| **Clinical Study Report Synopsis** | |
|---|---|
| Drug Substance | Cotadutide (MEDI0382) |
| Study Code | D5671C00002 |
| Edition Number | 1.0 |
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| NCT Number | NCT04019561 |

# A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Pharmacodynamic Effects of MEDI0382 in Obese Subjects With Non-alcoholic Fatty Liver Disease (NAFLD)/ Non-alcoholic Steatohepatitis (NASH)

**Study dates:** First subject enrolled: 23 September 2019
Last subject last visit: 06 May 2021
The analyses presented in this report are based on a clinical data lock date of 07 June 2021

**Phase of development:** Therapeutic exploratory (II)

**Co-ordinating Investigator:** PPD

**Sponsor's Responsible Medical Officer:** PPD Gaithersburg, MD USA 20878

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

## Study Center(s)

There were 23 sites in the United States of America (USA) and Puerto Rico.

## Publications

Robertson D, Challis B, Daniels SJ, Sarv J, Sánchez, J, Schumi J et al. PROXYMO demonstrates safety and efficacy of cotadutide, a novel incretin co-agonist in biopsy-proven non-cirrhotic NASH with fibrosis. https://www.aasld.org/sites/default/files/2021-11/TLM%202021%20Late%20Breaking%20Abstracts%2011.01.21.pdf. AASLD. Published 2021. Accessed 15Nov2021.

## Objectives and Criteria for Evaluation

**Table S1 Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| Primary | |
| To assess the safety (including hepatic safety) and tolerability of cotadutide compared with placebo. | Incidences of TEAEs and TESAEs through the end of the follow-up period. |
| Secondary | |
| To assess the effect of cotadutide on relative and absolute change in hepatic fat as assessed by MRI-PDFF compared with placebo. | • Percent change from baseline in HFF at Week 19.<br>• Absolute change from baseline to Week 19 in HFF. |
| CCI [redacted] | CCI [redacted] |
| To assess the effect of cotadutide on circulating markers of hepatic inflammation compared with placebo. | Change and percent change from baseline to Week 19 in:<br>• ALT.<br>• AST.<br>• GGT. |
| To assess the effect of cotadutide on body weight and BMI compared with placebo. | Change and percent change from baseline to Week 19 in body weight and BMI. |
| To assess the dose response of cotadutide on PD parameters | HFF, body weight, safety, other imaging parameters, parameters of hepatic inflammation. |
| To evaluate the immunogenicity of cotadutide. | Development of ADA and titer (if participants were ADA positive) during treatment and follow-up. |

ADA = anti-drug antibody(ies); ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; HFF = hepatic fat fraction; GGT = gamma glutamyl transferase; MRI = magnetic resonance imaging; PD = pharmacodynamic(s); PDFF = proton density fat fraction; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

## Study Design

This was a Phase II, randomized, double-blind, placebo-controlled study to evaluate the safety (including hepatic safety), tolerability, and efficacy effects of 2 dose levels of cotadutide in obese participants with non-alcoholic fatty liver disease (NAFLD)/ non-alcoholic steatohepatitis (NASH). The participants had biopsy-confirmed, non-cirrhotic NAFLD/NASH with liver fibrosis stages F1, F2, or F3. Participants were recruited in parallel and randomized using an interactive web response system in a 2:1:2:1 ratio to cotadutide 300 µg: matched placebo for cotadutide 300 µg: cotadutide 600 µg: matched placebo for cotadutide 600 µg. Participants were in the study for approximately 27 weeks (189 days), including a screening period of up to 4 weeks, a 19-week treatment period, and a 4-week safety follow-up period.

## Target Population and Sample Size

Key inclusion criteria for the target population were, as follows:

1 Participants aged ≥ 18 years at the time of consent.
2 Body mass index ≥ 30 kg/m$^2$ at screening.
3 Hemoglobin A1c ≤ 9.5% (inclusive) at screening if type 2 diabetes mellitus present, managed by either diet and/or a stable dose of metformin, sodium-glucose co-transporter 2 inhibitors, sulfonylureas or acarbose (ie, no major dose adjustments in prior 3 months to screening).
4 Definitive NAFLD/NASH with NASH activity score ≥ 4 with ≥ 1 in each component (ie, steatosis, lobular inflammation, and ballooning), as diagnosed by liver biopsy within 6 months of screening with liver fibrosis stage F1, F2 or F3. The number of participants with F1 was capped at 25% in the study.
5 Evidence of hepatic steatosis or liver fat (≥ 10%) by magnetic resonance imaging-proton density fat fraction.

Approximately 72 participants were planned to be randomized to cotadutide 300 µg (n = 24), cotadutide 600 µg (n = 24), and placebo (n = 24). A total of 74 participants were randomized to cotadutide 300 µg (n = 25), cotadutide 600 µg (n = 25), and placebo (n = 24).

## Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

The investigational product was cotadutide (MEDI0382), manufactured by MedImmune. The doses were 300 and 600 µg administered subcutaneously (SC). The drug product batch numbers were CCI [redacted].

The matched placebo was manufactured by MedImmune, administered SC. The drug product batch number was CCI .

**Duration of Treatment**

19 weeks

**Statistical Methods**

General Considerations

Endpoints were summarized by treatment group and at each visit using descriptive statistics. Unscheduled visits were only listed. For continuous variables, descriptive statistics included the number of participants (n), mean, standard deviation, median, minimum, and maximum. Descriptive statistics were summarized for the observed values of change from baseline and the percent change from baseline. For categorical variables and unless otherwise specified, the number and percentages of participants by categories was tabulated. Percentages were calculated based on the number of participants with no missing data. Changes from baseline, in certain categorical variables, were summarized using shift tables. The number and percentage of participants within each treatment group was generated for each category post-baseline by baseline category. If not otherwise specified, all the analyses included the post investigational product-discontinuation data for those participants who discontinued from investigational product but were still followed up for their scheduled visits. Measurements with missing or partial missing dates were not assigned to any analysis visit.

ANCOVA Model and Sensitivity Analyses

An analysis of covariance (ANCOVA) model was used to fit change and percent change, at Weeks 12 and 19. Data used in the model were data from baseline and the scheduled tested visit. Treatment group was considered as a fixed effect of the model with the baseline value as a covariate. A 2-sided difference test, with alpha level at 5% was used for the comparisons and for the t-type confidence interval (CI) calculation. Unless otherwise specified, last observation carried forward (LOCF) was applied to handle missing data. For log-normally distributed variables, the variable fitted in the model was change from baseline on a logarithmical scale, defined as the log transformation of the post-baseline visit value minus the log transformation of the baseline value.

In sensitivity analysis 1, a mixed model repeated measures was fit to percent change from baseline. Fixed factors of the model were treatment, visit, and treatment × visit interaction. The baseline value was used as a covariate. A 2-sided difference test, with alpha level at 5%, was used for the comparisons and for the t-type CI calculation.

In sensitivity analysis 2, the Wilcoxon rank sum test was calculated on percent change. Unless otherwise specified, LOCF was applied to handle missing data.

In sensitivity analysis 3, the descriptive analysis and the ANCOVA model were repeated for the same population used for the main ANCOVA analysis, but only data from the treatment period were included.

In sensitivity analysis 4, the descriptive analysis and the ANCOVA model were repeated for the per-protocol population.

Analyses of Primary Endpoints

The primary safety analyses were based on the as-treated population. Adverse events (AEs) were collected from time of first dose of investigational product, throughout the treatment period and including the follow-up period. Serious adverse events (SAEs) were collected from time of signature of informed consent, throughout the treatment period and including the follow-up period. Adverse events and SAEs were coded by the most up-to-date version of the Medical Dictionary for Regulatory Activities, and the type, incidence, severity, and relationship to investigational product were summarized by System Organ Class and Preferred Term and by treatment. Specific AEs were counted once for each participant for calculating percentages. In addition, if the same AE occurred multiple times within a participant, the highest severity and level of relationship observed was reported.

The event rate for nausea and/or vomiting was calculated as the total number of events when participants were on investigational product in the selected period divided by the total person-days of exposure to investigational product for the whole relevant group in the selected period. The total person-days of exposure is the sum of all the exposures, in days, of all the participants who were ever exposed to investigational product within the specific period, in the relevant group, for the selected period.

Parameters for laboratory test results, vital signs, and electrocardiograms were summarized. Parameters for ambulatory blood pressure monitoring (ABPM) were derived as the arithmetic means of single measurements over a period of time. The ABPM rate pressure product (RPP) was calculated as heart rate × systolic blood pressure (BP).

Analyses of Secondary Endpoints

The secondary efficacy analyses were primarily based on the intent-to-treat population, except where noted otherwise. The secondary immunogenicity analyses were based on the as-treated population.

An ANCOVA model was used to fit change and percent change in hepatic fat fraction (HFF), at Weeks 12 and 19. In addition, sensitivity analyses 1, 2, 3, and 4 were conducted. An ANCOVA model was used to fit change and percent change for each imaging parameter at Weeks 12 and 19. An ANCOVA model was used to fit change and percent change for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) at Weeks 12 and 19. For ALT, sensitivity analyses 1, 2, 3, and 4 were also performed.

An ANCOVA model was used to fit change and percent change in weight, and change in body mass index (BMI), at Weeks 12 and 19. Dose response was considered already evaluated through the other primary and secondary analyses performed by treatment group. No additional analyses were included. Participants who had at least one measurable concentration time point of investigational product were included in the immunogenicity analysis.

**Study Population**

A total of 192 participants participated in the study from 23 September 2019 (date first informed consent was signed) to 06 May 2021 (date of last participant last visit) at 23 sites in the USA and Puerto Rico. A total of 74 participants were randomized. A total of 55 participants completed treatment as planned; 6 participants randomized to 300 µg cotadutide, 6 participants randomized to 600 µg cotadutide, and 7 participants randomized to placebo, did not complete treatment. A total of 63 participants completed the study. Participant demographic characteristics, medical history, diet and exercise history, alcohol use, fibrosis stage, and T2DM status were generally balanced across treatment groups.

**Summary of Safety Results**

The mean duration of exposure to investigational product was balanced across treatment groups. Over 70% of participants received investigational product for at least 120 days (17 weeks).

The percentage of participants with at least one AE and at least one AE that led to discontinuation of investigational product, was higher in the cotadutide groups compared with placebo, and numerically higher for 600 vs 300 µg cotadutide. However, the percentage of participants with at least one SAE was balanced across treatment groups and similar to placebo. There were no AEs that led to withdrawal from the study and no deaths in this study.

The most common AEs in the total cotadutide group were nausea CCI , vomiting CCI , decreased appetite CCI , and in the placebo group were nausea CCI , headache CCI , and abdominal distension CCI . Most AEs were Grade 1 or 2 (mild or moderate) in severity. Grade 3 (severe) AEs experienced by participants (one Grade 3 event per participant) were appendicitis in the 300 µg cotadutide group, diverticulitis in the 600 µg cotadutide group, and syncope in the placebo group. The most common AEs considered related to investigational product ( > 10% of participants) in the total cotadutide group were nausea, vomiting, decreased appetite, and diarrhoea. There were no AEs considered related to investigational product experienced by > 10% of participants in the placebo group.

At least one AE of nausea or vomiting was reported by a higher percentage of participants in the total cotadutide group CCI compared with placebo CCI , and for a higher percentage of participants in the 600 vs the 300 µg cotadutide group. One participant discontinued 600 µg cotadutide due to AEs of nausea and

vomiting during up-titration on Day 26, and one participant discontinued 600 µg cotadutide due to an AE of nausea during up-titration on Day 46.

A total of 8 participants in the total cotadutide group experienced injection site reactions; 4 (15.4%) in the 300 µg cotadutide group and 4 (16.7%) on in the 600 µg cotadutide group, compared with 2 participants (8.3%) in the placebo group. Two participants with injection site reactions discontinued cotadutide treatment during the study.

Two participants (7.7%) in the 300 µg cotadutide group with T2DM each experienced 2 AEs of hypoglycaemia. No participants in the cotadutide group experienced hyperglycaemia and one participant (4.2%) in the placebo group with T2DM experienced hyperglycaemia. None of the AEs of hypoglycaemia or hyperglycaemia led to discontinuation of investigational product.

There were no AEs of pancreatitis, pancreatic carcinoma, or thyroid carcinoma reported in this study.

No AEs with fatal outcome were reported in this study. Three participants experienced one SAE each of appendicitis (300 µg cotadutide group), diverticulitis (600 µg cotadutide group), and syncope (placebo group). None of the SAEs were considered related to investigational product by the investigator. Only the SAE of diverticulitis led to discontinuation of investigational product. Two participants (7.7%) in the 300 µg cotadutide group, 4 participants (16.7%) in the 600 µg group, and one participant (4.2%) in the placebo group experienced AEs that led to discontinuation of investigational product. None of the AEs that led to discontinuation of investigational product were serious except for the one event of diverticulitis in the 600 µg cotadutide group. Except for one event of asthma in the 300 µg cotadutide group and one event of diverticulitis in the 600 µg cotadutide group, AEs that led to discontinuation of investigational product were also considered related to investigational product by the investigator.

There were no cases of potential Hy’s Law or Hy's Law in this study.

There were no changes in heart rate and ABPM heart rate from baseline to Week 19 in the 600 µg cotadutide group compared with placebo. There were reductions in systolic BP, diastolic BP, and RPP from baseline to Week 19 in the 600 µg cotadutide group compared with placebo. A trend of small reductions in ABPM systolic BP, diastolic BP, and RPP from baseline to Week 19 in the 600 µg cotadutide group compared with placebo was also observed.

**Summary of Efficacy Results**

Statistically significant and clinically relevant least square (LS) mean reductions in absolute (ie, change from baseline) and relative (ie, percent change from baseline) HFF from baseline

to Week 19 were observed for the 600 µg cotadutide group, and also compared with placebo CCI

Nominal LS mean reductions in absolute and relative HFF from baseline to Week 19 were observed for the 300 µg cotadutide group, and also compared with placebo CCI .

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Statistically significant and clinically relevant LS mean reductions, and nominal and clinically relevant LS mean percent reductions, in ALT from baseline to Week 19 were observed for the 600 µg cotadutide group compared with placebo (LS mean difference vs placebo for change from baseline CCI . Nominal and clinically relevant LS mean reductions and percent reductions in ALT from baseline to Week 19 were observed for the 300 µg cotadutide group compared with placebo (LS mean difference vs placebo for change from baseline CCI .

Statistically significant and clinically relevant LS mean reductions, and nominal and clinically relevant LS mean percent reductions, in AST from baseline to Week 19 were observed for the 600 µg cotadutide group compared with placebo (LS mean difference vs placebo for change from baseline CCI . Nominal and clinically relevant LS mean reductions and percent reductions in AST from baseline to Week 19 were observed for the 300 µg cotadutide group compared with placebo (LS mean difference vs placebo for change from baseline CCI .

Changes and percent changes in LS mean GGT from baseline to Week 19 were not observed for the 300 and 600 µg cotadutide groups compared with placebo.

Nominal LS mean reductions and percent reductions in body weight from baseline to Week 19 were observed for the 300 and 600 µg cotadutide groups compared with placebo, with greater body weight loss for participants treated with 600 vs 300 µg cotadutide CCI [redacted]

Nominal LS mean reductions in BMI and mean percent reductions in BMI from baseline to Week 19 were observed for the 600 µg cotadutide group compared with placebo CCI [redacted]. Changes in LS mean BMI and percent changes in mean BMI from baseline to Week 19 were not observed for the 300 µg cotadutide group compared with placebo.

**Conclusion(s)**

- The safety profile of 300 and 600 µg cotadutide in obese participants with biopsy-confirmed, non-cirrhotic NAFLD/NASH was generally similar to that observed with glucagon-like peptide-1 receptor agonists, and consistent with observations in previous Phase I and II clinical studies. No new safety findings associated with cotadutide were observed. The safety data support further clinical development in NASH with fibrosis.
- Key secondary efficacy endpoints were met for 600 µg cotadutide vs placebo, with statistically significant reductions in absolute and relative HFF, CCI [redacted], ALT, and AST observed at Week 19. No secondary endpoints were met for 300 µg cotadutide vs placebo, though nominal reductions were generally observed. In general, a dose-response relationship for participants treated with 300 and 600 µg cotadutide was observed for the key secondary endpoints.