Clinical Study Report Synopsis	
Drug Substance	Cotadutide
Study Code	D5671C00006
Edition Number	1
Date	17 October 2024
EudraCT/EU CT Number	2021-005484-53
NCT Number	NCT05364931

A Phase II Randomized, Double-blind, Placebo-controlled, Proof-of-Concept Study to Evaluate the Safety and Efficacy of Cotadutide in Participants with Non-cirrhotic Non-alcoholic Steatohepatitis with Fibrosis

Study dates:
First participant enrolled: 14 July 2022
Last participant last visit: 19 April 2024
The analyses presented in this report are based on a clinical data lock date of 12 July 2024

Phase of development:
Therapeutic exploratory (II)

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

1 SYNOPSIS

Study Centers

This study enrolled participants at 116 sites across 20 countries.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Objectives	Endpoints
Primary/Safety	
To evaluate the safety and tolerability of cotadutide as compared with placebo in participants with non-cirrhotic NASH with fibrosis	Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical and laboratory assessments, and ECG. Assessments related to AEs cover: • Occurrence/Frequency • Relationship to IP as assessed by the investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • AEs leading to dose reduction of IP • AEs of special interest • Adjudicated CV events including MACE, selected liver events, diabetic ketoacidosis, pancreatitis, pancreatic carcinoma, and thyroid carcinoma Vital signs parameters include SBP, DBP, and pulse. Assessments cover: • Observed value • Absolute change from baseline values over time • Abnormality at least once on treatment Laboratory parameters include Clinical Chemistry (including MELD score) and Hematology parameters as well as urinalysis. A complete list of parameters is presented in Section 8.2.5 of the CSP in Appendix 16.1.1. Assessments cover: • Observed value • Absolute change from baseline values over time • Abnormality/Clinically significant abnormality in laboratory parameters at least once on treatment • Treatment-emergent increase in hematuria, proteinuria, and glucose in urinalysis defined as change from negative/trace at baseline to + + , + + + , or + + + + at any visit after baseline or an increase of at least + +

	ECG measurements include heart rate, RR, PR, QRS, and QT intervals. Derived variables cover QTcF. Assessments cover: • Observed value • Absolute change from baseline values over time • ECG parameters fulfilling potentially clinically significant criteria (PCS) at any time during treatment, including QRS duration > 118 ms, PR interval > 210 ms, RR < 600 ms (resting heart rate > 100 bpm), and RR > 1330 ms (resting heart rate < 45 bpm) • QTcF exceeding 450, 480, and 500 ms at any time during treatment • Change in QTcF at any time during treatment as compared to baseline exceeding 30 ms and 60 ms
To assess the immunogenicity of cotadutide	• Incidence of ADAs to cotadutide and titer during treatment and follow-up
Exploratory	
To determine whether cotadutide is superior to placebo on resolution of NASH without worsening of liver fibrosis in participants with non-cirrhotic NASH with fibrosis	• Proportion of participants with resolution of NASH without worsening of liver fibrosis based on biopsy at Week 48
To assess the effect of cotadutide versus placebo on improvement in fibrosis by at least one stage without worsening of NASH	• Proportion of participants with improvement of liver fibrosis by at least one stage without worsening of NASH based on biopsy at Week 48

Resolution of NASH is defined as the absence of fatty liver disease or isolated simple steatosis without steatohepatitis and a NAS ballooning score of 0, inflammation score of 0 to 1, and steatosis score of any degree (from 0 to 3), as assessed by NASH Clinical Research Network/NAS score.

Improvement in fibrosis is defined as a one or more category improvement in the fibrosis category (NASH Clinical Research Network fibrosis stage) without worsening of NASH.

Worsening of NASH is defined as any increase in the ballooning, inflammation, or steatosis scores even if total NAS does not increase.

ADA, anti-drug antibody; AE, adverse event; CV, cardiovascular; DBP, diastolic blood pressure; ECG, electrocardiogram; IP, investigational product; MACE, major adverse cardiovascular event(s); MELD, model for end-stage liver disease; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; PCS, potentially clinically significant criteria; QRS, combination of the Q wave, R wave, and S wave on an electrocardiogram; QT, electrocardiogram interval measured from the onset of the QRS complex to the offset of the T wave; QTcF, Fridericia-corrected QT interval; SBP, systolic blood pressure

Study Design

This study was originally designed as a 2-part (Phase IIb [Part A]/III [Part B]) study. However, given the decision to terminate recruitment, only a portion of Part A was conducted.

This was a Phase II, global, randomized, parallel-group, double-blind, placebo-controlled, multicenter, proof-of-concept study. The study assessed safety of 300 µg and 600 µg

cotadutide compared with placebo, given once daily (qd) as a subcutaneous (SC) injection administered via a multidose pen, in adults with non-cirrhotic non-alcoholic steatohepatitis (NASH) with fibrosis stage F2 or F3. All efficacy endpoints were exploratory and included whether treatment with cotadutide resulted in a significant improvement compared to placebo in the proportion of participants with resolution of NASH without worsening of liver fibrosis at Week 48.

Participants who were eligible according to the inclusion/exclusion criteria were randomized in a 2:1:2:1 ratio to receive cotadutide 300 µg, placebo matching cotadutide 300 µg, cotadutide 600 µg, or placebo matching cotadutide 600 µg. Participants underwent dose titration steps every 4 weeks to reach the target dose of 300 µg or 600 µg qd.

An independent Data Monitoring Committee was established to monitor data on an ongoing basis to ensure safety of participants enrolled in this study and to ensure the integrity of the study.

Target Population and Sample Size

Eligible participants were ≥ 18 to ≤ 75 years of age (inclusive) with biopsy-proven NASH (historical biopsy performed ≤ 180 days from randomization or on-study biopsy) demonstrating a non-alcoholic fatty liver disease activity score (NAS) ≥ 4 (with a score of at least 1 for each component: steatosis, lobular inflammation, and ballooning) and liver fibrosis stage F2 or F3. At randomization, participants were stratified by the presence/absence of type 2 diabetes mellitus (T2DM) and by fibrosis stage. All liver biopsies were read by a central pathology review committee.

Approximately 7440 participants were originally planned to be screened/enrolled to achieve 1860 randomly assigned to study intervention, including 300 in Part A and 1560 in Part B. However, this study has prematurely stopped randomization as the cotadutide program was discontinued.

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

Participants received cotadutide 300 µg, placebo matching cotadutide 300 µg, cotadutide 600 µg, or placebo matching cotadutide 600 µg, delivered subcutaneously via a multidose prefilled pen device. The batch numbers were 30324.10/1 / L019485, 30324.11/1 / L020118, 30324.12/1 / L020141, 30324.19/1 / L021263, 30324.20/1 / L021446, 30324.3/1 / L019009, 30324.4/1 / L019008, 30324.5/1 / L019173, 30324.6/1 / L019172, 30324.7/1 / L019300, 30324.8/1 / L019301, and 30324.9/1 / L019484.

Duration of Treatment

The treatment period was 48 weeks.

Statistical Methods

The primary analysis was of safety. No formal hypothesis testing was performed. Treatments were compared in tables using descriptive statistics.

Exploratory efficacy analyses used nominal 2-sided 5% significance levels (equivalent to nominal 1-sided 2.5% significance levels) unless otherwise stated. The binary endpoints were analyzed using a Cochran-Mantel-Haenszel test with stratification by T2DM presence and F2/F3 fibrosis stages. For the exploratory analysis of binary histological endpoints using the full analysis set (FAS), participants missing histology data due to any reason were imputed as non-responders.

The primary estimand of interest for the histological endpoints used the treatment policy strategy. The treatment policy approach applies to intercurrent events of treatment discontinuation, deviations from the protocol titration schedule, changes in background medication, liver events, or use of prohibited medication or other protocol deviations. The treatment policy strategy was also used to handle the intercurrent events for continuous endpoints at Week 48.

For efficacy analyses, participants were analyzed according to their randomized investigational product (IP) assignment and dose, irrespective of the treatment they actually received.

Study Population

The study was discontinued prematurely and recruitment was terminated due to a strategic decision to stop the cotadutide development program in NASH. The participant disposition was similar across the treatment groups. In total, 586 patients were enrolled, 54 participants were randomized, 36 (66.7%) participants were assessed for post-baseline biopsy, and 41 (75.9%) participants completed the study. Demographics, baseline participant characteristics, and use of concomitant medications were generally similar across treatment groups.

Summary of Efficacy Results

In the FAS, the proportion of participants with resolution of NASH without worsening of liver fibrosis was 35.3%, 44.4%, and 26.3%, in the cotadutide 300 µg, cotadutide 600 µg, and placebo groups, respectively. Treatment with cotadutide 600 µg was associated with a response difference of 18.1% (95% confidence interval [CI] -13.0, 46.4, p = 0.257) compared to the placebo group. A lower response difference of 9.0% was observed in the cotadutide 300 µg group.

The proportion of participants in the FAS with improvement in liver fibrosis by at least one stage without worsening of NASH was 5.9%, 61.1%, and 21.1%, in the cotadutide 300 µg, cotadutide 600 µg, and placebo groups, respectively. Treatment with cotadutide 600 µg was

associated with a response difference of 40.1% (95% CI 8.1, 64.8, p = 0.022) compared to the placebo group. The response for this outcome measure in the cotadutide 300 µg group was not higher than in placebo.

Summary of Safety Results

The safety set comprised 54 participants who received at least one dose of IP. Mean duration of exposure was similar across the treatment groups.

The proportion of participants who experienced at least 1 adverse event (AE) was numerically greater in the cotadutide total group than in the placebo group: cotadutide total (94.3%) and placebo (68.4%). The 3 most common AEs reported by participants in the cotadutide total group were nausea (40.0%), vomiting (31.4%), and decreased appetite (20.0%).

Serious AEs were reported in 1 participant (cotadutide 300 µg group). There were no deaths reported. AEs possibly related to study medication, as judged by the investigator, were more frequent in the cotadutide total group than in the placebo group: cotadutide total (71.4%) and placebo (31.6%). The majority of AEs were mild or moderate in intensity.

AEs leading to discontinuation of study medication were more frequent in the cotadutide total group than in the placebo group: cotadutide total (14.3%) and placebo (5.3%). Only 3 participants (2 in the cotadutide 600 µg group and 1 in the placebo group) experienced an AE leading to withdrawal from the study.

The frequency of the AE of special interest (AESI) nausea and vomiting was greater in the cotadutide total treatment group than in the placebo treatment group, while the frequency of injection site reactions was less in the cotadutide total treatment groups than in placebo. Greater increases in mean change in heart rate from baseline over 48 weeks were seen with both doses of cotadutide compared with placebo.

There were no cases meeting potential Hy's Law or Hy's Law criteria in the study, and there were no new clinically relevant trends in clinical laboratory evaluations or ECGs.

Conclusion(s)

- Due to a strategic decision to stop the cotadutide development program in NASH, enrollment into the study was stopped early, resulting in a limited sample size (54 randomized participants) and only 36 participants (66.7%) with a post-baseline biopsy.
- Safety and tolerability of cotadutide 300 and 600 µg administered SC once daily in adults with non-cirrhotic NASH with fibrosis were generally consistent with the known safety profile for cotadutide.
- Cotadutide treatment at both doses demonstrated numerical improvements in resolution of NASH without worsening of liver fibrosis.

- A higher proportion of participants in the cotadutide 600 µg treatment group than the placebo group showed improvement of liver fibrosis by at least one stage without worsening of NASH.