Clinical Study Report

1 TITLE PAGE

A Thorough QTc Evaluation of the Effect of Cotadutide on Cardiac Repolarization in Healthy Participants: A Randomized, Double-blind, Placebo-controlled, 3-arm Parallel Study with a Nested Crossover Design for Positive Control with Moxifloxacin Administration

Investigational Medicinal Products:	Test Product:	Cotadutide (MEDI0382)
	Reference Product:	Placebo
	Positive Control:	Moxifloxacin
Indication Studied:	Non-alcoholic steatohepatitis	
Parexel Study Number:	PXL273814	
Sponsor Study Number:	D5671C00010	
EudraCT Number:	2022-002479-12	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Investigator Name and Address:	PPD	
Study Duration:	03 Jan 2023 (first participant first visit) to 10 Mar 2023 (last participant last visit)	
Version and Date of Report:	Version 1.0, dated 03 Nov 2023	

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines. The essential documentation related to this study has been retained by relevant parties.

Confidentiality Statement

2 SYNOPSIS

Title of Study:	A Thorough QTc Evaluation of the Effect of Cotadutide on Cardiac Repolarization in Healthy Participants: A Randomized, Double-blind, Placebo-controlled, 3-arm Parallel Study with a Nested Crossover Design for Positive Control with Moxifloxacin Administration.	
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Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Center:	Parexel Early Phase Clinical Unit - Berlin	
Publication:	Not applicable	
Study Duration:	First participant first visit: 03 Jan 2023	Last participant last visit: 10 Mar 2023

Introduction:

This was a randomized, double-blind, placebo-controlled study that assessed the potential of cotadutide to affect the QTc interval. Cotadutide (MEDI0382) is a synthetic analog of the human hormone glucagon that has been modified, using only natural amino acids, to have a balanced activity at both Glucagon-like peptide-1 (GLP-1) and glucagon receptors. The combination of GLP-1 and glucagon receptor agonist activity was expected to delay disease progression and potentially reverse disease in non-alcoholic steatohepatitis (NASH), and type 2 diabetes mellitus with chronic kidney disease, through direct disease-modifying effects alongside improved lipid homeostasis, enhanced glycemic control, and body weight loss.

A synoptic clinical study report (CSR) instead of a full CSR is used in Study D5671C00010. The study was discontinued prematurely due to a strategic decision to stop the cotadutide development program in NASH. The collected data in the synoptic report will not contribute to the evaluation of cotadutide product effectiveness or provide definitive information on the potential to affect the QTc interval or clinical pharmacology. The premature closure was not due to any new safety findings or any change in the known risk-benefit profile.

At the time when the study was terminated, participants who were ongoing in treatment included 16 participants in Arm 1, 8 participants in Arm 2A, and 6 participants in Arm 2B. One participant from Arm 2B had discontinued the study due to an adverse event of ventricular tachycardia. Planned cotadutide dosing escalation was not completed due to early study termination. The maximum dose of cotadutide administered was CCI µg, while the planned doses of CCI µg, CCI µg, CCI µg, and CCI µg cotadutide were not administered (these doses were required for the primary and secondary study objectives) due to early study termination.

Study Objective(s):

The study objectives that were planned for this study are stated below, however most of the objectives were not assessed as the CCI and CCI µg dosing was not completed due to early termination of the study.

Primary objective(s):

- To assess the effect of cotadutide CCI and CCI µg (therapeutic dose) on the QTc interval at steady state compared to placebo using a Concentration-QTc (C-QTc) interval analysis (Not assessed).

Secondary objective(s):

- To assess assay sensitivity as the effect of moxifloxacin CCI mg on the QTc interval compared to placebo.
- To investigate the effect of cotadutide CCI and CCI µg on QTc, heart rate (HR), electrocardiogram interval measured from the onset of the P-wave to the onset of the QRS Complex (PR), and ECG interval measured from the onset of the QRS complex to the J point (QRS) interval at protocol-defined time points (Not assessed).
- To assess the presence of categorical outliers for QTc, HR, PR, and QRS after cotadutide CCI and CCI µg (Not assessed).
- To investigate morphological changes in the T-U complex after cotadutide CCI and CCI µg (Not assessed).
- To assess the pharmacokinetic of cotadutide in the study participants.
- To investigate the effect of cotadutide CCI µg on blood pressure (BP) and HR by ambulatory blood pressure monitoring (ABPM) (Not assessed).
- To examine the safety and tolerability of cotadutide by adverse events (AEs), laboratory variables, 12-lead safety electrocardiograms (ECGs), telemetry, and vital signs.
- To evaluate the immunogenicity of cotadutide.

Exploratory objective(s):

- CCI [redacted]

Study Design:

This was a randomized, double-blind, placebo-controlled, 3-arm parallel study, with a nested crossover design for positive control with moxifloxacin administration, in healthy male and female adult participants.

Participants were randomized in a 2:1:1 ratio to receive treatment with either cotadutide (Arm 1) or cotadutide-placebo (Arm 2). The cotadutide-placebo treatment arm (Arm 2) further included 2 subgroups (Arms 2A and 2B).

Participants in Arm 1 received a single dose of moxifloxacin-placebo prior to and after their treatment with cotadutide. Dosing commenced at CCI µg cotadutide and was up-titrated every 2 weeks. Participants in Arm 2A received a single dose of moxifloxacin CCI mg prior to treatment with cotadutide-placebo planned for up to 13 weeks, followed by a single dose of moxifloxacin-placebo. Participants in Arm 2B received a single dose of moxifloxacin-placebo prior to treatment with cotadutide-placebo planned for up to 13 weeks, followed by a single dose of moxifloxacin CCI mg.

The study comprised of:

- Screening period of up to 28 days.
- In-patient visit (4-night stay): Participants received a single dose of cotadutide-placebo and had a 25-hour period of ECG/QT evaluation to allow extraction of 12-lead ECGs pre-dose and at 9 prespecified time points (Day -2). An ABPM device was fitted and worn overnight (Day -1 to Day 1). A second 25-hour period of ECG evaluation was conducted (Day 1).

Pre-dose assessments were conducted, and participants received a single dose of moxifloxacin CCI mg or moxifloxacin-placebo (Day 1). The next day, participants received treatment with cotadutide or cotadutide-placebo and remained in the unit until approximately 4 hours after dosing (Day 2).

- 13 weeks treatment (planned): Cotadutide and cotadutide-placebo was self-administered subcutaneously via injection pen devices, once daily in the morning at approximately the same time every day, planned for 13 weeks. Dosing commenced at CCI µg and was up-titrated every 2 weeks.

  Participants returned every 2 weeks to re-supply with investigational medicinal product (IMP) and take their first dose at a new dose level in the clinic.
- A final follow-up visit was planned approximately 28 days after the last dose.
- Early Discontinuation Visit: Was performed at study termination.

Study Participants:

Planned for Inclusion:	Randomized:	Completed Study:
80 participants	31 participants	0 participants

Main Inclusion Criteria:

Healthy male and/or female participants, aged 18 to 55 years (inclusive), having suitable veins for cannulation or repeated venipuncture and a body mass index between CCI and CCI kg/m^2 (inclusive) at Screening Visit and baseline. Female participants of childbearing potential had a negative pregnancy test at the Screening Visit and on Day -3 and were willing to use a highly effective method of contraception to avoid pregnancy for the entire study period. They also refrained from egg cell donation and breastfeeding while on study and for 4 weeks after the final Follow-up Visit.

Investigational Medicinal Product(s):

Arm Name	Cotadutide	Cotadutide-placebo	Moxifloxacin	Moxifloxacin-placebo
Intervention name	Cotadutide/MEDI0382	Cotadutide-placebo	Moxifloxacin	Moxifloxacin-placebo
Type	Drug and Device Combination	Placebo and Device Combination	Drug	Placebo
Dose Formulation	Solution for injection in pre-filled pen injector [a]	Solution for injection in pre-filled pen injector [a]	Film-coated tablet	Film-coated tablet
Dosage Level	CCI to CCI µg	Placebo to match	CCI mg	Placebo
Unit dose strength(s)	CCI mg/mL (CCI to CCI µg) CCI mg/mL (CCI to CCI µg)	Placebo to match CCI to CCI µg dose, and Placebo to match CCI to CCI µg dose	CCI mg/tablet	Placebo
Route of administration	Subcutaneous injection (abdomen or thigh)	Subcutaneous injection (abdomen or thigh)	Oral	Oral

Regimen	Once daily dosing of cotadutide. Dose escalation from CCI to CCI µg, with up-titration every 2 weeks. [b]	Once at baseline (CCI µg), then once daily dosing of cotadutide-placebo (regimen to match cotadutide regimen)	CCI mg tablet	1× placebo tablet
IMP and NIMP	IMP	IMP	IMP	IMP
Availability of IMP	Centrally packaged and sourced by AstraZeneca. Was shipped to Hubertus Pharmacy when Regulatory Authority (BfArM) approval was in place and shipped to site by Hubertus Pharmacy when Regulatory Authority (BfArM) and EC approvals were in place.	Centrally packaged and sourced by AstraZeneca. Was shipped to Hubertus Pharmacy when Regulatory Authority (BfArM) approval was in place and shipped to site by Hubertus Pharmacy when Regulatory Authority (BfArM) and EC approvals were in place.	Sourced from the German market and shipped to site when Regulatory Authority (BfArM) and EC approvals were in place.	Placebo to moxifloxacin was packaged and labeled by AstraZeneca. Was shipped to Hubertus Pharmacy when Regulatory Authority (BfArM) approval was in place and shipped to site by Hubertus Pharmacy when Regulatory Authority (BfArM) and EC approvals were in place.
Batch/Manufacturing Lot Number(s):	**Product:** Device CCI mg/mL MEDI0382 in CCI mL cartridge, Combi-seal **Lot Number:** CCI **Expiry:** CCI 3	**Product:** Device: Placebo MEDI0382 in CCI mL cartridge, Combi-seal **Lot Number:** CCI **Expiry:** CCI		**Product:** Placebo to Match AZD9291 (Moxifloxacin) tablets **Batch/Lot:** CCI Expiry: CCI
	Product: Cotadutide CCI mg/mL solution for injection in CCI µL multidose pen **Lot Number**: CCI **Expiry**: CCI	**Product**: Cotadutide-Placebo to Match in CCI µL (CCI) Multidose Pen **Lot Number**: CCI **Expiry**: CCI		**Product**: Tablets Placebo for Moxifloxacin **Manufacturing Lot/Batch No**: CCI **Expiry**: CCI
	Product: Cotadutide (MEDI0382) solution for injection CCI mg/mL, CCI U/CCI µL, Pre-filled multidose pen **Manufacturing**			

	Lot/Batch No: CCI [redacted] **Expiry**: CCI [redacted]			
	Product: PTM Cotadutide (MEDI0382) solution for injection, Pre-filled multidose pen **Manufacturing Lot/Batch No**: CCI [redacted] **Expiry**: CCI [redacted]			
	Product: Cotadutide (MEDI0382) solution for injection CCI [redacted] mg/mL, Pre-filled multidose pen **Manufacturing Lot/Batch No**: CCI [redacted] **Expiry**: CCI [redacted]			
	Product: PTM Cotadutide (MEDI0382) solution for injection, Pre-filled multidose pen **Manufacturing Lot/Batch No**: CCI [redacted] **Expiry**: CCI [redacted]			

BfArM = Bundesinstitut für Arzneimittel und Medizinprodukte; IMP = Investigational medicinal product; NIMP= Non-investigational medicinal product.

[a] Pre-filled pen injector. Instruction for Use was handed out to participants.

[b] The dose up-titration schedule could be modified due to tolerability-related data.

Duration of Treatment:

The participants were to receive cotadutide and cotadutide-placebo, once daily in the morning at approximately the same time every day, planned for approximately 13 weeks.

Participants randomized to receive cotadutide received a single oral dose of moxifloxacin-placebo tablet on Day 1 prior to their treatment with cotadutide on Day 2. Participants randomized to receive cotadutide-placebo received a single oral dose of moxifloxacin CCI [redacted] mg or moxifloxacin-placebo tablet on Day 1 prior to their treatment with cotadutide-placebo on Day 2.

Treatment Compliance:

Dosing took place at the Clinical Unit on visit days via self-administered dose with medical supervision and self-administered at home on all days without in-clinic administration for cotadutide and cotadutide-placebo. The moxifloxacin and moxifloxacin-placebo administration were overseen by unblinded study site personnel to maintain the double-blind.

The administration of all study intervention at the study center was recorded in ClinBase™.

While at the Clinical Unit, compliance was assured by direct supervision and witnessing of study intervention administration.

For cotadutide and cotadutide-placebo it was not recommended to inspect by opening used/returned pens, so it was particularly important to discuss with the participant at each visit whether he/she had used the medicine on a daily basis, in the prescribed dose, and whether the medicine had been stored under appropriate conditions.

If there was a suspicion that a participant was not using the correct dose or was not administering the drug regularly, retraining and discussion with the participant took place. If, despite additional training, the participant still did not comply with the investigator's instructions, discontinuation of study intervention was to be considered.

If a participant forgot to inject a study intervention dose, the dose could be administered as soon as the participant remembered. However, if it was more than 12 hours since the participant had to administer the dose, the participant skipped the missed dose and took the next dose as usual on the following day. The participant was not to take a double dose to make up for the missed dose.

If a participant missed several consecutive doses of study intervention, there was a potential risk for increased nausea when the participant resumed treatment. Therefore, the investigator was to consult with the sponsor for guidance on restarting treatment.

Criteria for Evaluation:

Safety Variables:

- Adverse events including injection site reactions (ISRs).
- Laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, pregnancy, viral serology, COVID-19 testing, drugs of abuse, alcohol and cotinine testing, and glomerular filtration rate).
- Physical examination.
- Analysis of ABPM parameters (systolic blood pressure, diastolic blood pressure, and heart rate).
- Electrocardiogram (ECG) and Cardiac Telemetry.
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse, and tympanic temperature).

Pharmacokinetic Parameters:

Cmax, AUCtau, AUClast, tmax, and tlast

Immunogenicity Parameters:

- Anti-drug antibodies to cotadutide in serum

Statistical Methods:

Determination of Sample Size:

CCI [redacted]

Presentation and Analysis of Pharmacokinetic Data:

A listing of pharmacokinetic (PK) blood sample collection times, as well as derived sampling time deviations

was provided. Plasma concentrations were summarized for the PK Analysis Set for each time point by analyte and treatment. No PK analysis was carried out due to early study termination and lack of data to calculate PK parameters. No reportable plasma PK parameters were listed for each participant, analyte, and treatment. No separate listing was provided for the diagnostic PK parameters. All eligible PK data were presented for the PK Analysis Set using descriptive statistics. No inferential statistical analysis of PK parameters was conducted.

Presentation and Analysis of Immunogenicity Data:

The presence or absence of anti-drug antibodies (ADA) to the study drug collected, including the titer for samples confirmed positive for ADA for each treatment arm was listed by participant and time point. Tabulations were provided for each treatment arm. The results were presented based on the Safety Analysis Set. The results of the ADA assessments were listed for each participant and time point. This included the classification of the response (positive/negative) and the measured titers where appropriate. Summary tables were presented, by treatment arm, for the number and percentage of participants with positive/negative results at each time point, based on the Safety Analysis Set.

Presentation and Analysis of ABPM Data:

Graphical displays and descriptive statistics for systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR collected over 22 hours during Day –1 by treatment and visit. Mean ABPM during the 22-hour period, daytime and night-time, hourly, and over the first 4 and 8 hours was evaluated. Categorical analysis (eg, outliers) was also be performed.

Presentation and Analysis of Cardiodynamic ECG Data (Including the Exploratory Objective):

CCI [redacted]

CCI [redacted]

Presentation and Analysis of Safety Data:

All safety data (scheduled and unscheduled) were presented in the data listings and analyzed using the Safety Analysis Set. All safety data is presented by treatment received during study period ie, cotadutide, cotadutide-placebo, moxifloxacin, and moxifloxacin-placebo, as opposed to by study treatment groups. Continuous variables were summarized using descriptive statistics by treatment. Categorical variables were summarized in frequency tables by treatment. Adverse events were summarized by system organ class (SOC) and Preferred Term using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. The number of participants who had any AEs, serious adverse event (SAEs), adverse event leading to the discontinuation of IMP (DAEs), and AEs with severe intensity were summarized, and a tabulation by causality (AEs considered related by the investigator) was presented. Furthermore, separate listings of SAEs, DAEs, and AEs that led to death were presented. Adverse events that occurred before dosing were reported separately. Additional analyses were provided for AEs of nausea and vomiting by 7-day periods and computed for each 7-day period during dosing. Tabulations and listings of data for AEs, vital signs, clinical laboratory tests including estimated glomerular filtration rate (eGFR), ECG monitoring (resting 12-lead [listing only] and digital electrocardiogram [dECG]), cardiac telemetry, and physical examinations, were presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment was reported as an AE.

Data were summarized for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from baseline when baseline was defined.

Protocol Deviations:

There were no important protocol deviations in the study (Table 14.1.2 and Appendix 16.2.21).

Prior and Concomitant medications:

None of the reported medical histories were considered likely to affect the outcome of the study (Table 14.1.6, Appendix 16.2.4.2).

Three (9.7%) participants reported the use of prior medication for hormonal contraceptives for systemic use, other analgesics and antipyretics, and viral vaccine (Table 14.1.7, Appendix 16.2.4.3). None of these were considered likely to affect the outcome of the study.

One participant received dolormin (naproxen; class: anti-inflammatory and antirheumatic products, non-steroids) and one participant received paracetamol (class: antipyretics) during the study as concomitant medication (Table 14.1.8, Appendix 16.2.4.3). The use of paracetamol was allowed during the study, while the use of dolormin was reported as a non-important protocol deviation.

Pharmacokinetic Results:

No non-compartmental analysis was carried out due to no intensely sampled PK data being obtained prior to study termination. Samples for cotadutide were obtained for Days 2, 16 and 30 prior to study termination. Day 2 samples were non-quantifiable.

Immunogenicity Results:

None of the participants had a positive confirmatory ADA assay result on Day 2, Day 30 or at the early termination visit (Table 14.2.2.2).

ECG Results:

While participants received cotadutide dosing as per schedule, there were no planned additional 25 hr ECG readings after cotadutide dosing until later in the study at Day 57, Day 91, and Day 93, at which point study had been terminated. Therefore, the full ECG report does not include information on participants who were dosed with cotadutide or cotadutide-placebo.

Mean ECG parameters on Day -2 were within normal ranges as expected in a healthy population.

Compared to Day 1, pre-dose, HR within the first 4 hours post-dose stayed reasonably stable across the treatment groups. At later time points HR increased which is a pattern often seen and thought to be due to food intake and less restrictions in terms of activity in-between time points beyond 4 hours. The pattern of mean HR was similar across study treatments.

Compared to Day 1, pre-dose, QTcF within the first 4 hours post-dose stayed reasonably stable in the placebo arms (Arm 1 and 2B), whereas a 14-15 ms increase was seen in Arm 2A between 2 and 4 hours post-dose. At later time points a similar pattern was seen across treatment arms.

Compared to Day 1, pre-dose, PR and QRS showed similar trends across time points and treatment arms.

Full ECG report is presented in appendix 16.1.13.

Safety Results:

All safety data is presented by treatment received during study period ie, cotadutide, cotadutide-placebo, moxifloxacin, and moxifloxacin-placebo.

No SAEs or AEs with an outcome of death were reported (Table 14.3.2.1).

One AE of ventricular tachycardia led to discontinuation of IMP. This AE was reported in a participant from the Moxifloxacin-placebo group. The participant had no relevant medical history and displayed normal ECG parameters at screening and on Day -3 (appendix 16.2.10.1). However, abnormal cardiac telemetry was observed approximately 1.75 hours post-dose on Day 1 (appendix 16.2.11.2). This AE was mild, non-serious, and possibly related to the IMP as assessed by the Investigator. The AE resolved within a few seconds.

AEs were reported in a total of 14 participants. In the cotadutide treatment arm, the majority of reported AEs

(31.3%) were in the system organ class of gastrointestinal disorders. A total of 10 participants had AE's that were assessed to be related to IMP treatment as assessed by the Investigator, 5 (31.3%) on cotadutide, none on cotadutide-placebo, 1 (12.5%) on moxifloxacin, and 4 (17.4%) on moxifloxacin-placebo.

A slightly higher proportion of participants with AEs were observed in the cotadutide group (6 [37.5%]) compared to other groups (moxifloxacin 1 [12.5%], moxifloxacin-placebo 4 [17.4%], cotadutide-placebo 3 [21.4]) (Table 14.3.2.1).

In the cotadutide group, AEs were reported in 6 (37.5%) participants. Of these, 5 (31.3%) participants had AEs that were possibly related to the IMP as assessed by the Investigator (dizziness, abdominal distension, nausea, and vomiting) (Table 14.3.2.3). The most frequently reported AEs by preferred term were nausea in 4 (25.0%) participants, abdominal distension in 3 (18.8%) participants, and vomiting in 2 (12.5%) participants. All other AEs were reported by one participant each.

In the cotadutide-placebo group, AEs were reported in 3 (21.4%) participants. None of these AEs (COVID-19, nasopharyngitis, nausea, dysmenorrhea, and medical device site reaction) were related to the IMP as assessed by the Investigator.

In the moxifloxacin group, 1 (12.5%) AE of nausea was reported in a participant that was possibly related to the IMP as assessed by the Investigator (Table 14.3.2.3).

In the moxifloxacin-placebo group, AEs were reported in 4 (17.4%) participants, all of which were possibly related to the IMP as assessed by the Investigator. These AEs included headache (2 participants), ventricular tachycardia (1 participant), and injection site erythema (1 participant) (Table 14.3.2.3). Among these AEs one AE of ventricular tachycardia led to discontinuation of IMP (Appendix 16.2.7.3). The AE of injection site erythema was possibly due to the cotadutide-placebo injection that all participants received on Day -2.

All of the reported AEs were mild in intensity and had recovered/resolved at the time of clinical data lock (appendix 16.2.7.1).

No clinically relevant trends were observed for the hematology, clinical chemistry parameters or coagulation results over time nor for the change from baseline (Table 14.3.4.1, Table 14.3.4.2, and Table 14.3.4.3 respectively).

No clinically relevant trends were observed for glomerular filtration rate results over time (Table 14.3.4.4).

A number of participants had laboratory values that were higher or lower than the predefined normal ranges (appendix 16.2.8.1); however, none of them were considered clinically significant by the Investigator.

None of the abnormal laboratory values were reported as AEs.

No clinically relevant trends were observed for vital signs during the study (Table 14.3.5.1).

No vital signs-related AEs were reported (Table 14.3.2.2 and appendix 16.2.7.1).

No clinically relevant trends were observed for any ECG parameter (ECG mean heart rate, PR interval aggregate, QRS duration aggregate, QT interval aggregate, QTcF interval aggregate, and RR interval aggregate) over time nor for the change from baseline (Table 14.3.6.1).

Physical assessment on Day 16 revealed an injection site haematoma that was reported as an AE in one participant (appendix 16.2.11.2 and appendix 16.2.7.1). However, this was not considered to be clinically relevant.

Discussion and Conclusion:

This CSR is presented in a synoptic format as the study was prematurely terminated.

PK parameters for cotadutide were not calculated due to early study termination which meant no intense PK sampling occurred. Sparse sampling that did occur prior to termination was insufficient for parameter calculation.

Change from baseline ECG results were in line with what is typically seen in the placebo and moxifloxacin arms in a thorough QT study. Due to the early closure of the study, no conclusions could be drawn with regards to the study objectives.

No safety concerns were raised, and no clinically relevant trends were observed for laboratory results (including glomerular filtration rate), vital signs, and ECG findings at the administered doses of the IMP. No proper conclusion can be drawn on the overall safety of the IMP given the incomplete dosing due to early study termination.

Version and Date of Report: Version 1.0, dated 03 Nov 2023

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.