part B) (Note that the primary endpoint was updated in CSP Amendment 5 [03 May 2019]).
Secondary	
• To assess the effect of cotadutide on hepatic glycogen levels versus liraglutide after 35 days of treatment (Part B only)	• Percentage change in fasting hepatic glycogen concentration adjusted for liver volume as measured by MRS at T = 24 hours post standardised morning meal from baseline (Day 1) to the end of 35 days of treatment (Day 36, Part B only)
• To assess the effect of cotadutide on hepatic fat fraction versus placebo after 35 days of treatment (Part B only)	• Change in hepatic fat fraction from baseline as measured by MRI (Day -1) to the end of 35 days of treatment (Part B only)
• To characterise the immunogenicity profile of cotadutide titrated up to a dose level of 300 µg	• Development of ADA and titre (if confirmed positive)
To evaluate the safety and tolerability of cotadutide titrated up to a dose level of 300 µg	Measures of safety and tolerability (vital signs, ECGs, laboratory test results, AEs)

Exploratory objectives have not been included here but can be found in the CSR.
ADA = anti-drug antibody/antibodies; CSP = clinical study protocol; CSR = clinical study report; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy.

Study design

This was a 2-part (Part A and Part B) exploratory Phase II study.

Part A was a randomised, double-blind, placebo-controlled study to evaluate the effect of cotadutide administered once daily SC for 28 days on hepatic glycogen metabolism in overweight and obese participants with T2DM. Part A was planned to randomise up to 20 participants at one centre in Sweden. Eligible participants were consented, screened for suitability, and randomised within 60 days to receive double blind cotadutide titrated from 100 to 300 µg, or placebo. An interim analysis (ie, Part A analysis) was performed after Part A participants had completed the study. Participants from Part A were not re-enrolled in Part B.

Part B was a randomised, double-blind, placebo-controlled and open-label active comparator study to evaluate the effect of cotadutide on hepatic glycogen metabolism in overweight and obese participants with T2DM. In Part B it was planned to randomise approximately 30 participants at one centre in Sweden and one in the Netherlands; there was also a centre in the UK, however no participants were recruited due to COVID-19. Participants in Part B were randomised to receive double-blind cotadutide titrated from CCI or placebo, or open-label liraglutide titrated from 0.6 to 1.8 mg once daily for 35 days.

Eligible participants were randomised at a 1:1 ratio following screening to receive either cotadutide SC or placebo SC (Part A) or randomised at a 1:1:1 ratio following screening to receive either cotadutide SC, placebo SC, or open-label liraglutide (Part B). The IXRS assigned a unique randomisation code and treatment group to the participant at the time of randomisation.

In Part A, neither the participant nor any of the investigator or sponsor staff who were involved in the treatment or clinical evaluation of the participants were aware of the treatment received. In Part B, the cotadutide and placebo multidose pens were indistinguishable. The participant and site staff were blinded with respect to whether they were receiving cotadutide or placebo. The liraglutide used in Part B was open-label.

Target population and sample size

Participants aged ≥ 18 years, with a body mass index ≥ 27 and ≤ 40 kg/m^2, a diagnosis of T2DM on metformin monotherapy, and a HbA1c of ≤ 8.0% were to be enrolled in the study. Females must not have been pregnant and lactating females were to be excluded. Females of childbearing potential should have been using appropriate contraception.

Part A was planned to randomise up to 20 participants at one centre in Sweden. In Part A the sample size of 8 completers in each cotadutide and placebo groups provided ~80% power to detect a difference of 19% reduction in the baseline glycogen concentration adjusted for liver volume (as measured by MRS at T = 4 hours post standardised liquid morning meal) after 28 days of treatment in the cotadutide versus placebo arms.

In Part B it was planned to randomise approximately 30 participants at one centre in Sweden and one in the Netherlands; there was also a centre in the UK which was originally targeted to begin recruitment in June 2020, however no participants were recruited due to COVID-19. In Part B the sample size of 10 completers in each cotadutide and placebo groups provided > 80% power to detect a 24.2% reduction in fasting glycogen concentration adjusted for liver volume (as measured by MRS at T = 24 hours post standardised liquid morning meal) after 35 days of treatment in the cotadutide versus placebo arms.

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

Cotadutide was manufactured by MedImmune and supplied as a solution for injection in a 1.0 mL prefilled syringe. Cotadutide was administered as one dose SC CCI . The introduction of a multi-dose pen device to administer the IP facilitated the introduction of CCI starting dose. The cotadutide Pen was supplied as a solution for injection in a multidose prefilled pen device containing 2.7 mL. Each pen could deliver doses of CCI , in increments of CCI intended for SC administration. Liraglutide (Victoza) was sourced from Novo Nordisk and supplied as a solution for injection in a multi-dose prefilled pen containing 3 mL intended for SC administration. The following batch numbers of cotadutide, matched placebo, and liraglutide were used:

- Cotadutide Pre-filled Syringes: CCI
- Placebo Pre-filled Syringes: 361703/00001
- Cotadutide Pen: CCI
- Placebo Pen: 25375.5; 25375.8
- Liraglutide: JS68N26

Duration of treatment

In Parts A and B participants underwent a 5-day washout period at the beginning of the study starting from Day -4 where metformin therapy was suspended. Metformin dosing resumed on Day 2. This washout was repeated at the end of the treatment period starting from Day 24 in Part A and Day 32 in Part B.

Across Part A of the study (up to 126 days in total including screening) participants had a total of 6 study visits, 6 nights of inpatient stay and underwent a total of 10 MRS scans alongside additional assessments and blood sampling. In Part B, participants participated in the study for approximately 133 days and had a total of 7 study visits (including 2 remote contacts), 6 nights of inpatient stay and underwent a total of 8 MRS scans alongside additional assessments and blood sampling. The duration of MRS scans was approximately 40 minutes with the exception of the baseline and end of treatment scans used for liver fat evaluation (Part B only) which was prolonged and up to 1 hour 45 minutes in duration.

Statistical methods

The study objectives were evaluated with analyses that included data from both Part A and Part B. Analyses were also performed separately for each study part. In general, the efficacy analyses were analysed with the ITT population and all other analyses were performed with the as-treated population.

The primary endpoint for Part A (change in hepatic glycogen concentration [measured by MRS, adjusted for liver volume] at T = 4 hours post standardised morning meal from baseline (Day -1) to the end of 28 days of treatment) was analysed using an ANCOVA model with baseline covariate and treatment group. Pairwise comparisons between cotadutide and placebo were performed within this analysis.

The primary endpoint for Part B (percentage change in fasting hepatic glycogen concentration (adjusted for liver volume) as measured by MRS at T = 24 hours post standardised morning meal from baseline [Day 1] to the end of 35 days of treatment [Day 36]), was compared between the cotadutide and placebo groups using an ANCOVA model adjusting for baseline value and treatment group.

As there was only one post-baseline measurement MRS, participants who did not have a valid baseline evaluation or a valid Day 28 (Part A) and Day 35 (Part B) MRS evaluation at 4 hours (Part A) and 24 hours (Part B) post standardised morning meal did not contribute to the analysis.

The secondary and exploratory efficacy analyses with the ITT population were performed using an ANCOVA model adjusting for baseline value and treatment group. The analyses were performed as well as analysed separately for each part.

The safety analyses were based on the as-treated population. Treatment-emergent adverse events and SAEs were summarised by type, incidence, severity and relationship to IP by SOC and PT.

For the immunogenicity analysis, all participants in the safety analysis set with reported anti-drug antibody/antibodies (ADA) results (ADA positive or ADA negative, titer, were shown in the data listing. Results of cross reactivity to GLP-1 (positive or negative), cross reactivity to glucagon (positive or negative) were not available at the time of writing the CSR.

Study population

In Part A, a total of 21 participants participated in the study from 31 May 2018 (date first participant enrolled for Part A) to 23 November 2018 (date of last participant last visit for Part A) at one site in Sweden. Two participants in the cotadutide group discontinued treatment. All participants in the placebo group completed the study. Baseline characteristics and demographics were generally well balanced across the treatment groups.

In Part B, a total of 30 participants participated in the study from 17 December 2019 (date first participant enrolled for Part B) to 14 April 2021 (date of last participant last visit for Part B) at 2 sites (one in Sweden and one in the Netherlands). All participants in the

cotadutide and placebo group completed the study. Baseline characteristics and demographics were generally well balanced across the treatment groups.

Summary of efficacy results

Part A: the primary endpoint measure, the change from baseline in mean hepatic glycogen concentration at 4 hours post standardised liquid meal was significantly different in the cotadutide group at -100.2 mmol/L (90% CI: -150.2, -50.1) in comparison to placebo at 5.5 mmol/L (90% CI: -47.2, 58.3); a difference in LS means of -105.7 mmol/L (90% CI: -178.8, -32.6; p = 0.023). This translated into a statistically significant percentage reduction in glycogen of -26.5% in the cotadutide group from baseline (90% CI: -48.4, -4.6; p = 0.050).

Part B: the primary endpoint measure of percentage change in fasting hepatic glycogen concentration at 24 hours post standardised morning meal after 35 days of cotadutide was statistically significantly lower than observed in the placebo group: -25.87% (90% CI: -40.88, -10.86; p = 0.008) in LS mean for cotadutide versus placebo. This translated into a statistically significant reduction of -75.05 mmol/L (90% CI: -114.00, -36.11; p = 0.004).

The percentage change in fasting hepatic glycogen concentration at 24 hours post standardised liquid meal after 35 days of cotadutide (secondary endpoint) was also statistically significantly lower than observed in the liraglutide group: -21.99% (90% CI: -34.55, -9.43; p = 0.008) in LS mean for cotadutide versus liraglutide. This translated into a statistically significant reduction of -63.44 mmol/L (90% CI: -102.30, -24.59; p = 0.012).

The secondary endpoint of measure of change in hepatic fat fraction at 24 hours post standardised liquid meal in the cotadutide group was statistically significantly lower than observed in both the placebo group and the liraglutide group: -4.12 (90% CI: -5.98, -2.27; p = 0.002) in LS mean for cotadutide versus placebo, and -1.75 (90% CI: -3.12, -0.38; p = 0.044) in LS mean for cotadutide versus liraglutide, respectively. The percentage change from baseline in hepatic fat fraction at 24 hours post standardised liquid meal in the cotadutide group was statistically significantly lower than observed in both the placebo group and the liraglutide group: -35.06% (90% CI: -66.54, -3.58; p = 0.070) in LS mean for cotadutide versus placebo, and -11.72% (-20.13, -3.30; p = 0.030).

Summary of immunogenicity results

Part A: The ADA incidence was 8.3% (1/12) in cotadutide-treated participants with a titer of 80 on Day 28; no placebo participants were ADA positive.

Part B: The ADA incidence was 33.3% (3/9) in cotadutide-treated participants with a median titer of 40; no placebo participants were ADA positive.

Summary of safety results

In Part A, 83.3% participants in the cotadutide arm received between 15 and 28 doses of cotadutide. All participants in the placebo arm received between 15 and 28 doses. In Part B, all participants in the cotadutide, placebo, and liraglutide arms received between 29 and 35 doses of investigational product.

For Part A and Part B there were no TEAEs of Grade ≥ 3 severity, SAEs, or TEAEs with a fatal outcome reported.

For Part A, the proportion of participants who experienced TEAEs, including TEAEs related to IP and TEAEs leading to discontinuation, was greater in the cotadutide arm than in the placebo arm. The most common TEAEs (≥ 40% of participants) reported in the cotadutide arm were nausea, dyspepsia, fatigue, headache, and vomiting; the most common TEAE in the placebo arm was headache (33.3%). Two participants (16.7%) in the cotadutide arm had TEAEs that led to permanent discontinuation of the IP (1 participant had an TEAE of abdominal pain, and the other had a TEAE of vomiting).

For Part B, the proportion of participants who experienced TEAEs was greater in the cotadutide arm than in the placebo arm, however, the proportion was similar between the cotadutide arm and the liraglutide arm. The proportion of participants who experienced TEAEs related to IP, was greater in the cotadutide arm than in the placebo arm and the liraglutide arm. The most common TEAEs (≥ 30% of participants) reported in the cotadutide arm were nausea and fatigue; no TEAEs occurred in ≥ 30% of participants in the placebo or liraglutide arms. No participants in ay treatment arm had TEAEs that led to permanent discontinuation of the IP.

For Part A: the incidence of nausea, and vomiting, was higher in the cotadutide arm than the placebo arm. During the first 7 days of treatment with cotadutide (100 µg), the number of participants that experienced nausea increased from Day 1 to Day 7; nausea was reported as a TEAE at least once on every study day from Day 1 to 7. Vomiting was reported by fewer participants and less frequently. Reports of both nausea and vomiting were highest during the first week of treatment compared with all subsequent weeks.

For Part B: the incidence of nausea was higher in the cotadutide arm than in the placebo and liraglutide arms, but the incidence of vomiting in the cotadutide arm was comparable to that observed in the liraglutide arm. During the first 7 days of treatment with cotadutide (50 µg), the number of participants that experienced nausea remained similar from Day 1 to Day 7; nausea was reported as a TEAE at least once on every study day from Day 1 to 7. Vomiting was reported by no participants in the first 7 days of treatment. Reports of both nausea and vomiting were highest from the third week of treatment. It should also be noted that overall

there was a comparable frequency of GI SOC AEs between the cotadutide and liraglutide arms.

Adverse events of injection site reactions were reported for 3 participants in the cotadutide arm in Part A and 1 participant in Part B. All events were Grade 1 and reported as recovered/resolved.

There were no clinically meaningful trends in haematology or clinical chemistry parameters observed in the study.

During the treatment period for Part A and Part B, there was a trend towards a decrease in systolic BP (but not diastolic BP) and an increased in pulse rate observed in participants treated with cotadutide (or liraglutide in Part B) versus participants treated with and placebo.

Conclusions

- The primary and secondary objectives of this study were met, demonstrating that cotadutide promotes a significantly greater reduction in fasting and post-prandial hepaticglycogen and hepatic fat fraction in comparison to placebo and the GLP-1 receptor agonist liraglutide. These results are suggestive of target engagement at the glucagon receptor and highlight differentiation of cotadutide from the GLP-1 receptor agonist class.
- Cotadutide, titrated up to a dose level of 300 μg was well tolerated. No new safetyconcerns were reported.

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