Clinical Study Protocol	
Study Intervention	Cotadutide
Study Code	D5671C00006
Version	3.0
Date	15 May 2023

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

Sponsor Name: AstraZeneca AB

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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D5671C00006

Amendment Number: 2

Study Intervention: Cotadutide, placebo

Study Phase: Phase II

Short Title: A study to evaluate the safety and efficacy of cotadutide given by subcutaneous injection in adult participants with non-cirrhotic non-alcoholic steatohepatitis with fibrosis

Acronym: PROXYMO-ADVANCE

Study Physician Name and Contact Information will be provided separately

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
CSP version 2	07-Nov-2022
CSP version 1	28-Jan-2022

CSP version 3: 15 May 2023

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment:

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. This study was designed to evaluate the safety and efficacy of cotadutide given by SC injection in adult participants with biopsy-proven NASH with fibrosis stage F2 or F3. After careful consideration, the sponsor has decided to discontinue the development of cotadutide (a daily injectable GLP-1/glucagon co-agonist) to focus efforts on other, more convenient treatments for patients with NASH. Randomized participants and participants in active screening (having signed the ICF) will be allowed to continue participation in the study as per protocol unless they decide to withdraw from the study. The Phase III (Part B) portion of the study will no longer be conducted. As a consequence of these changes, the number of participants in the study will be significantly reduced. Therefore, the primary objective for this study will be safety, and efficacy objectives will be considered exploratory. The protocol has been revised accordingly to reflect these key changes.

Substantial changes to the protocol are summarized below.

Section # and Name	Description of Change and Brief Rationale
Study title	Updated title to reflect the key changes in the study design.
Section 1 (Protocol Summary) Section 3.2 (Objectives and Endpoints: Part B) Section 3.3 (Estimands) Section 4 (Study Design) Section 5.4 (Screen Failures) Section 6.3.1 (Method for Assigning Treatment Groups) Section 6.3.3 (Methods for Unblinding) Section 7.1 (Discontinuation of Study Intervention) Section 8 (Study Assessments and Procedures) Section 9 (Statistical Considerations) Appendix F (Patient-Reported Outcomes)	Removal of content related to Part B (Phase III) due to the decision to not conduct that part of the study, including, but not limited to, removal of: • General description of Part B throughout • Endpoints that were only planned for Part B • Part B study schema, SoA, sample size, and statistical analysis • Description of dose adaptation decision process and implementation.
Section 1.1 (Synopsis) Section 3.1 (Objectives and Endpoints: Part A) Section 4.1 (Overall Design) Section 4.2.3 (Rationale for Endpoints) Section 8.1.5 (Exploratory Biomarker Assessments) Section 9 (Statistical Considerations)	Revised the study objectives and endpoints due to the decision to discontinue enrollment. The primary objective and endpoints for this study were updated to safety. Efficacy endpoints are all exploratory. • Reduced the number of histology-based endpoints for Part A. • Eliminated the objectives/endpoints for absolute change from baseline in body weight, eGFR, and uACR. • Combined objectives related to glycemic control and lipid profile. • Assessment of change from baseline in HbA1c will no longer be restricted to participants with T2DM. The rationale for endpoints and statistical considerations were also updated, and “proof of concept” was added to the study description.
Section 1.1 (Synopsis) Section 3.3 (Estimands) Section 9 (Statistical Considerations)	Revised statistical analysis description to reflect the updated study design and objectives and endpoints. • Updated the statistical hypotheses and sample size description. • Removed analysis and adaptations descriptions for Part B. • Removed the multiplicity plan. • Revised the analysis of efficacy endpoints to use nominal p value. • Simplified the primary estimand to use a treatment policy approach for intercurrent events. • Added the Per Protocol population definition.
Section 1.1 (Synopsis) Section 2.1 (Study Rationale) Section 4.1 (Overall Design)	Provided explanation for the change in study design.

Section # and Name	Description of Change and Brief Rationale
Section 1.1 (Synopsis) Section 1.2 (Schema) Section 4.1 (Overall Design) Section 9.2 (Sample Size Determination)	Updated the number of countries, screened participants, and randomized participants.
Section 1.3.2.1 (Part A Schedule of Activities: Treatment Period and Follow-up)	Removed the requirement for ADA monitoring for participants who test positive at the follow-up visit. No safety concerns related to the development of ADAs have been identified in the cotadutide clinical development program to date. Because the cotadutide NASH clinical program has been terminated, further ADA monitoring after the follow-up visit is not needed.
Section 2.3.1 (Risk Assessment)	Added gallbladder-related disorders to the potential risks to align with the IB.
Section 1.3.2.1 (Part A Schedule of Activities: Treatment Period and Follow-up) Section 3.1 (Objectives and Endpoints: Part A) Section 4.2.3.2 (Rationale for Exploratory Endpoints) Section 8.1.3 (FibroScan and FibroScan-derived Biomarkers) Section 8.1.5 (Exploratory Biomarker Assessments)	Clarified the FibroScan-derived biomarkers by adding the Agile 3+ endpoint (and components) and the components of FAST score.
Section 6.5.2 (Prohibited Concomitant Medications)	Added instructions to address use of any drugs with new regulatory approvals for the treatment of NASH with fibrosis. Use of the newly approved treatment can be considered after discussion with study physician, if the investigator deems it not to be safe for the participant to postpone the start of such treatment until study end.
Section 7.1 (Discontinuation of Study Intervention)	Changed the liver-related potential reason for discontinuation to "suspected or confirmed diagnosis of DILI" for consistency with Figure 2 and Figure 3 and added cross reference to the figures.
Section 8.4.2 (Immunogenicity Assessments) Section 9.4.4 (Analysis of Pharmacokinetics and Immunogenicity)	Due to change in scope of the study: • Revised text on assessment of cross-reactivity to GLP-1 and glucagon from "will be performed" to "may be performed." • Removed the analysis of presence of neutralizing ADAs and the effect of immunogenicity on biomarkers and efficacy.

Nonsubstantial changes to the protocol are summarized below.

Section # and Name	Description of Change and Brief Rationale
Section 1.3.2.1 (Part A Schedule of Activities: Treatment Period and Follow-up)	Clarified text on requirement for follow-up visits after early discontinuation or end of treatment visits.
Section 2.2.1 (Disease Background)	Minor update to language on approved pharmacological therapies to align with Section 2.3.2 (Benefit Assessment).
Section 2.2.2 (Cotadutide Background)	Updated the IB edition to 10.0 to reflect the most recently approved IB.
Section 3.1 (Objectives and Endpoints: Part A)	Moved the definitions of NASH endpoints to the footnote of the objectives and endpoints table for clarity.
Section 5.2 (Exclusion Criteria)	Changed the units for platelets to match units used by the central laboratory.
Section 5.4 (Screen Failures)	Removed GGT from the list of central laboratory criteria for retesting to correct an administrative error.
Section 6.5.2 (Prohibited Concomitant Medications)	Added paracetamol to the description for clarity.
Section 6.7 (Missed Dose)	Clarified that 7-day interruptions of IP that constitute an important protocol deviation must be consecutive.
Section 7.3 (Lost to Follow Up)	Correction of text on participants who become unreachable.
Section 8.2.5 (Clinical Safety Laboratory Assessments)	Added eGFR to the list of safety assessments because it was removed from the efficacy assessments.
All sections	Minor typographical and administrative edits.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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

Short Title: A study to evaluate the safety and efficacy of cotadutide given by subcutaneous injection in adult participants with non-cirrhotic non-alcoholic steatohepatitis with fibrosis

Rationale: This study was originally a 2-part Phase IIb/III study to evaluate the safety and efficacy of cotadutide in adults with biopsy-proven non-cirrhotic NASH with fibrosis stage F2 or F3. GLP-1 receptor mono-agonists reduce liver fat and improve histological features of NASH (Armstrong et al 2016, Petit et al 2017, Newsome et al 2021). Cotadutide, an oxyntomodulin-like peptide with targeted balanced GLP-1 and glucagon receptor activity, has been associated with robust improvements in body weight, glucose and insulin homeostasis, markers of hepatic health, lipid lowering, collagen turnover, liver fibrosis profile, and renoprotection in a number of animal models of NASH, CKD, obesity, and T2DM. Importantly, cotadutide has demonstrated robust and significant histologic benefits, including reduction in NASH disease activity and improvement in fibrosis in animal models (Boland et al 2020). In obese patients with T2DM, cotadutide had a robust and significant treatment effect on HFF (Ambery et al 2018) and other non-invasive measures of NAFLD (Nahra et al 2021). In patients with biopsy-proven non-cirrhotic NASH with fibrosis (F1, F2, F3), cotadutide has demonstrated robust and significant improvements in HFF, liver enzymes, and non-invasive markers of NASH and fibrosis.

After careful consideration, foremost being the identification of other, more convenient treatments in development for patients with NASH, the sponsor decided to discontinue development of cotadutide and recruitment into this study. Randomized participants and participants in active screening in the Phase II (Part A) portion of the study will be allowed to continue participation. The Phase III portion of the study (Part B) will not be conducted. Given the reduced sample size, the primary goal of this study is to evaluate the safety of cotadutide in participants with non-cirrhotic NASH with fibrosis. All efficacy evaluations will be exploratory objectives.

Objectives and Endpoints: Part A

Table 1 Objectives and Endpoints: Part A

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. 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 ++ Electrocardiogram 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 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
• To assess the effect of cotadutide versus placebo on resolution of NASH and improvement in fibrosis	• Proportion of participants with both resolution of NASH and improvement in fibrosis by at least one stage based on biopsy at Week 48
• To assess the effect of cotadutide versus placebo on improvement in fibrosis by at least one stage	• Proportion of participants with improvement in fibrosis by at least one stage based on biopsy at Week 48
• To assess the effect of cotadutide versus placebo on improvement in NAS	• Proportion of participants with improvement in NAS based on biopsy at Week 48 • Change from baseline in NAS based on biopsy at Week 48
• To assess the effect of cotadutide versus placebo on change in fibrosis	• Change from baseline in fibrosis stage based on biopsy at Week 48 • Proportion of participants with progression, no change, or regression in fibrosis stage based on biopsy at Week 48
• To assess the effect of cotadutide versus placebo on improvement in each key histological feature of NASH	• Proportion of participants with improvement in key histological features of NASH based on biopsy at Week 48, including: ° Inflammation ° Steatosis ° Ballooning
• To characterize using AI-based histology assessment the effect of cotadutide versus placebo on NASH histology, including: ° Resolution of NASH without worsening of liver fibrosis	• AI-based histology assessment of: ° Proportion of participants with resolution of NASH without worsening of liver fibrosis based on biopsy at Week 48

° Improvement of liver fibrosis by at least one stage without worsening of NASH ° Resolution of NASH and improvement in fibrosis ° Improvement in fibrosis by at least one stage ° Improvement in NAS ° Change in fibrosis ° Improvement in each key histological feature 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 ° Proportion of participants with both resolution of NASH and improvement in fibrosis by at least one stage based on biopsy at Week 48 ° Proportion of participants with improvement in fibrosis by at least one stage based on biopsy at Week 48 ° Proportion of participants with improvement in NAS based on biopsy at Week 48 ° Change from baseline in NAS based on biopsy at Week 48 ° Change from baseline in fibrosis stage based on biopsy at Week 48 ° Proportion of participants with progression, no change, or regression in fibrosis stage based on biopsy at Week 48 ° Proportion of participants with improvement in histological features of NASH based on biopsy at Week 48, including: Inflammation Steatosis Ballooning
• To assess the effect of cotadutide versus placebo on circulating markers of hepatic inflammation	• Change from baseline in liver enzymes including ALT and AST through Week 48
• To assess the effect of cotadutide versus placebo on lipid profile and glycemic control	• Change from baseline in triglycerides, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, total cholesterol, and HbA1c through Week 48
• To summarize the PK profile of cotadutide	• Cotadutide PK exposure will be summarized and compared with prior data for consistency
• To assess the effect of cotadutide versus placebo on liver stiffness	• Change from baseline at Week 48 in: ° LSM as assessed by FibroScan ° Percentage CAP as assessed by FibroScan
• To assess the effect of cotadutide versus placebo on disease-specific biomarkers	• Changes from baseline at Week 48 in non-invasive disease-specific biomarkers, including but not limited to: ° Collagen turnover (Pro-C3) ° ELF score ° FIB-4 ° APRI ° NFS ° BARD score ° FAST score ° Agile 3+

• To determine whether cotadutide is superior to placebo for weight reduction	• Percent change from baseline in body weight at Week 48
• To assess the effect of cotadutide versus placebo on glucose, adiponectin, and C-peptide	• Change from baseline in fasting plasma glucose, adiponectin, and C-peptide at Week 48
• To determine whether treatment with cotadutide compared with placebo will result in a reduction of BP	• Change from baseline in SBP through Week 48

ADA, anti-drug antibody; AE, adverse event; AI, artificial intelligence; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BARD, body mass index, AST/ALT ratio, diabetes; BP, blood pressure; CAP, controlled attenuation parameter; CV, cardiovascular; DBP, diastolic blood pressure; ECG, electrocardiogram; ELF, enhanced liver fibrosis; FAST, FibroScan-AST; FIB-4, fibrosis-4; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IP, investigational product; LDL, low-density lipoprotein; LSM, liver stiffness measurement; 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; NFS, non-alcoholic fatty liver disease fibrosis score; PK, pharmacokinetic(s); QTcF, Fridericia-corrected QT interval; SBP, systolic blood pressure

Overall Design

This study was originally designed as a 2-part (Phase IIb/III) study. However, given the decision to terminate recruitment, only Part A (Phase II) will be conducted.

This is a Phase II, global, randomized, parallel-group, double-blind, placebo-controlled, multicenter, proof-of-concept study to assess the safety and efficacy of 300 µg and 600 µg cotadutide compared with placebo, given once daily as an SC injection administered via a multidose pen, in adults with non-cirrhotic NASH with fibrosis stage F2 or F3.

The study will assess safety of cotadutide treatment. All efficacy endpoints are exploratory and include whether treatment with cotadutide results 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 are eligible according to the inclusion/exclusion criteria will be 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 will be ≥ 18 to ≤ 75 years of age (inclusive) with biopsy-proven NASH (historical biopsy performed ≤ 180 days from randomization or on-study biopsy) demonstrating a 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 will be stratified by the presence/absence of T2DM and by fibrosis stage. Each cotadutide treatment group will be placebo-matched with respect to titration schedule and dose levels. Participants will be screened in approximately 20 countries.

All liver biopsies will be read by a central pathology review committee.

An independent DMC will be 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.

Disclosure Statement: This is a parallel group treatment study that is blinded to the participants and investigators. The study will include 4 treatment arms.

Number of Participants:

Approximately 600 participants will be screened/enrolled and approximately 55 are planned to be randomized to study intervention.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study but are not randomly assigned/assigned in the study, are considered "screen failures."

Intervention Groups and Duration:

Participants will be in the study for at least approximately 1.2 years (60 weeks), including a screening period of up to 8 weeks, a 48-week treatment period, and a 4-week safety follow-up period.

Participants will undergo dose titration steps every 4 weeks to reach the target dose of 300 µg or 600 µg qd. Dose titration will start from 50 µg cotadutide (or matching placebo) qd and increase to 100 µg qd after 4 weeks, and then increase by 100 µg increments every 4 weeks, until reaching the final intended dose at Week 12 for the 300 µg treatment groups and Week 24 for the 600 µg treatment groups.

The study will be blinded. After all participants have completed the study and database lock has occurred, the study will be unblinded and analyzed.

Data Monitoring Committee: Yes

Statistical Methods

The primary analyses will be of safety, and analyses will be performed using the safety analysis set. Safety data will be presented using descriptive statistics unless otherwise specified and will not be formally tested. Safety events and findings will be summarized by treatment group. No formal hypothesis testing will be performed.

Exploratory efficacy analyses will use nominal 2-sided 5% significance levels (equivalent to nominal 1-sided 2.5% significance levels) unless otherwise stated.

The primary estimand of interest for the histological endpoints will use the treatment policy strategy. The treatment policy approach will apply 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 will also be used to handle the intercurrent events for continuous endpoints.

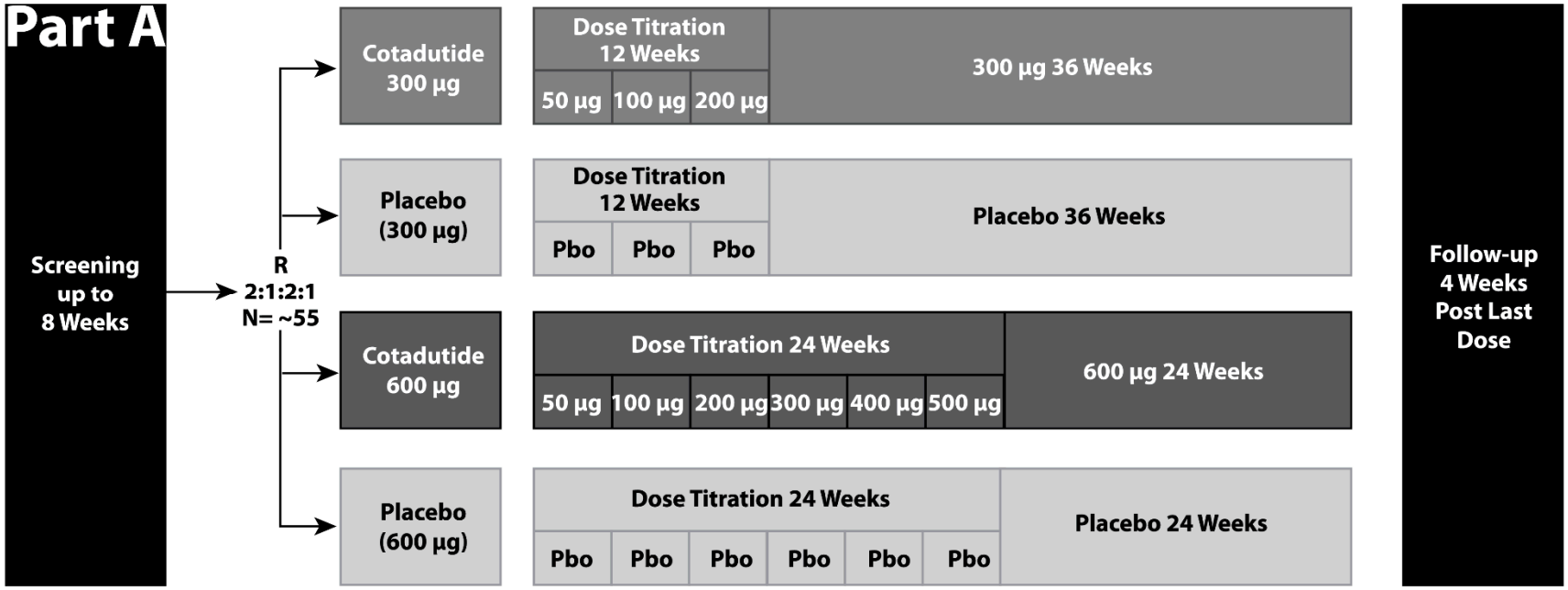
Participants will be analyzed according to their randomized IP assignment and dose, irrespective of the treatment they actually received. Analyses will be performed using the FAS and/or per protocol analysis sets, as appropriate. The FAS will include all randomized and treated participants who received at least one dose of IP irrespective of their protocol adherence, addition or modification of background medications, discontinuation of study intervention or switches to alternative medications, and continued participation in the study.

For the exploratory analysis of binary histological endpoint(s) using FAS, participants with missing histology data due to any reason will be imputed as non-responders. The binary endpoint(s) will be analyzed using a Cochran-Mantel-Haenszel test with stratification by T2DM presence and F2/F3 fibrosis stages. The treatment effects will be summarized by the difference in proportions, 95% CI, and p-value.

In Part A, 300 participants were originally planned to be randomized to provide > 90% power for the test of each dose versus pooled placebo to detect a difference of 20% in NASH resolution assuming a placebo response rate of 15%. As a result of the decision to terminate recruitment, approximately 55 participants are planned to be randomized in the study.

1.2 Schema

Figure 1 Study Design



Pbo, placebo; R, randomization

1.3 Schedule of Activities

1.3.1 Schedule of Activities: Screening

The SoA for participants with a qualifying historical biopsy is presented in Table 2, and the SoA for participants undergoing an on-study biopsy for screening is presented in Table 3.

Table 2 Schedule of Activities in the Screening Period for Participants with a Historical Biopsy (Part A)

	Screening (procedures may occur over more than one day)
Visit	V1
Procedure/Study Day	Day-56 to -1
Informed consent (Appendix A 3)	X
Optional informed consent for Genomics Initiative research (Appendix D 2)	X
Confirmation of fasting (Section 5.3.2)	X
Inclusion and exclusion criteria (Sections 5.1 and 5.2)	X
Demography	X
Full physical examination including height and weight (Section 8.2.2)	X
Medical history (includes AUDIT questionnaire and substance usage) (Section 8.2.1)	X
Historical liver biopsy (Section 8.1.1) [a]	X
Serum pregnancy test (WOCBP only) (Section 8.2.5)	X
Hepatitis B and C and HIV screening (Section 8.2.5) [b]	X
Urinalysis for drugs of abuse (Section 8.2.5)	X
Clinical safety laboratory assessments, including eGFR and MELD score calculation (Section 8.2.5)	X
Amylase and lipase (Section 8.2.5)	X
Coagulation parameters (Section 8.2.5)	X
12-lead ECG (Section 8.2.4) [c]	X
Vital signs (Section 8.2.3) [d]	X
Assessment of AEs (Section 8.3) [e]	X
Concomitant medication (Section 6.5)	X
Blood sampling for ELF (Section 8.1.5)	X
FIB-4 computed score (Section 8.1.5)	X
HbA1c (Section 8.1.5)	X
Fasting serum lipid panel (Section 8.1.5)	X
Calcitonin (Section 8.2.5)	X

Table 2 Schedule of Activities in the Screening Period for Participants with a Historical Biopsy (Part A)

	Screening (procedures may occur over more than one day)
Visit	V1
Procedure/Study Day	Day-56 to -1
Check participant's ability to self-administer SC injection [f]	X
Demonstration of and training on self-administration of SC injection (Section 6.2) [g]	X
Review diet and lifestyle advice (Section 5.3.1)	X
Enrollment in IRT/RTSM	X

Participants should withhold alcohol and refrain from intense exercise for 24 hours prior to each study site visit.

[a] Review of participant's medical history, including historical biopsy procedure report and histopathological findings report that meet the inclusion and exclusion criteria in Section 5.1 and 5.2. In the event the historical biopsy is deemed not evaluable and a participant screen fails, an on-study liver biopsy may be scheduled. Such an on-study biopsy, if considered, should only be performed on a date that is ≥ 180 days after the date of the historical biopsy and after all other eligibility criteria are met. Biopsy tissue and/or biopsy tissue block and/or slides should be sent for the central histopathology review laboratory to determine eligibility at least 21 days prior to planned day of randomization.

[b] HbsAg, anti-HCV, HCV RNA, HIV-1 and HIV-2 antibodies.

[c] ECGs will be recorded in triplicate after a 10-minute supine rest period with no more than about 2 minutes between individual ECGs, completing all 3 ECGs within a maximum of about 5 minutes. ECGs should be collected prior to vital signs, PK sample collection, or other assessments as these may alter autonomic tone.

[d] Whenever vital signs and blood draws are scheduled for the same nominal time, the blood draws should occur last.

[e] AE/SAEs will be collected from the time of signature of informed consent, throughout the treatment period and the follow-up period.

[f] At screening, the investigator will judge if the participant is able to self-administer SC injection.

[g] Activities related to demonstration and training on SC administration can be conducted at Visit 1 and/or prior to randomization at Visit 2.

AE, adverse event; AUDIT, Alcohol Use Disorder Identification Test; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; HbA1c, hemoglobin A1c; HbsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IRT, interactive response technology; MELD, model for end-stage liver disease; PK, pharmacokinetic(s); RTSM, randomization and trial supply management; SAE, serious adverse event; SC, subcutaneous; V, visit; WOCBP, women of childbearing potential

Table 3 Schedule of Activities in the Screening Period for Participants Undergoing On-study Biopsy (Part A)

	Screening (procedures may occur over more than one day)
Visit	V1
Procedure/Study Day	Day -56 to -21 [a]
Informed consent (Appendix A 3)	X
Optional informed consent for Genomics Initiative research (Appendix D 2)	X
Confirmation of fasting (Section 5.3.2)	X
Inclusion and exclusion criteria (Sections 5.1 and 5.2)	X
Demography	X
Full physical examination including height and weight (Section 8.2.2)	X
Medical history (includes AUDIT questionnaire and substance usage) (Section 8.2.1)	X
Serum pregnancy test (WOCBP only) (Section 8.2.5)	X
Hepatitis B and C and HIV screening (Section 8.2.5) [b]	X
Urinalysis for drugs of abuse (Section 8.2.5)	X
Clinical safety laboratory assessments, including eGFR and MELD score calculation (Section 8.2.5)	X
Amylase and lipase (Section 8.2.5)	X
Coagulation parameters (Section 8.2.5)	X
12-lead ECG (Section 8.2.4) [c]	X
Vital signs (Section 8.2.3) [d]	X
Assessment of AEs (Section 8.3) [e]	X
Concomitant medication (Section 6.5)	X
FibroScan (Section 8.1.3) [f]	X
Blood sampling for ELF (Section 8.1.5) [g]	X
Blood sampling for NIS4 [g, h]	X
FIB-4 computed score (Section 8.1.5) [h]	X
FAST score (Section 8.1.3) [g, h]	X
HbA1c (Section 8.1.5)	X
Fasting serum lipid panel (Section 8.1.5)	X
Calcitonin (Section 8.2.5)	X
Check participant's ability to self-administer SC injection [i]	X
Demonstration of and training on self-administration of SC injection (Section 6.2) [j]	X

Table 3 Schedule of Activities in the Screening Period for Participants Undergoing On-study Biopsy (Part A)

	Screening (procedures may occur over more than one day)
Visit	V1
Procedure/Study Day	Day -56 to -21 [a]
Review diet and lifestyle advice (Section 5.3.1)	X
Enrollment in IRT/RTSM	X
Liver biopsy for histology (Section 8.1.1) [a]	X

Participants should withhold alcohol and refrain from intense exercise for 24 hours prior to each study site visit.

[a] For participants without a historical biopsy, the screening liver biopsy procedure is to be performed after all other screening procedures are complete and after confirmation that the participant meets all other inclusion/exclusion criteria. The biopsy procedure may be conducted on a different day but is part of Visit 1. Sites to ensure biopsy tissue block and/or slides are sent to the central histopathology review laboratory to determine eligibility at least 21 days prior to the planned day of randomization.

[b] HbsAg, anti-HCV, HCV RNA, HIV-1 and HIV-2 antibodies.

[c] ECGs will be recorded in triplicate after a 10-minute supine rest period, with no more than about 2 minutes between individual ECGs, completing all 3 ECGs within a maximum of about 5 minutes. ECGs should be collected prior to vital signs, PK sample collection, or other assessments as these may alter autonomic tone.

[d] Whenever vital signs and blood draws are scheduled for the same nominal time, the blood draws should occur last.

[e] AE/SAEs will be collected from the time of signature of informed consent, throughout the treatment period and the follow-up period.

[f] If a site has access to appropriate FibroScan equipment, as well as compatible software and probes, they must complete the assessments per the schedule for any participant who does not have a previous FibroScan assessment conducted within 90 days of initiating screening activities. If not and the assessment cannot be conducted, this will not constitute a deviation from the protocol. Fibroscan study must be performed in a fasting state.

[g] A pre-biopsy screening strategy prior to conduct of on-study liver biopsy, using a sequential combination of the following, namely, BMI, FIB-4, NIS4 (if available), FAST score or FibroScan, ELF, is strongly recommended. Investigator may choose an alternative pre-biopsy screening strategy that may not include one or more of the above parameters. It is recommended that investigators discuss the alternative pre-biopsy screening strategy with the sponsor prior to conduct of on-study biopsy.

[h] FAST score will be calculated only at sites that have the required software.

[i] At screening, the investigator will judge if the participant is able to self-administer SC injection.

[j] Activities related to demonstration and training on SC administration can be conducted at Visit 1 and/or prior to randomization at Visit 2.

AE, adverse event; AUDIT, Alcohol Use Disorder Identification Test; BMI, body mass index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ELF, enhanced liver fibrosis; FAST, FibroScan-AST; FIB-4, Fibrosis-4; HbA1c, hemoglobin A1c; HbsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IRT, interactive response technology; MELD, model for end-stage liver disease; NIS4, non-invasive diagnostic score 4; PK, pharmacokinetic(s); RTSM, randomization and trial supply management; SAE, serious adverse event; SC, subcutaneous; V, visit; WOCBP, women of childbearing potential

1.3.2 Schedule of Activities: Treatment Period and Follow-up

1.3.2.1 Part A Schedule of Activities: Treatment Period and Follow-up

Table 4 Schedule of Activities for Part A: Treatment Period and Follow-up

	Treatment Period										E/D Visit [b]	Follow-up 4 weeks after EOT or E/D (± 5d) [a]
Week	0	4	8	12	16	20	24	32	40	48		
Visit	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11 (EOT)		
Day (visit window ± x days) [a]	1	29 ± 5d	57 ± 5d	85 ± 5d	113 ± 5d	141 ± 5d	169 ± 5d	225 ± 5d	281 ± 5d	337 ± 5d		
Confirmation of fasting (Section 5.3.2)	X									X	X	
Demonstration of and training on self-administration of SC injection (Section 6.2) [c]	X											
Review of adherence to diet and lifestyle advice (Section 5.3.1)	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication (Section 6.5)	X	X	X	X	X	X	X	X	X	X	X	X
12-lead dECG (Section 8.2.4) [d]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (Section 8.2.3) [e]	X [f]	X	X	X	X	X	X	X	X	X	X	X
Abbreviated (symptom-directed) physical examination including weight (Section 8.2.2, Section 8.1.4)	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs and injection site reactions (Section 8.3; Section 8.2.6.1) [g, h]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical safety laboratory assessments, including eGFR and MELD score calculation (Section 8.2.5)	X	X	X	X	X	X	X	X		X	X	X
Amylase and lipase (Section 8.2.5)	X						X	X		X	X	X
Coagulation parameters (Section 8.2.5)	X						X	X		X	X	X
Calcitonin (Section 8.2.5)	X									X	X	

Table 4 Schedule of Activities for Part A: Treatment Period and Follow-up

	Treatment Period										E/D Visit [b]	Follow-up 4 weeks after EOT or E/D (± 5d) [a]
Week	0	4	8	12	16	20	24	32	40	48		
Visit	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11 (EOT)		
Day (visit window ± x days) [a]	1	29 ± 5d	57 ± 5d	85 ± 5d	113 ± 5d	141 ± 5d	169 ± 5d	225 ± 5d	281 ± 5d	337 ± 5d		
Urine pregnancy test (WOCBP only) (Section 8.2.5)	X			X			X			X	X	X
Liver biopsy for histology (Section 8.1.1)										X [i]	X [j]	
FibroScan, LSM, CAP, FAST Score, Agile 3+ (Section 8.1.3) [k, l]	X									X	X	
Randomization in IRT/RTSM (Section 6.3)	X											
Study intervention administration in clinic [m]	X	X	X	X	X	X	X	X	X			
Study intervention dispensed for at home administration	X	X	X	X	X	X	X	X	X			
Instructions for use dispensed	X	X	X	X	X	X	X	X	X			
Uptitration step for 300 µg cotadutide/placebo		X	X	X								
Uptitration step for 600 µg cotadutide/placebo		X	X	X	X	X	X					
Study intervention compliance (Section 6.4)		X	X	X	X	X	X	X	X	X	X	
Urine for albumin and creatinine	X			X			X			X	X	
HbA1c (Section 8.1.5)	X			X			X			X	X	
Fasting serum lipid panel (Section 8.1.5)	X									X	X	
Pre-dose blood for PK analysis (Section 8.4)	X	X		X			X			X	X	X
Serum for immunogenicity (ADA) (Section 8.4.2) [n]	X	X		X			X			X	X	X
Blood sampling for ELF (Section 8.1.5)	X									X	X	

Table 4 Schedule of Activities for Part A: Treatment Period and Follow-up

	Treatment Period										E/D Visit [b]	Follow-up 4 weeks after EOT or E/D (± 5d) [a]
Week	0	4	8	12	16	20	24	32	40	48		
Visit	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11 (EOT)		
Day (visit window ± x days) [a]	1	29 ± 5d	57 ± 5d	85 ± 5d	113 ± 5d	141 ± 5d	169 ± 5d	225 ± 5d	281 ± 5d	337 ± 5d		
Blood sampling for Pro-C3 (Section 8.1.5)	X									X	X	
FIB-4 computed score (Section 8.1.5)	X									X	X	
Blood for fasting plasma glucose-(Section 8.1.5)	X									X	X	
Blood for C-peptide (Section 8.1.5)	X									X	X	
Blood for adiponectin (Section 8.1.5)	X									X	X	
Genomics Initiative optional, exploratory genetic sample (Section 8.6, Appendix D) [o]	X											
Optional biomarker serum sample (for biomarker research) (Section 8.5.2)	X									X	X	

Participants should withhold alcohol and refrain from intense exercise for 24 hours prior to each study site visit.

[a] Visit windows should be calculated from Day 1. Visit 2 (randomization) may be scheduled any day following confirmation that participant meets all eligibility criteria including eligibility reading from the central pathology review of the biopsy (historical or on-study) sample and laboratory report assessments from the central laboratory (eg, the screening period does not need to be a full 8 weeks). Follow-up visit conducted 4 weeks (± 5 d) after EOT visit or E/D visit. For participants who discontinue study intervention permanently and do not continue with study visits, follow-up visit should be performed 4 weeks (± 5 d) after the E/D visit. For participants who discontinue study intervention early but continue with study visits, follow-up visit should be performed 4 weeks (± 5 d) after the EOT.

[b] Performed in event of early discontinuation of study intervention or withdrawal from study.

[c] Activities related to demonstration and training on SC administration can be conducted at Visit 1 and/or prior to randomization at Visit 2.

[d] ECGs will be recorded in triplicate after a 10-minute supine rest period, with no more than about 2 minutes between individual ECGs, completing all 3 ECGs within a maximum of about 5 minutes. ECGs should be collected prior to vital signs, PK sample collection, or other assessments as these may alter autonomic tone.

[e] Whenever vital signs and blood draws are scheduled for the same nominal time, the blood draws should occur last.

[f] At Visit 2, vital signs should be assessed prior to first dose of study intervention.

[g] AE/SAEs will be collected from the time of signature of informed consent, throughout the treatment period and follow-up period.

[h] Assessment of injection site reactions to be conducted after injection of study intervention.

[i] The post-baseline biopsy to occur within a window from -2 weeks prior to Visit 11 (Week 48) until 4 weeks after Visit 11.

[j] Biopsy should only be conducted as part of the E/D visit activities in participants who have received study intervention for at least 36 weeks and who are unwilling or unable to wait until Week 48. For participants who continue the study after an E/D visit and have a biopsy at the E/D visit, an additional biopsy should not be collected at Week 48. Biopsy should be scheduled within -2 weeks prior to +4 weeks after the E/D visit.

[k] If a site has access to appropriate FibroScan equipment, as well as compatible software and probes, they must complete the assessments per the schedule with extended visit windows. For V2, FibroScan must be performed pre-dose within extended visit window of -14 days but only for participants who meet all inclusion/exclusion criteria (including histology central read) and are determined to be eligible for randomization. For all other visits, Fibroscan must be performed within extended visit window of ±14 days. If a site does not have access to appropriate FibroScan equipment, as well as compatible software and probes, and the assessment cannot be conducted, this will not constitute a deviation from the protocol. FibroScan should be conducted in a fasting state.

[l] FAST score will be calculated only at sites that have the required software.

[m] Study intervention should be administered after all assessments have been conducted and samples have been collected.

[n] ADA samples will be collected prior to administration of IP.

[o] Genomics sample: If for any reason, the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study. The optional informed consent for Genomics Initiative research must be signed prior to sample collection. Refer to Appendix D for inclusion/exclusion criteria specific to the Genomics Initiative and further details on the optional Genomics Initiative sample.

ADA, anti-drug antibody; AE, adverse event; CAP, controlled attenuation parameter; dECG, digital electrocardiogram; E/D, early study intervention discontinuation; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ELF, enhanced liver fibrosis; EOT, end of treatment; FAST, FibroScan-AST; FIB-4, fibrosis-4; HbA1c, hemoglobin A1c; IP, investigational product; IRT, interactive response technology; LSM, liver stiffness measurement; MELD, model for end-stage liver disease; PK, pharmacokinetic(s); Pro-C3, released N-terminal propeptide of type III collagen; RTSM, randomization and trial supply management; SAE, serious adverse event; V, visit; WOCBP, women of childbearing potential

1.3.2.2 Part B Schedule of Activities: Treatment Period and Follow-up

Due to the decision to end recruitment into the study, Part B of the study will not be conducted.

1.3.3 Unscheduled Visits for Dose Modification

If an investigator feels a site visit is required for a participant to discuss dose modification (Section 6.6), activities that should be conducted are presented in Table 5. Further activities may be conducted as judged by the investigator.

Table 5 Schedule of Activities for Unscheduled Dose Modification Site Visit

	Unscheduled Titration Visit
Review of adherence to diet and lifestyle advice (Section 5.3.1)	X
Concomitant medication (Section 6.5)	X
Vital signs (Section 8.2.3) [a]	X
Abbreviated (symptom-directed) physical examination including weight (Section 8.2.2; Section 8.1.4)	X
Assessment of AEs and injection site reactions (Section 8.3; Section 8.2.6.1) [b, c]	X
Study intervention administration in clinic [d]	X
Study intervention dispensed for at home administration	X
Instructions for use dispensed	X
Dose titration step for cotadutide/placebo	X
Study intervention compliance (Section 6.4)	X

Participants should withhold alcohol and refrain from intense exercise for 24 hours prior to each study site visit.

[a] Whenever vital signs and blood draws are scheduled for the same nominal time, the blood draws should occur last.

[b] AE/SAEs will be collected from the time of signature of informed consent, throughout the treatment period and follow-up period.

[c] Assessment of injection site reactions to be conducted after injection of study intervention.

[d] Study intervention should be administered after all assessments have been conducted and samples have been collected.

AE, adverse event; SAE, serious adverse event

1.3.4 Unscheduled Visit for Safety or Any Other Reason

Unscheduled visits for safety or any other reason may be initiated as needed, at the discretion of the investigator. A list of activities for unscheduled safety visits is presented in Table 6.

Table 6 Schedule of Activities for Unscheduled Visit for Safety or Any Other Reason

	Unscheduled Safety Visit
Review of adherence to diet and lifestyle advice (Section 5.3.1)	X
Concomitant medication (Section 6.5)	X
Clinical safety laboratory assessments based on clinical judgment (Section 8.2.5)	X
Vital signs (Section 8.2.3) [a]	X
Abbreviated (symptom-directed) physical examination including weight (Section 8.2.2; Section 8.1.4)	X
Assessment of AEs and injection site reactions (Section 8.3; Section 8.2.6.1) [b, c]	X
Study intervention administration in clinic [d]	X

Participants should withhold alcohol and refrain from intense exercise for 24 hours prior to each study site visit.

[a] Whenever vital signs and blood draws are scheduled for the same nominal time, the blood draws should occur last.

[b] AE/SAEs will be collected from the time of signature of informed consent, throughout the treatment period and follow-up period.

[c] Assessment of injection site reactions to be conducted after injection of study intervention.

[d] Study intervention should be administered after all assessments have been conducted and samples have been collected.

AE, adverse event; SAE, serious adverse event

2 INTRODUCTION

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 GLP-1 and glucagon receptors. The combination of GLP-1 and glucagon receptor agonist activity is expected to delay disease progression and potentially reverse disease in NASH with fibrosis, and CKD with T2DM, through direct disease-modifying effects alongside improved lipid homeostasis, enhanced glycemic control, and body weight loss.

2.1 Study Rationale

Non-alcoholic steatohepatitis has a prevalence of approximately 2% to 3% in the general population and can lead to cirrhosis, hepatocellular carcinoma, and end-stage liver disease. It has been previously demonstrated that GLP-1 receptor mono-agonists reduce liver fat and improve histological features of NASH (Armstrong et al 2016, Petit et al 2017, Newsome et al 2021). Cotadutide, an oxyntomodulin-like peptide with targeted balanced GLP-1 and

glucagon receptor activity, has been associated with improvements in body weight, glucose and insulin homeostasis, markers of hepatic health, lipid lowering, collagen turnover, liver fibrosis profile, and renoprotection in a number of animal models of NASH, CKD, obesity, and T2DM. Importantly, cotadutide has demonstrated robust and significant histologic benefit to reduce NASH disease activity leading to NASH resolution and on improvement in fibrosis in animal models of NASH with fibrosis (Boland et al 2020). In 2 separate studies in obese patients with T2DM, cotadutide had a significant treatment effect on HFF, and treatment with cotadutide for 54 weeks in obese T2DM led to significant treatment effects on non-invasive measures of NAFLD as well as effects on body weight, glucose lowering, and lipid profile parameters (Ambery et al 2018, Nahra et al 2021).

In a Phase II randomized, double-blind, placebo-controlled study (D5671C00002; PROXYMO) in overweight/obese participants (n = 74) with biopsy-proven non-cirrhotic NASH with fibrosis, treatment with cotadutide at 300 µg and 600 µg doses for 19 weeks was generally safe and well-tolerated. The AE profile was consistent with the incretin class, and the majority of events were mild-to-moderate in severity. Cotadutide demonstrated dose- and time-dependent improvements in HFF and other measures of NASH. Dose-dependent reductions in liver enzymes were observed, with robust and significant treatment effects on AST and ALT in the 600 µg group. Additionally, improvements in biomarkers of NASH and fibrosis were observed.

This study was originally a 2-part Phase IIb/III study to evaluate the safety and efficacy of cotadutide in adults with biopsy-proven non-cirrhotic NASH with fibrosis stage F2 or F3. After careful consideration, the sponsor decided to discontinue development of cotadutide and recruitment into this study to focus efforts on other, more convenient treatments for patients with NASH. Randomized participants and participants in active screening (having signed the ICF) will be allowed to continue participation in the study as per protocol unless they decide to withdraw from the study. The Phase III (Part B) portion of the study will no longer be conducted. As a consequence of these changes, the number of participants in the study will be significantly reduced. Therefore, the primary objective for this study will be safety, and efficacy objectives will be considered exploratory.

2.2 Background

2.2.1 Disease Background

Non-alcoholic steatohepatitis is part of the spectrum of liver diseases known as NAFLD, ranging from simple steatosis or non-alcoholic fatty liver to NASH. Non-alcoholic steatohepatitis, the progressive form of the disease with a prevalence of approximately 2% to 3% in the general population, can lead to cirrhosis and its complications, hepatocellular carcinoma, and end-stage liver disease (Bellentani et al 2010). Non-alcoholic steatohepatitis is expected to become the leading cause for liver transplantation over the next decade (Wong et

al 2014, Pais et al 2016, Cholankeril et al 2017).

Non-alcoholic steatohepatitis is closely associated with metabolic risk factors including obesity, T2DM, and dyslipidemia. Epidemiological studies have demonstrated the prevalence of comorbid obesity and T2DM in approximately 80% of patients with NASH and at least 45% of patients with NASH, respectively (Younossi et al 2016). Pathophysiologically, NASH is frequently associated with a hyperinsulinemic or insulin-resistant state, leading to adipose tissue dysfunction and increased hepatic de novo lipogenesis. Therefore, it is believed that both increased adipose tissue lipolysis and hepatic de novo lipogenesis contribute to increased liver fat and formation of lipid metabolites causing lipotoxicity. Lipotoxicity, oxidative stress, and mitochondrial dysfunction are believed to contribute to the hallmarks of NASH including signs of cell death or hepatocyte ballooning, lobular or portal inflammation, and ultimately in some patients, liver fibrosis (Marra et al 2013, Neuschwander-Tetri 2017).

Non-alcoholic steatohepatitis is defined histologically as a multicomponent condition composed of hepatic steatosis, inflammation, and hepatocyte ballooning in varying proportions. Approximately 25% to 35% of patients with NASH develop liver fibrosis (Mishra and Younossi 2012). Fibrosis stage (F1 to F4) has been shown to have significant prognostic value in NASH correlating with liver-related outcomes and mortality (Angulo et al 2015, Dulai et al 2017). Several factors have been shown to increase the risk of liver fibrosis progression to cirrhosis including presence of comorbid T2DM, increasing age, hypertension, and high BMI (Angulo 2007, Angulo et al 2015).

There are currently no approved pharmacological therapies for NASH, and lifestyle modifications are the mainstay of treatment. Many patients do not achieve or maintain dietary goals and weight loss. Consequently, the development of new therapies for NASH is an area of high unmet medical need, particularly given the expected increasing burden of this disease in parallel with the rising global epidemics of obesity and T2DM (Estes et al 2018).

2.2.2 Cotadutide Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of cotadutide is provided in the IB.

Cotadutide has shown potent agonism of both the GLP-1 receptor and glucagon receptor in human and animal in vitro assays. In vivo, this has translated into the anticipated pharmacological effects on body weight reduction, improved glucose and insulin homeostasis, improvements in markers of hepatic health, lipid lowering, reduced collagen turnover, an improved liver fibrosis profile, and renoprotective effects in a number of animal models of NASH, CKD, obesity, and T2DM. For a summary of nonclinical pharmacology and toxicology studies, see the IB edition 10.0 Section 4.

Safety

For an overall summary of safety in humans, see the IB edition 10.0 Section 5.2.1.

In completed clinical studies, the safety profile of cotadutide was generally similar to that observed with GLP-1 receptor agonists. In the cotadutide groups, treatment-emergent AEs in the SOCs of Gastrointestinal Disorders, Metabolism and Nutrition Disorders, and Nervous System Disorders were generally more common compared with placebo. In general, including in the PROXYMO study of overweight and obese participants with biopsy-proven non-cirrhotic NASH with fibrosis, treatment-emergent AEs of nausea and vomiting were reported at higher incidences in the cotadutide groups compared with placebo. Most treatment emergent AEs were Grade 1 or 2 in severity and not serious.

Efficacy

For an overall summary of efficacy in humans, see the IB edition 10.0 Section 5.2.2.

In obese patients with T2DM, treatment with cotadutide was associated with improvements in glycemic control and hepatic parameters and reductions in body weight in clinical studies (Nahra et al 2021).

In overweight/obese participants with biopsy-proven non-cirrhotic NASH with fibrosis (PROXYMO study D5671C00002), statistically significant reductions in HFF, ALT, AST, Pro-C3, and APRI from baseline to Week 19 (end of treatment) were observed for the 600 µg cotadutide group compared with placebo, and nominal reductions were observed for the 300 µg group. Nominal reductions in body weight from baseline to Week 19 were observed for the 300 µg cotadutide group and the 600 µg cotadutide compared with placebo. Nominal reductions in HbA1c and total cholesterol from baseline to Week 19 in participants with NASH with or without comorbid T2DM were observed for the 300 and 600 µg cotadutide groups compared with placebo. In general, greater changes in efficacy parameters were observed for 600 versus 300 µg cotadutide compared with placebo.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of cotadutide may be found in the IB.

2.3.1 Risk Assessment

The current IB has further information on the potential benefits of cotadutide and an assessment of the potential and known risks. Risks associated with cotadutide and with study-related procedures are presented in Table 7 along with mitigation strategies. Additionally, participants will be monitored throughout the study for signs, symptoms, and/or laboratory analyses suggestive of hepatic decompensation. Participants with hepatic decompensation will

be excluded from further participation in this study (Section 5.2) and will be treated immediately according to standard of care. Specified clinical events, including all potential cases of DILI and CV events, will be adjudicated by an external, independent, and blinded events adjudication committee (Section 8.3.10).

Table 7 Risk Assessment

Identified and potential risks of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Cotadutide		
Identified risks associated with cotadutide: • Nausea • Vomiting • Injection site reactions • Increased heart rate Potential risks include: • Alterations in blood pressure • QT interval prolongation • Anaphylactic-type reactions • Skin rash • Hypoglycemia (with sulfonylurea, glitinides, and insulin) • Diabetic ketoacidosis (following insulin reduction) • Acute renal failure secondary to dehydration • Pancreatitis • Pancreatic carcinoma • Thyroid cancer • Gallbladder-related disorders	Potential risks for cotadutide are based on available published data for GLP-1 receptor agonists and glucagon, as well as clinical and nonclinical data. Some potential risks (pancreatitis, pancreatic carcinoma, thyroid cancer, gallbladder-related disorders) are based solely on GLP-1 agonists as a class finding	• Inclusion/exclusion criteria (Section 5.1 and Section 5.2) • Safety monitoring (Section 8.2) • Uptitration dosing schedule (Section 4.3) • Pen device and instruction on proper injection technique (Section 6.2)

Table 7 Risk Assessment

Identified and potential risks of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study Procedures		
Liver biopsy	• The most common risks associated with liver biopsy are mild pain and minimal bleeding at the procedure site. • Rare complications of liver biopsy include major bleeding (0.1%) and death (0.01%) (Nalbantoglu and Brunt 2014).	Risks associated with liver biopsy will be minimized by: • Requiring that each investigator or designee that obtains a liver biopsy is experienced and qualified to perform the procedure • Excluding patients with cirrhosis, hepatic decompensation, and/or coagulopathy (Section 5.2) • Checking relevant laboratory parameters prior to the procedure (eg, INR and platelet count) (Section 1.3)
Blood draws	Routine blood draws have a well-established risk profile.	The risk is addressed by following institutional standards.
Injection administration	• Pain at the injection site	• Pen device • Training in proper SC injection technique • Rotation of injection sites

GLP-1, glucagon-like peptide; INR, international normalized ratio; SC, subcutaneous

2.3.2 Benefit Assessment

There are currently no approved pharmacological therapies for NASH, with lifestyle modifications being the mainstay of treatment. Several factors have been shown to increase the risk of liver fibrosis progression to cirrhosis and eventual decompensation including presence of comorbid T2DM, increasing age, hypertension, and high BMI. The successful development of new therapies for NASH would address a high unmet medical need, particularly given the expected increasing burden of this disease in parallel with the rising global prevalence of obesity and especially T2DM. A significant unmet need exists among patients with NASH, especially those with comorbid obesity and T2DM, for treatments that simultaneously improve liver health, reduce CV and renal disease, provide glycemic control, and promote weight loss. In a Phase IIb study in participants with overweight or obesity and T2DM with prevalent NAFLD, treatment with cotadutide for 54 weeks resulted in significant decrease in HbA1c and body weight as well as improvements in triglycerides, AST and ALT levels, and indices of liver fibrosis such as propeptide of type III collagen level (Pro-C3), FIB-4 index, and NFS. In a Phase II study in overweight and obese participants with biopsy-proven non-cirrhotic NASH with fibrosis, statistically significant reductions in HFF, ALT, AST, Pro-

C3, and APRI from baseline to Week 19 (end of treatment) were observed for the 600 µg cotadutide group compared with placebo, and nominal reductions were observed for the 300 µg group. Changes in body weight and glycemia were generally consistent with prior observations within the program.

Participants randomized to the placebo control arm in the study may benefit from frequent medical monitoring, lifestyle coaching, and close assessment of their disease and associated pathologies that may not otherwise be performed, especially the identification of progression to cirrhosis.

2.3.3 Overall Benefit: Risk Conclusion

The study design aims to minimize potential risks to participants based on the protocol inclusion and exclusion criteria, safety monitoring, titrated dosing scheme, and other measures (Table 7). Taking into account the measures to minimize risk to participants in this study, the potential and identified risks associated with cotadutide are justified by the anticipated benefits that may be afforded to participants with non-cirrhotic NASH with stage F2 or F3 fibrosis.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1 Objectives and Endpoints: Part A

Table 8 Objectives and Endpoints: Part A

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. 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 ++ Electrocardiogram 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
• To assess the effect of cotadutide versus placebo on resolution of NASH and improvement in fibrosis	• Proportion of participants with both resolution of NASH and improvement in fibrosis by at least one stage based on biopsy at Week 48

• To assess the effect of cotadutide versus placebo on improvement in fibrosis by at least one stage	• Proportion of participants with improvement in fibrosis by at least one stage based on biopsy at Week 48
• To assess the effect of cotadutide versus placebo on improvement in NAS	• Proportion of participants with improvement in NAS based on biopsy at Week 48 • Change from baseline in NAS based on biopsy at Week 48
• To assess the effect of cotadutide versus placebo on change in fibrosis	• Change from baseline in fibrosis stage based on biopsy at Week 48 • Proportion of participants with progression, no change, or regression in fibrosis stage based on biopsy at Week 48
• To assess the effect of cotadutide versus placebo on improvement in each key histological feature of NASH	• Proportion of participants with improvement in key histological features of NASH based on biopsy at Week 48, including: ° Inflammation ° Steatosis ° Ballooning •
• To characterize using AI-based histology assessment the effect of cotadutide versus placebo on NASH histology, including: ° Resolution of NASH without worsening of liver fibrosis ° Improvement of liver fibrosis by at least one stage without worsening of NASH ° Resolution of NASH and improvement in fibrosis ° Improvement in fibrosis by at least one stage ° Improvement in NAS ° Change in fibrosis ° Improvement in each key histological feature of NASH	• AI-based histology assessment of: ° Proportion of participants with resolution of NASH without worsening of liver fibrosis based on biopsy at Week 48 ° Proportion of participants with improvement of liver fibrosis by at least one stage without worsening of NASH based on biopsy at Week 48 ° Proportion of participants with both resolution of NASH and improvement in fibrosis by at least one stage based on biopsy at Week 48 ° Proportion of participants with improvement in fibrosis by at least one stage based on biopsy at Week 48 ° Proportion of participants with improvement in NAS based on biopsy at Week 48 ° Change from baseline in NAS based on biopsy at Week 48 ° Change from baseline in fibrosis stage based on biopsy at Week 48 ° Proportion of participants with progression, no change, or regression in fibrosis stage based on biopsy at Week 48 ° Proportion of participants with improvement in histological features of NASH based on biopsy at Week 48, including: Inflammation Steatosis Ballooning

• To assess the effect of cotadutide versus placebo on circulating markers of hepatic inflammation	• Change from baseline in liver enzymes including ALT and AST through Week 48
• To assess the effect of cotadutide versus placebo on lipid profile and glycemic control	• Change from baseline in triglycerides, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, total cholesterol, and HbA1c through Week 48
• To summarize the PK profile of cotadutide	• Cotadutide PK exposure will be summarized and compared with prior data for consistency
• To assess the effect of cotadutide versus placebo on liver stiffness	• Change from baseline at Week 48 in: ° LSM as assessed by FibroScan ° Percentage CAP as assessed by FibroScan
• To assess the effect of cotadutide versus placebo on disease-specific biomarkers	• Changes from baseline at Week 48 in non-invasive disease-specific biomarkers, including but not limited to: ° Collagen turnover (Pro-C3) ° ELF score ° FIB-4 ° APRI ° NFS ° BARD score ° FAST score ° Agile 3+
• To determine whether cotadutide is superior to placebo for weight reduction	• Percent change from baseline in body weight at Week 48
• To assess the effect of cotadutide versus placebo on glucose, adiponectin, and C-peptide	• Change from baseline in fasting plasma glucose, adiponectin, and C-peptide at Week 48
• To determine whether treatment with cotadutide compared with placebo will result in a reduction of BP	• Change from baseline in SBP through 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; AI, artificial intelligence; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BARD, body mass index, AST/ALT ratio, diabetes; BP, blood pressure; CAP, controlled attenuation parameter; CV, cardiovascular; DBP, diastolic blood pressure; ECG, electrocardiogram; ELF, enhanced liver fibrosis; FAST, FibroScan-AST; FIB-4, fibrosis-4; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IP, investigational product; LDL, low-density lipoprotein; LSM, liver stiffness measurement; 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; NFS, non-alcoholic fatty liver disease fibrosis score; PK, pharmacokinetic(s); QTcF, Fridericia-corrected QT interval; SBP, systolic blood pressure

3.2 Objectives and Endpoints: Part B

Due to the decision to end recruitment into the study, Part B of the study will not be

conducted.

3.3 Estimands

The primary clinical questions of interest are:

Part A

In patients with non-cirrhotic NASH with liver fibrosis with a treatment strategy to titrate to a maximum dose of 300 or 600 µg cotadutide versus placebo, what is the difference in proportion achieving **resolution of NASH without worsening of liver fibrosis at Week 48** in patients regardless 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 primary estimands are described by the following attributes:

Population: Patients with non-cirrhotic NASH with liver fibrosis (F2 or F3), with or without T2DM.

Endpoints: Resolution of NASH without worsening of liver fibrosis at Week 48

Treatment condition: Treatment strategy to titrate to a maximum dose of 300 µg or 600 µg cotadutide or matching placebo. The planned titration schedule is described in Section 4.1, and possible modifications to the titration schedule are described in Section 6.6. Permitted concomitant medications are described in Section 6.5.1, and restricted or prohibited concomitant medications are described in Section 6.5.2.

- Treatment Policy Strategy: If a biopsy is obtained within the analysis window, the endpoint will be defined based on the observed biopsy result regardless of the occurrence of intercurrent events of treatment discontinuation, deviations from the protocol titration schedule, changes in background medication, liver event, or use of prohibited medications or other protocol deviations.

Population-level summary: Difference in proportion of responders

Rationale for estimand: The endpoints and intercurrent event strategies for the primary estimands are aligned to current regulatory guidance for investigation of non-cirrhotic NASH therapies.

4 STUDY DESIGN

4.1 Overall Design

This study was originally designed as a 2-part, Phase IIb/III, global, randomized, parallel-group, double-blind, placebo-controlled, multicenter, proof of concept study to assess the safety and efficacy of 300 and 600 µg cotadutide compared with placebo, given once daily as an SC injection administered via a multidose pen, in adults with non-cirrhotic NASH with fibrosis stage F2 or F3. After carefully considering several factors, foremost being the identification of other, more convenient treatments for patients with NASH, the sponsor made a strategic decision to discontinue development of cotadutide and recruitment into this study. Randomized participants and participants in active screening will be allowed to continue participation. Given the reduced sample size, the primary goal of this study is to evaluate the safety and tolerability of cotadutide in participants with non-cirrhotic NASH with fibrosis. The Phase III portion of the study (Part B) will not be conducted.

Part A (Phase II) will assess the safety and efficacy of 300 µg and 600 µg cotadutide treatment.

Participants will be ≥ 18 to ≤ 75 years of age (inclusive) with biopsy-proven NASH (historical biopsy performed ≤ 180 days from randomization or on-study biopsy) demonstrating a NAS ≥ 4 (with a score of at least 1 for each component: steatosis, lobular inflammation, and ballooning) and liver fibrosis stage F2 or F3. Approximately 600 participants will be screened/enrolled in the study (in approximately 20 countries) to achieve approximately 55 randomly assigned to study intervention.

At randomization, participants will be stratified by the presence/absence of T2DM and by fibrosis stage (Section 6.3.1). Participants will undergo dose titration steps every 4 weeks to reach the target dose of 300 µg or 600 µg qd. Dose titration will start from 50 µg cotadutide (or matching placebo) qd and increase to 100 µg qd after 4 weeks, and then increase by 100-µg increments every 4 weeks, until reaching the final intended dose at Week 12 for the 300 µg treatment groups and Week 24 for the 600 µg treatment groups. To mitigate the risk of gastrointestinal AEs, it is important to follow the 4-week dose escalation intervals (refer to Section 6.6 for dose modifications). Each cotadutide treatment group will be placebo-matched with respect to titration schedule and dose levels.

An independent DMC will be established to monitor data on an ongoing basis to ensure safety of participants enrolled in this study (Section 9.6).

Figure 1 (Section 1.1) is an overview of the study design. Details on treatments given during the study are presented in Section 6. Details on what is included in the efficacy and safety endpoints are presented in Section 3.

4.1.1 Part A Overall Design

Part A will evaluate whether treatment with cotadutide results in a significant improvement compared to placebo in the proportion of participants with resolution of NASH without worsening of liver fibrosis at Week 48. In Part A, 300 adult participants who are eligible according to the inclusion/exclusion criteria were planned to be 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. The representation by each fibrosis stage (F2 or F3) was to be capped at approximately 70%. Due to termination of recruitment, approximately 55 participants are planned to be randomized. Participants will be in the study for up to 1.2 years (60 weeks), including a screening period of up to 8 weeks, a 48-week treatment period, and a 4-week safety follow-up period. Participants will return unused study intervention at the end of treatment (or early discontinuation) visit, and assessments will be conducted as described in the SoA (Section 1.3). The follow-up visit should be scheduled to occur 4 weeks (± 5 days) later.

4.1.2 Part B Overall Design

Due to the decision to end recruitment into the study, Part B of the study will not be conducted.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Population

In order to focus on the patient population with the greatest need and potential effect on health (currently identified as the target population within NASH with fibrosis who warrant pharmacologic intervention), this study will be conducted in patients with non-cirrhotic NASH with liver fibrosis. Participants with biopsy-proven non-cirrhotic NASH with NAS ≥ 4 with a component score of ≥ 1 for steatosis, lobular inflammation, and ballooning, as well as liver fibrosis stage F2 or F3 on histology with or without T2DM will be recruited. Participants will be stratified based on fibrosis stage and the presence or absence of T2DM at randomization. Participants with stage F4 fibrosis (cirrhosis, compensated and decompensated) will not be included.

4.2.2 Rationale for Treatment Duration

Histological evidence of NASH resolution may be observed as early as 36 weeks after initiation of treatment (Harrison et al 2019). Therefore, a 48-week treatment period as proposed in Part A should be sufficient to detect a potential signal on NASH resolution, while also providing sufficient treatment exposure for safety monitoring.

4.2.3 Rationale for Endpoints

4.2.3.1 Rationale for Primary/Safety Endpoints

Standard safety endpoints will be assessed, including vital signs, ECG, safety laboratory analysis, AEs, and SAEs. Increases in heart rate have been observed in clinical studies conducted to date with cotadutide (studies D5670C00001, D5670C00002, and D5670C00004), accompanied by a trend toward a reduction in BP with repeat dosing. A particular focus on CV safety will involve monitoring of CV events, which will be adjudicated by an external, independent, and blinded events adjudication committee (Section 8.3.10).

The ADA and titer (if participants are ADA positive) will be used to assess potential immunogenicity in NASH.

4.2.3.2 Rationale for Exploratory Endpoints

The goal for therapies for NASH with fibrosis is to slow or reverse disease progression. However, rate of disease progression in NASH with fibrosis and event rates for liver outcomes require prolonged trial durations to evaluate and demonstrate improvements in liver outcome events. Histological features of NASH, including fibrosis, appear to have predictive value for liver outcomes and have been designated as surrogate endpoints of efficacy for novel NASH therapeutics. Therefore, improvements in histology-based endpoints in response to cotadutide treatment will be explored in this trial.

Currently applied manual methods of disease staging for NASH with fibrosis, particularly for staging of fibrosis, have limited sensitivity and reproducibility. AI-based methods are expected to provide improved sensitivity and reproducibility of histopathology reporting. AI-based histopathology assessments will be collected for all histology endpoints.

The endpoint on body weight will provide assessment of the beneficial effect of cotadutide on body weight in non-cirrhotic NASH with fibrosis and allow for correlation with improvement in NASH liver histology and other parameters related to metabolic control. Glycemic control as measured by HbA1c will be assessed in participants with T2DM as a high proportion of patients with NASH have comorbid T2DM. Evaluation of triglycerides will provide assessment of the beneficial effects of cotadutide on lipid profile in participants with NASH and attendant comorbidities.

Cotadutide is expected to lead to improvements in glucose and lipid homeostasis. Therefore, measures of metabolic homeostasis in circulation will be measured including but not limited to HbA1c, lipid profile, adiponectin, and C-peptide.

Although histology remains the preferred tool for diagnosis and assessment of treatment effects for NASH with fibrosis, given the invasive nature of a liver biopsy, there is a major unmet need to identify non-invasive tools that can reduce or replace the number of biopsies in

clinical trials. In order to validate and qualify one or more non-invasive tools for such purposes, these tools need to be calibrated against histology in both observational and interventional settings. It is also possible that the temporal profile for changes in these non-invasive markers may be faster than that for histology. Therefore, a number of non-invasive assessments of steatosis, steatohepatitis, and fibrosis will be performed throughout the course of this study. Data from these assessments are expected to inform on the value of each of these non-invasive tools as potential candidates to replace biopsy-based histology. Such data also carry the potential of being able to be deployed in clinical treatment settings to predict and monitor responsiveness to cotadutide therapy.

Hepatocellular injury will be assessed by liver enzymes (ie, ALT and AST). In addition, liver fibrosis will be assessed non-invasively by the ELF™ test, which is a composite measure of hyaluronic acid, TIMP-1, and the amino-terminal propeptide of type III procollagen (PIIINP).

Non-invasive imaging-based tools are emerging as potential candidates to inform on disease progression and treatment effects in NASH. FibroScan-based transient elastography and FibroScan-based markers (FAST score, Agile 3+ score) will be used to assess liver stiffness and related biology, indicators of reduced tissue elasticity associated with inflammation and fibrosis (LSM [kPa]), and independently of steatosis (CAP [dB/m]) as well.

A marker of collagen extracellular matrix turnover (specifically, released N-terminal propeptide of type III collagen [Pro-C3]) will be measured.

Various non-invasive indices such as FIB-4, APRI, BARD, NFS, FLI have been reported to have value for monitoring of disease and treatment response. These indices leverage routinely measured parameters and will be assessed in the current trial.

4.2.4 Participant Input into Design

During protocol development, the study team met with patients living with NASH to provide their feedback on the study. Five participants were interviewed from 3 countries (Italy, United States, United Kingdom). The visit schedule, visit procedures, and study burden were discussed to gain a better understanding of whether participants will be able to manage the visit schedule for the duration of the trial and whether the procedures would cause them to withdraw from the study. These interviews provided an opportunity for the patients to provide their input as a person living with NASH.

The following support will be added to the study based on patient input:

- The sites being considered for the study should have the capabilities to complete all the assessments at one location where possible as recommended by the patients.

- A digital platform will be included as part of study support to house study communication, information, and resources. Some sites will have their own platform and may prefer that method of communication to support their patients.
- The study team will work with local countries supporting the study at AstraZeneca to encourage an option for transportation support for patients and caregivers participating in the study (where acceptable for local ethics boards).
- The study team will work with sites to encourage reminders and stress the need for diabetic patients to have morning appointments while fasting. In addition, where allowed by local ethics boards, meals or snacks after fasting visits may be provided.

4.3 Justification for Dose

Observed and modeled data within the program have shown that while both the 300 µg and 600 µg doses lead to weight loss and glycemic control in obese and T2DM participants, respectively, the 600 µg dose appears to have more robust effects. Cotadutide led to beneficial effects on HFF, ALT, AST and body weight in non-cirrhotic NASH with fibrosis in PROXYMO, with robust effects at the 600 µg dose and more modest effects at the 300 µg dose (Section 2.2.2). Cotadutide 600 µg also led to improvements over baseline in high molecular weight adiponectin, non-invasive diagnostic score 4, APRI, and Pro-C3. Known translatability of decreases in non-invasive measures such as HFF, ALT, AST, Pro-C3, and APRI to improvements in histology and the totality of the efficacy data available together provide confidence that the 600 µg dose has the potential to deliver meaningful histologic and clinical benefits in NASH with fibrosis. While the 300 µg dose may have a less robust effect than the 600 µg dose, the 300 µg dose demonstrated benefit on liver-related biology in obese patients with T2DM when treated for up to 54 weeks. Therefore, the current trial will evaluate the treatment effects of the 300 µg and 600 µg doses in a population of non-cirrhotic NASH with fibrosis for up to 48 weeks. Importantly, the 300 µg and 600 µg dose levels were found to have an acceptable safety (including hepatic safety) profile in non-cirrhotic NASH with fibrosis and in previous trials in obesity and T2DM. Taken together it is reasonable to carry forward the 300 µg and 600 µg dose levels for further assessment in non-cirrhotic NASH with fibrosis.

To mitigate the risk of gastrointestinal AEs it is important to follow the 4-week dose escalation intervals. Dose titration will start from 50 µg, increase to 100 µg daily after 4 weeks, and then increase by 100 µg increments every 4 weeks, until reaching the final intended dose at Week 12 for the 300 µg treatment groups and Week 24 for the 600 µg treatment groups.

4.4 End of Study Definition

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs

under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last participant for any protocol related activity.

Food and Drug Administration requirements defines 2 completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the 4-week follow-up visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participant must be ≥ 18 to ≤ 75 years of age (inclusive) at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Histologically confirmed NASH per NASH Clinical Research Network criteria as diagnosed by histology from a liver biopsy performed ≤ 180 days from randomization and fulfilling all of the following histological criteria, read by a central pathology review committee:

   (a) NAS ≥ 4 with a score of ≥ 1 for each component: steatosis, lobular inflammation, and ballooning

(b) Presence of fibrosis stage F2 or F3

OR

(c) Willingness to undergo a liver biopsy at screening, result of which should fulfill the above histological criteria

Investigators should determine eligibility for liver biopsy on participants who are found to be eligible with respect to all other criteria, based on local procedures and clinical judgment, including the use of non-invasive techniques (such as FibroScan, FIB-4, and other clinical and laboratory-based measures).

3 HbA1c ≤ 10.5% in patients with T2DM managed on a stable dose of antidiabetic medication and/or diet for at least 90 days prior to screening. HbA1c testing may be repeated once.

Sex

4 Male or female (non-pregnant and non-breastfeeding)

Reproduction and Contraception

There is no requirement for male participants to alter their usual contraceptive practices. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

5 Female participants of childbearing potential must use at least one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Women of childbearing potential who are sexually active with a non-sterilized male partner must agree to use at least one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 4 weeks after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician. All WOCPB must have a negative serum pregnancy test result at Visit 1.

(a) Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

- Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and are found to have follicle-stimulating hormone levels in the postmenopausal range.

- Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

(b) Highly effective birth control methods include sexual abstinence (when this is the preferred and usual lifestyle of the participant), a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together, and neither is considered to be a highly effective birth control method.

6 Female participants must refrain from egg cell donation and breastfeeding while on study and for 4 weeks after the final dose of study intervention.

Informed Consent

7 Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

8 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 History of, or any existing condition that, in the opinion of the investigator, would interfere with evaluation of the study intervention, put the participant at risk, influence the participant's ability to participate, or affect the interpretation of the results of the study

2 Liver disease of other etiologies (eg, alcoholic steatohepatitis; drug-induced, viral, or autoimmune hepatitis; primary biliary cirrhosis; primary sclerosing cholangitis; hemochromatosis; alpha 1 antitrypsin deficiency; Wilson's disease). Participants cured of HCV infection less than 2 years prior to the Screening visit are not eligible

3 History of cirrhosis and/or hepatic decompensation, including evidence of portal hypertension (eg, low platelet count, splenomegaly, ascites, history of hepatic encephalopathy, esophageal varices, or variceal bleeding)

4 Prior or planned liver transplantation

5 Prior or planned bariatric surgery

6 Alcohol consumption > 21 units (units calculated per local regulations) per week (21 standard drinks per week) for men and > 14 units per week (14 standard drinks per week) for women on average within 2 years prior to baseline liver biopsy (historical or at screening). Evidence of alcohol dependence as assessed by the AUDIT questionnaire at screening

7 Type 1 diabetes mellitus, a history of diabetic ketoacidosis, or symptoms of acutely decompensated blood glucose control (eg, thirst, polyuria, weight loss)

8 History of acute pancreatitis (unless previously resolved gallstone pancreatitis and post cholecystectomy), or current chronic pancreatitis

9 Clinically significant inflammatory bowel disease, gastroparesis, or other severe disease or surgery affecting the upper gastrointestinal tract (including bariatric surgery) that may affect gastric emptying or could affect the interpretation of the safety and tolerability data

10 History of any of the following that in the opinion of the investigator is not stable within 90 days prior to the screening visit:
   (a) > 5% weight loss (self-reported or documented)
   (b) Treatment with glucose-lowering agent(s)
   (c) Treatment with lipid-lowering agent(s)
   (d) Participation in weight loss programs

11 Clinically significant CV or cerebrovascular disease within 90 days prior to screening, including but not limited to, myocardial infarction, acute coronary syndrome, unstable angina pectoris, transient ischemic attack, or stroke, or participants who have undergone percutaneous coronary intervention or a coronary artery bypass graft within the past 90 days or who are due to undergo these procedures at the time of screening

12 Cardiac arrhythmia
   (a) Second or third degree atrial ventricular block or sinus node dysfunction with clinically significant pause, not treated with pacemaker
   (b) Ventricular arrhythmia requiring treatment
   (c) Participants with atrial fibrillation/flutter with ventricular rate (> 100 bpm at rest)

13 Severe congestive heart failure (New York Heart Association Class IV)

14 History of malignant neoplasms within 5 years prior to screening, except for adequately treated basal cell, squamous cell skin cancer, or any in situ carcinoma

15 History of substance dependence or positive screen for drugs of abuse at screening or psychiatric disorder likely to impact participant safety or compliance with study procedures, at the discretion of the investigator

Prior/Concomitant Therapy

16 Recent (within 90 days of screening biopsy or historical biopsy through screening) use of therapies associated with development of NAFLD (eg, methotrexate, tamoxifen,

amiodarone, or long-term use of tetracyclines or systemic corticosteroids [inhaled, nasal, topical are allowed])

17 Recent (within 180 days of screening biopsy or historical biopsy through screening) use of obeticholic acid or other therapy under investigation for NASH

18 Pioglitazone or high dose vitamin E (> 400 IU) unless on a stable dose for at least 180 days prior to the baseline biopsy (either screening or historical) and not initiated after the biopsy was taken

19 Recent (within 90 days of screening biopsy or historical biopsy through screening) use of GLP-1 receptor agonist or GLP-1 receptor agonist containing therapies and weight loss medication(s) (approved and/or off-label use)

Prior/Concurrent Clinical Study Experience

20 Participation in another clinical study with an IP administered within the last 30 days or 5 half-lives of the therapy (whichever is longer) at the time of screening or the time of the historical biopsy, not covered under exclusion criteria 16 or 17

21 Concurrent participation in another interventional study of any kind or prior randomization in this study

22 Severe allergy/hypersensitivity to any of the proposed study treatments or excipients

Diagnostic Assessments

23 Contraindication to liver biopsy (eg, bleeding diathesis, such as hemophilia, suspected hemangioma, or suspected echinococcal infection) or inability to safely obtain a liver biopsy as determined by the investigator (Section 8.1.1)

24 Participants with serum triglyceride concentrations above 1000 mg/dL (11.3 mmol/L) at screening

25 Abnormal laboratory values at screening, including any of the following:

(a) AST or ALT $\geq 5 \times$ ULN

(b) Alkaline phosphatase $> 2 \times$ ULN

(c) Impaired renal function defined as eGFR $\leq$ 30 mL/minute/1.73 m^2 at screening (estimated according to the CKD Epidemiology collaboration) (Inker et al 2021)

(d) Albumin < 3.5 g/dL (35 g/L)

(e) INR $\geq$ 1.3

(f) TBL $\geq$ 1.3 mg/dL in the absence of known Gilbert's syndrome or in individuals with Gilbert's syndrome, TBL $\geq$ 3 mg/dL

(g) Platelet count $< 150 \times 10^3$ /µL

(h) Any other clinically significant abnormalities in serum chemistry, hematology, or urinalysis results as judged by the investigator

26 Severely uncontrolled hypertension defined as SBP ≥ 180 mmHg or DBP ≥ 110 mmHg on the average of 2 seated BP measurements after being at rest for at least 10 minutes at screening or randomization

27 Basal calcitonin level ≥ 50 ng/L (ie, ≥ 50 pg/mL) at screening, or history/family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 1 or multiple endocrine neoplasia type 2

28 Any positive results for HIV infection, positive results for hepatitis B surface antigen or hepatitis C antibody test along with a positive HCV RNA test

Other Exclusions

29 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

30 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements

31 Fibrosis stage F2 if the cap has been reached on F2 participants or fibrosis stage F3 if the cap has been reached on F3 participants

5.3 Lifestyle Considerations

5.3.1 Diet and Lifestyle Education

Diet and lifestyle education advice should begin at the screening visit for all participants. Participants will be advised to adhere to specific dietary and lifestyle recommendations from screening until the end of the safety follow-up period and will be reminded at each study visit. The guidance will be in accordance with the sites' local processes.

In addition to the scheduled clinic visits, investigators may contact participants during the titration phase by telephone. During the telephone contacts, participants should be asked about their general wellbeing and reminded to adhere to diet and lifestyle advice. Participants should also be counseled about mitigation of gastrointestinal side-effects.

5.3.2 Meals and Dietary Restrictions

Participants should fast overnight for at least 8 hours, ie, no food or beverage except water, prior to study site visits according to the SoA (Section 1.3).

5.3.3 Alcohol

Participants should withhold alcohol for 24 hours prior to each study site visit.

5.3.4 Activity

Participants should refrain from intense exercise for 24 hours prior to each study site visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study during the 56-day screening period (screen failure) may be rescreened if the reason for screen failure was transient (including but not limited to laboratory tests or unforeseen personal events that mandate missed screening visits as determined by and at the discretion of the investigator documenting a rationale for rescreening). Rescreening may be considered at any time prior to randomization and in particular, although not limited to, for reasons related to the COVID-19 pandemic (ie, lack of available kits, local lockdowns and imposed quarantines). Up to 2 rescreenings are allowed in the study. Rescreened participants should re-sign informed consent on the rescreening visit. If a participant is rescreened, he/she must continue to meet all inclusion/exclusion criteria. Procedures performed within 56 days from randomization that meet the eligibility criteria should not be repeated.

Participants who do not meet one or more of the central laboratory criteria for complete blood count with platelets, INR, ALT, AST, alkaline phosphatase, and TBL may have their applicable laboratory test(s) retested once as part of the screening procedure if the reason for failing the laboratory criteria was transient (as determined by and at the discretion of the investigator documenting a rationale for retest). If they fail twice to meet the applicable laboratory criteria during the screening period, they may still be rescreened.

Participants who do not meet the central HbA1c inclusion criteria for participation in the study may have their HbA1c retested once as part of the screening procedure. If they fail twice to meet the HbA1c inclusion criterion during the screening period, they may still be rescreened but no sooner than 12 weeks following the date of the second failed test.

For participants for whom rescreening or retest is considered and for whom a historical biopsy was already submitted for central eligibility read, it is recommended that sites wait for the central histopathology eligibility read report prior to scheduling a rescreening or retest visit.

In the event the historical biopsy is deemed not evaluable and the site has determined that no additional historical samples are available for an additional central pathology review and a participant screen fails, participant may be rescreened and an on-study liver biopsy may be scheduled only if the on-study liver biopsy is scheduled for a date that is ≥ 180 days after the date of the historical biopsy and after all other screening procedures are completed and once it

has been confirmed that the participant meets all other inclusion/exclusion criteria.

Rescreened participants should be assigned the same participant number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol. Study intervention in this study refers to cotadutide or placebo.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Intervention name	Cotadutide	Placebo
Type	Drug and Device Combination	Drug and Device Combination
Dose formulation	Solution for injection[a]	Solution for injection[a]
Unit dose strength(s)	Multidose prefilled pen device containing 2.7 mL at a concentration of 1 mg/mL for doses 50-100 µg. Multidose prefilled pen device containing 2.7 mL at a concentration of 5 mg/mL for doses 200-600 µg.	Multidose prefilled pen device containing 2.7 mL at a concentration of 1 mg/mL for doses 50-100 µg. Multidose prefilled pen device containing 2.7 mL at a concentration of 5 mg/mL for doses 200-600 µg.
Dosage level(s)	50 to 600 µg once daily	Matched to 50 to 600 µg cotadutide once daily
Route of administration	Single SC injection	Single SC injection
Administration instructions	One single injection per calendar day, preferably at the same time of the day following guidance in the IFU	One single injection per calendar day, preferably at the same time of the day following guidance in the IFU
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	Study intervention will be provided in a carton [a]. Each carton	Study intervention will be provided in a carton [a]. Each carton

Intervention name	Cotadutide	Placebo
	and prefilled pen will be labeled as required per country requirement.	and prefilled pen will be labeled as required per country requirement.
Current/former name(s) or alias(es)	MEDI0382	NA

[a] Both the liquid drug product and prefilled pen constitute the investigational product. AEs and SAEs that occur with the investigational product should be reported per the processes outlined in Section 8.3.

AE, adverse events; IFU, instructions for use; IMP, investigational medicinal product; NA, not applicable; NIMP, non-investigational medicinal product; SAE, serious adverse event; SC, subcutaneous

6.1.2 Medical Devices

Medical devices (stand-alone medical device products) not manufactured by or for AstraZeneca but provided for use in this study are:

1 Professional, multichannel electrocardiograph devices for cardiac safety monitoring (MAC2000). Electrocardiographs will be delivered only to sites participating in Part A of the study.

2 Laboratory kits that include tubes, butterflies, urine containers, glass slides, and other items required to collect blood and urine samples that will be evaluated by central laboratory.

3 Single-use disposable pen needles to be used with pen injection devices (applicable only for countries where it is not possible to locally reimburse the cost of needle purchase).

Medical devices will be used per manufacturer's instructions, which will be provided to the sites prior to site initiation visit. All device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (Section 8.3.13) and appropriately managed by the sponsor.

6.2 Preparation/Handling/Storage/Accountability

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

5 Participants will be supplied with cooling bags, needles, alcohol wipes, and biohazard bags to properly administer the study intervention and return used pens to the sites. Sharps containers will be provided to patients for safe needle disposal. Sponsor will reimburse the cost of needles and alcohol wipes. Biohazard bags, cooling bags and sharps containers will be supplied by the sponsor.

At screening, the investigator will assess whether the participant is able to self-administer SC injection. Participants will be trained on proper SC injection technique at Visit 1 (screening) or at Visit 2 prior to randomization (Section 1.3). For handling of study intervention and instructions on administration, see the Instructions for Use. Study intervention should be stored at the recommended storage conditions according to the label. Storage conditions are also to be found in the Instructions for Use.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method for Assigning Treatment Groups

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the log-in information and directions for the IRT/RTSM will be provided to each site.

A participant is considered randomized into the study when the investigator notifies the IRT/RTSM that the participant meets eligibility criteria and the IRT/RTSM provides the assignment of blinded IP kit numbers to the participant.

In Part A, participants will be randomized 2:1:2:1 to receive cotadutide 300 µg, placebo matching cotadutide 300 µg, cotadutide 600 µg, or placebo matching cotadutide 600 µg. The randomization will be stratified by the presence/absence of T2DM and by fibrosis stage.

T2DM at the time of randomization is based on:

- Established diagnosis of T2DM
  OR
- HbA1c ≥ 6.5% (48 mmol/mol) by central laboratory assessment at Visit 1

Study intervention will be dispensed at the study visits summarized in Section 1.3.

Returned study intervention should not be re-dispensed to the participants.

6.3.2 Methods to Ensure Blinding

The IRT/RTSM will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each site.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.3.3 Methods for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

6.3.3.1 Unblinding for Analysis

After all participants of the study have completed the study, a database lock will be performed and the data will be unblinded and analyzed.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will self-administer the study intervention under medical supervision from the investigator or designee. The date and time of dose administered in the clinic will be recorded in the source documents and in the eCRF.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by the investigator or designee by counting the returned unused pens during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen based on patient recall should be recorded in the eCRF.

It is not recommended to inspect by opening used/returned pens, so it is particularly important to discuss with the patient at each visit whether he/she has used the medicine on a daily basis, in the prescribed dose, and whether the medicine has been stored under appropriate conditions. If there is a suspicion that a patient is not using the correct dose or is not administering the drug regularly, retraining and discussion with the patient should take place. If, despite additional training, the patient still does not comply with the investigator's instructions, discontinuation of study intervention should be considered (Section 7.1).

A record of the number of pens dispensed to each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The study physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “excluded” as listed in Section 6.5.2. Specifically, participants with T2DM should continue to take their antidiabetic medication at the regular dose prescribed and any other medication prescribed for the treatment of comorbidities associated with T2DM. When intensifying T2DM treatment during the trial, investigators should follow guidelines such the American Diabetes Association and European Association for the Study of Diabetes treatment guidelines or other similar regionally accepted treatment guidelines.

Participants should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Participants should receive care for hypertension and CV risk factors according to local guidelines.

Participants on a stable dose (for at least 180 days) of pioglitazone or high-dose vitamin E (> 400 IU) at the time of the baseline biopsy will be permitted to remain on this medication during the course of the study, provided no changes are made to the dose.

6.5.2 Prohibited Concomitant Medications

Participants must be instructed not to take any medications, including NASH-related over-the-counter products, without first consulting with the investigator

Use of the following medications will be restricted (Table 9) or prohibited (Table 10) as specified:

Table 9 Restricted Medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it is allowed):
Systemic corticosteroids by oral, intravenous, or intramuscular route	Not to be used within 90 days prior to baseline biopsy (historical or screening) and during the study unless prescribed for a very brief period of less than 14 days
Prokinetic agents such as domperidone and metoclopramide	Only to be used during the study for the treatment of nausea and vomiting if a centrally acting antiemetic is deemed ineffective or not tolerated by the participant
Analgesics and antipyretics	Careful use of paracetamol (acetaminophen) is allowed, not to exceed 3 g/d

Table 10 Prohibited Medications

Prohibited medication/class of drug:	Usage
Therapies associated with development of NAFLD such as methotrexate, tamoxifen, amiodarone, or long-term use of tetracyclines or systemic corticosteroids	Within 90 days prior to baseline biopsy (historical or screening) until the end of the study. Systemic corticosteroid and tetracycline use are restricted during the study unless prescribed for a very brief period of ≤ 14 days.
Therapies in classes under investigation for the treatment of NASH (except for SGLT-2 inhibitors), such as obeticholic acid, pioglitazone, and Vitamin E	Within 180 days of baseline biopsy until the end of the study. In the case of pioglitazone or high-dose vitamin E, these drugs are restricted during the study unless the participant has been on a stable dose for at least 180 days prior to baseline biopsy (historical or on-study). Potential drugs with new regulatory approvals for the treatment of NASH with fibrosis stage F2/F3 could be considered after discussion with study physician, if the investigator deems it not to be safe for the participant to postpone the start of such treatment until study end.
GLP-1 receptor agonists and GLP-1 receptor agonist containing therapies	Within 90 days of baseline biopsy (historical or on-study) until the end of the study

Table 10 Prohibited Medications

Prohibited medication/class of drug:	Usage
Drugs approved for weight loss (eg, orlistat, bupropion/naltrexone, phentermine-topiramate, phentermine, lorcaserin), as well as those drugs used off-label	Concurrent or previous use within 90 days of baseline biopsy (historical or on-study) until the end of the study
Herbal preparations or dietary supplements marketed for control of body weight or appetite or with any suspected hepatotoxicity	Concurrent or prior use in the period starting within 14 days prior to the start of screening and for the duration of the study. Furthermore, starting new herbal preparations or dietary supplements of any kind is not allowed once screening activities are initiated.

GLP-1, glucagon-like peptide-1; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SGLT-2, sodium-glucose co transporter 2

If any unintentional use of a prohibited medication occurs, consult with the AstraZeneca study physician for a case-by-case resolution.

6.5.3 Management of Nausea and Vomiting

If a participant experiences nausea or vomiting in relation to study intervention, in the first instance, conservative measures should be advised, including reducing meal size and maintaining adequate hydration. If there is persistent vomiting, a participant may be given an antiemetic to control his/her symptoms; a 5-hydroxytryptamine-3 receptor antagonist (eg, ondansetron) or anti-histamine (eg, cyclizine) is preferable rather than antiemetics, which may affect gastric emptying, and dopamine receptor antagonists (eg, metoclopramide or domperidone). Investigators should monitor participants with vomiting for signs of hypovolemia. Participants with impaired renal function could be especially sensitive to hypovolemia; such participants should be informed about the importance of adequate hydration in case of nausea and vomiting. These participants should also undergo additional laboratory testing for potential creatinine increases as appropriate. Additional laboratory testing will be recorded in the eCRF.

6.5.4 Management of Type 2 Diabetes Mellitus

6.5.4.1 Use of Medications Known to Cause Hypoglycemia in Type 2 Diabetes Mellitus

Insulin and insulin secretagogues are known to cause hypoglycemia. Therefore, patients treated with insulin or sulfonylurea have a higher risk of experiencing hypoglycemic events compared with those treated with other antidiabetic agents. Investigators should consider insulin and sulfonylurea dose reduction for any participant whom they consider may be at risk of hypoglycemia upon initiation of study intervention.

6.5.4.2 Therapies for Management of Type 2 Diabetes Mellitus

Participants with T2DM should be managed on a stable dose of antidiabetic (glucose-

lowering) medication and/or diet for at least 90 days prior to screening (Section 5.1). Minimal change (≤ 20%) to the total daily insulin dose within the 90-day period prior to screening will not be considered exclusionary. For participants with T2DM, additional management of glycemic control should be according to local guidelines as required. Details concerning permitted and prohibited therapies for the management of T2DM are provided in Table 11.

Table 11 Permitted and Prohibited Therapies for the Management of Type 2 Diabetes Mellitus

Permitted therapies	Prohibited therapies
• Any type of insulin • Biguanides • Sulfonylurea • Glitinide • Acarbose/alpha-glucosidase inhibitors • SGLT2 inhibitor • DPP-4 inhibitor	• GLP-1 analog • GLP-1 analog/insulin combination (eg, IDegLira) • Pramlintide

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide; SGLT2, sodium-glucose cotransporter 2

6.5.4.3 Management of Hypoglycemia

A hypoglycemic event is considered severe if associated with severe cognitive impairment requiring external assistance for recovery, as defined by the American Diabetes Association; clinically significant hypoglycemia is defined as a capillary or venous plasma glucose reading of < 3.0 mmol/L (54 mg/dL). Few events of clinically significant hypoglycemia (< 3 mmol/L) have been reported in participants treated with cotadutide up to 300 µg. All participants with T2DM will be advised to check their capillary plasma glucose level if they have symptoms of hypoglycemia (hunger, dizziness, shaking, sweating, or irritability) or feel unwell. Local protocols for treatment and follow-up of any hypoglycemic episode should be followed. Any clinically significant hypoglycemia (glucose < 3.0 mmol/l) should be reported by investigators as an AE regardless of whether the participant is experiencing symptoms or not. Pharmacological treatments administered for hypoglycemia (eg, dextrose/glucose tablets, glucagon, etc) should be recorded in the eCRF as concomitant medications. When possible, participants with T2DM should be prioritized for early/morning visits on days when the participant is fasting (Section 1.3).

6.5.4.4 Management of Hyperglycemia

When hyperglycemia is suspected, if deemed appropriate by the investigator and in accordance with local T2DM guidelines, additional venous fasting plasma glucose measurements may be performed. In addition, home glucose and urine ketone monitoring to be performed by participants as directed by the investigator based on local clinical practice.

In participants who have sustained hyperglycemia, the following options are preferred:

- An increase in insulin (if used)
- Open-label changes to antidiabetic therapy such as uptitration of sulfonylurea/glitinide dose (if these agents were dose adjusted at the beginning of the study)

Additional drugs listed under the permitted therapies in Table 11 may also be used at the discretion of the investigator or the participant's general practitioner. Any changes should be documented in the relevant section of the eCRF.

6.6 Dose Modification

It is strongly recommended that the investigator make every effort to work with the participant to uptitrate to the target dose.

If a participant is unable to successfully uptitrate to 200 µg or needs to reduce the dose below 200 µg, they should discontinue treatment with study intervention. The lowest target dose of IP allowed for a participant to continue in the study is 200 µg.

Once the participant uptitrates to the 200 µg dose, in the event the participant experiences significant tolerability issues during the uptitration or maintenance phase, the investigator may allow the participant to remain at the current dose level for up to 14 days if a dose uptitration step is imminent, before resuming the uptitration regimen, without it constituting a deviation from the protocol.

Once the participant uptitrates to the 300 µg dose, in the event the participant experiences significant tolerability issues during the uptitration or maintenance phase, the investigator may reduce the dose level to the previous titration step for 14 days or remain at the current dose level for up to 14 days if a dose uptitration step is imminent, before resuming the uptitration regimen, without it constituting a deviation from the protocol.

The investigator may contact the sponsor for assistance with questions related to titration and tolerability. For management of conditions other than nausea and vomiting, dose reductions of cotadutide may be considered following discussion with the sponsor. Any sponsor agreed dose modification will not constitute a protocol deviation.

6.7 Missed Dose

If a participant forgets to inject a study intervention dose, the dose can be administered as soon as the participant remembers. However, if it is more than 12 hours since the participant should have administered the dose, the participant should skip the missed dose and take the next dose as usual on the following day. Please note that when taking the next dose after a missed dose, participant should not take a double dose to make up for the missed dose.

If a participant has missed several consecutive doses of study intervention, there might be a

risk for increased nausea when the participant restarts treatment. Therefore, the investigator should consult with the sponsor for guidance on restarting treatment.

Any interruption of the IP for 7 consecutive days during the uptitration phase or for 14 days during the treatment period (after reaching the target dose of 300 or 600 µg) will constitute an important protocol deviation.

6.8 Treatment of Overdose

For this study, any dose of cotadutide greater than 600 µg within a calendar day will be considered an overdose.

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the sponsor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate. Refer to Section 8.3.12.5 for details of AE/SAE reporting related to overdose.

6.9 Intervention After the End of the Study

There is no intervention following the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. Participants who discontinue study intervention early will have an early discontinuation visit as described in the SoA (Section 1.3). After the early discontinuation visit, participants will be encouraged to remain in the study for all remaining visits and study procedures as outlined in the SoA, with the exception of the urine pregnancy test, dispensation of study intervention and Instructions for Use, and PK sampling. Participants will be encouraged to have the biopsy at Week 48 as planned in the SoA. Participants who are unwilling or unable to wait until Week 48 will have the biopsy procedure as part of the early discontinuation visit if they have received study intervention for at least 36 weeks. Samples for clinical safety laboratory assessments, amylase and lipase, coagulation parameters, and calcitonin do not need to be collected at visits occurring more than 30 days after discontinuation of study intervention except as needed for lab abnormalities/AEs that require follow-up to resolution.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

An individual participant will not receive any further IP if any of the following occur:

- Withdrawal of consent/assent from further treatment with IP.
- Lost to follow-up.
- Noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits).
- Pregnancy in a female participant.
- An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing; specific examples include:
  - Clinically significant tachyarrhythmias, including but not limited to life-threatening arrhythmia, eg, sustained ventricular tachycardia or ventricular fibrillation.
  - Acute pancreatitis
    - Participants will be instructed to contact the investigator or other healthcare provider if they experience persistent severe abdominal pain, with or without vomiting, because this is the hallmark symptom of acute pancreatitis warranting prompt evaluation of serum amylase and lipase and prompt abdominal ultrasound. If pancreatitis is suspected, study medication should be discontinued. If pancreatitis is confirmed, appropriate treatment should be initiated, and the participant should be carefully monitored until recovery.
  - Suspected or confirmed diagnosis of DILI
    - In case a participant shows an AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN, refer to Appendix E. Figure 2 and Figure 3 provide additional guidance in evaluating for DILI in this study population.

Refer to the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and 4-week follow-up.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons (after discussion with the sponsor). This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

- Refer to SoA for data to be collected at the time of study withdrawal and 4-week follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to be lost to follow up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

The COVID-19 pandemic and associated guidelines, recommendations, national laws, and local restrictions are constantly evolving. Thus, where possible, other measures for carrying out protocol-related activities, such as but not limited to home nursing, may be required to ensure participant safety.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1 Efficacy Assessments

8.1.1 Liver Biopsy-based Histopathology

Liver biopsy samples taken at baseline (either historical [collected within 180 days of randomization] or taken during the screening period), at Week 48, or at Early Discontinuation will be assessed centrally by a Central Pathology Review Committee to determine the NAS and fibrosis staging. Details of liver biopsy procedure are described in the Histopathology Manual.

8.1.2 Artificial Intelligence-based Histopathology

Artificial intelligence-based histopathology assessments will be conducted for all histology endpoints related to NAS and fibrosis staging (Bosch et al 2021, Taylor-Weiner et al 2021) at the time points specified in Section 1.3.

8.1.3 FibroScan and FibroScan-derived Biomarkers

FibroScan® will be used to assess liver stiffness and CAP at sites where it is feasible to do so, at the time points specified in Section 1.3. If a site has access to appropriate FibroScan equipment, as well as compatible software and probes, they must complete the assessments per the schedule. If not and the assessment cannot be conducted, this will not constitute a deviation from the protocol. The LSM must be performed in a fasting state and according to site standard procedures. At sites with FibroScan equipment with CAP option available, measurements of liver steatosis must be performed at the specified visits. FibroScan-derived biomarkers will be assessed. FAST score (a combination of FibroScan-derived CAP, LSM, and AST level) and Agile 3+ score (a combination of FibroScan-derived LSM, AST, ALT, platelet, age, sex, and diabetes status) will be calculated for participants at sites that have the required software or access to the website.

8.1.4 Height and Weight

Standing height and body weight will be measured at the time points specified in the SoA (Section 1.3).

Height will be measured once at screening only and recorded in centimeters.

The participant's weight should be measured after the participant has removed bulky clothing including shoes. The participant's body weight will be recorded in kilograms to 1 decimal place. Whenever possible, the same scale should be used throughout the study and calibrated on a regular basis as recommended by the manufacturer.

8.1.5 Exploratory Biomarker Assessments

Table 12 presents protocol-defined exploratory biomarker assessments. These assessments will be made in accordance with the Laboratory Manual and Section 1.3.

Table 12 Exploratory Biomarker Assessments

Assessment	Biomarker
Hepatic inflammation	ALT and AST (Section 8.2.5)
Disease-specific biomarkers	Collagen turnover: Pro-C3 ELF™ (components): PIIINP, hyaluronic acid, and TIMP-1 FIB-4 index (components): platelet count, ALT, AST APRI (components): AST, platelet count NFS (components): ALT, AST, platelet count, albumin BARD score (components): ALT, AST FAST score [a] (components): CAP, LSM, AST (Section 8.1.3) Agile 3+ [a] (components): LSM, AST, ALT, platelet count, age, sex, diabetes status (Section 8.1.3)
Glucose control	HbA1c, fasting plasma glucose, adiponectin, C-peptide
Blood pressure	SBP (Section 8.2.3)
Lipids	Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, non-HDL cholesterol
Optional biomarkers (serum based)	Biomarker research, including markers disease status and response to cotadutide (Section 8.5.2)

[a] FAST score and Agile 3+ will be calculated only at sites that have the required software.
ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BARD, body mass index, AST/ALT ratio, diabetes; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis score; FAST, FibroScan-AST; FIB-4, fibrosis-4; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LSM, liver stiffness measurement; NFS, non-alcoholic fatty liver disease fibrosis score; PIIINP, amino-terminal propeptide of type III-procollagen, Pro-C3, released N-terminal propeptide of type III collagen; SBP, systolic blood pressure; TIMP-1, tissue inhibitor of metalloproteinase type-1

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Medical History

Complete medical history will include history and current medical conditions; past or present CV disorders; respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, or any other diseases or disorders; drug and surgical history; and history of alcohol and tobacco use. If the participant reports a history of gallbladder ultrasound performed < 12 months prior to screening, the ultrasound report should be obtained and should be noted on the eCRF. Presence or absence of gallbladder disease/cholelithiasis should be noted for all participants and recorded on the eCRF.

The AUDIT questionnaire (Appendix F) to assess alcohol use habits will be completed at screening only (Section 1.3). The results will be used for determining participant eligibility (Section 5.2).

8.2.2 Physical Examinations

Physical examination will be performed at timepoints as specified in Section 1.3.

- A full physical examination will be performed and include assessments of the following: general appearance including skin inspection, lymph nodes, thyroid, musculoskeletal/extremities, CV system, lungs, abdomen, and reflexes.
- An abbreviated physical examination will include, at a minimum, assessments of the skin, extremities, CV system, lungs, and abdomen.

Clinically significant abnormalities in physical examination findings at study termination must be followed up by the investigator and evaluated with additional tests/procedures if necessary, until the underlying cause is diagnosed or resolution occurs. As appropriate, the diagnosis and resolution date of the physical examination abnormalities must be reported as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses. New or worsening abnormalities may qualify as AEs; additional details are provided in Section 1.3.

8.2.3 Vital Signs

Vital sign measurements (SBP, DBP, pulse, body temperature, and respiratory rate) will be obtained in accordance with appropriate guidelines after the participant has rested in the seated position for at least 10 minutes in a quiet setting without distractions at the visits specified in Section 1.3.

Vital sign measurements should be taken prior to IP administration (where applicable) and before blood drawing. BP and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not

available. BP readings should be taken while the participant is in a comfortable seated position with the arm supported at the level of the heart. At screening the seated BP will be recorded 2 times in both the left and the right arms. The 2 measurements should be made in 1 arm before transferring the cuff to the other arm. Whenever possible, the arm with the highest mean seated systolic BP readings will be the one used for all subsequent readings throughout the study.

At each study visit, after the participant has rested in the seated position for at least 10 minutes, 3 consecutive BP readings will be taken at intervals of at least 1 minute and recorded in the eCRF.

If BP is uncontrolled at study entry, investigators should carefully monitor the BP levels according to applicable guidelines, with consideration for the individual patient and potential comorbidities. BP treatment should be optimized to reduce the overall CV risk.

Route of body temperature measurement will be according to local procedures but should be consistent throughout the study for an individual participant.

8.2.4 Electrocardiograms

ECGs will be recorded at the sites using 12-lead ECG recorders in the supine position after the participant has been resting for at least 10 minutes, according to the SoA (Section 1.3). The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

Digital ECGs will be recorded in triplicate on standardized study ECG machines and assessed centrally.

Standardized 12-lead digital ECG equipment and all requisite hook up supplies will be provided. ECGs will be uploaded via a secure portal for high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment. Where digital transmission is not possible, a process for receipt and analysis of scanned or paper ECGs is also established.

Confirmed ECGs will be available on a study portal within the contracted turnaround time.

On-screen measurements of the RR, PR, QRS, and QT interval durations will be performed, and variables for QTcF, QTcB, and heart rate will be calculated. Each fiducial point (onset of P wave, onset of Q wave, offset of S wave, and offset of T wave) will be electronically marked. The original ECG waveform and such annotations will be saved separately in XML format for independent review.

The investigator or authorized delegate will make an initial assessment of whether the ECG

findings are normal or abnormal and if abnormal, clinically significant or not. In the case of a discrepancy between the investigator's initial assessment and the central ECG reading, the central reading will take precedence.

If a site requires expedited reporting for ECGs due to suspected ECG abnormalities or for urgent decision making, the site should contact the ECG provider per instructions to request expedited ECG processing.

In case of an ECG device malfunction, the site should follow the steps recommended within the Cardiac Safety Study Manual in order to have the ECG analyzed in a timely manner.

8.2.5 Clinical Safety Laboratory Assessments

The clinical chemistry, hematology and urinalysis assessments will be performed at a central laboratory. A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study. Blood and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis will be collected at the visits indicated in the SoA (Section 1.3).

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. The investigator should follow all clinically significant laboratory abnormalities occurring during the study that were not present at baseline. These abnormalities should be evaluated with additional tests, if necessary, until the underlying cause is diagnosed, or resolution occurs. The diagnosis and resolution date must be reported to the sponsor.

Information about how AEs based on laboratory tests should be recorded and reported are provide in Section 8.3.5.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date of collection will be recorded on the appropriate eCRF.

Laboratory variables to be measured are listed in Table 13.

Table 13 Laboratory Safety Variables

Hematology/hemostasis (whole blood)	Clinical chemistry (plasma or serum)
B-Hemoglobin	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatase
B-Platelet count	S/P-AST

Table 13 Laboratory Safety Variables

B-Red blood cell count	S/P-ALT
B-Hematocrit	S/P-Albumin
B-Mean corpuscular hemoglobin concentration	S/P-Potassium
B-Mean corpuscular volume	S/P-Calcium, total
B-Red cell distribution width	S/P-Sodium
B-Red blood cell morphology	S/P-Blood urea nitrogen
	S/P-Phosphorous
Urinalysis (dipstick)	S/P-Bicarbonate
U-Hemoglobin/erythrocytes/blood	S/P-Glucose
U-Protein	S/P-Chloride
U-Microscopic analysis (if positive for blood, nitrites, or protein)	S/P-GGT
U-Glucose	
U-Ketones	
U-pH	
U-Specific gravity	
U-Bilirubin	
U-Color	
U-Appearance	
U-Nitrites	
U-Leukocytes	
U-Urobilinogen	
U-Drugs of abuse, standard panel (Screening only)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; B, blood; GGT, gamma glutamyl transferase; P, plasma; S, serum; U, urine

NB. In case a participant shows an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN please refer to Appendix E. Actions required in cases of increases in liver biochemistry and evaluation of HL, for further instructions. Figure 2 and Figure 3 provide additional guidance in evaluating for DILI in this study population.**Reproduction (Female Participants of Childbearing Potential Only)**

- Serum beta-hCG at screening only
- Urine hCG, by dipstick, thereafter
- Follicle-stimulating hormone at screening only (if not measured in the previous 12 months)

Additional Laboratory Assessments

Safety

- Serum calcitonin
- Serum amylase and lipase
- HBsAg, anti-HCV, HCV RNA (screening only)
- HIV-1 and HIV-2 antibodies (screening only)
- Coagulation parameters (prothrombin time, activated partial thromboplastin time, and INR)
- MELD score (composite of INR, sodium, bilirubin, and creatinine)
- Direct bilirubin (in the presence of Gilbert's syndrome)
- eGFR (CKD-EPI creatinine formula [Inker et al 2021])

8.2.6 Other Safety Assessments

8.2.6.1 Assessment of Injection Sites

Site staff will assess the injection site for injection site reactions at the times specified in the SoA (Section 1.3). Injection site reactions will be recorded as AEs. The site of injection should be rotated to avoid previously injected sites. In the case of an injection site reaction, these should be initially managed with a cold compress. Symptomatic treatment with antihistamines may be required in the presence of itching, and/or topical corticosteroids to reduce erythema and tenderness, particularly if the reaction progresses over several days. Oral nonsteroidal anti-inflammatory therapy may also be considered.

8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE. Information about how to follow up AEs is provided in Section 8.3.2.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected from the time of signing of the ICF throughout the treatment period and the 4-week follow-up period.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs/SAEs that are unresolved at the participant's final visit of the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

'The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP(s) (yes or no)
- Investigator causality rating against the study procedure(s) (yes or no)
- Action taken with regard to IP(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between Investigational Product, study procedure, medical device and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication, study procedures, or medical devices. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: "Have you had any health problems since the previous visit?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the IP or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally

related to the disease under study.

8.3.6 Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the IP and may require close monitoring and collection of additional information by the investigator. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP.

Adverse events of special interest for this study include:

- Nausea
- Vomiting
- Increased heart rate
- Injection site reaction
- Blood pressure alteration (hypotension/hypertension)
- Hypoglycemia
- Diabetic ketoacidosis
- Anti-drug antibody
- Pancreatitis
- Pancreatic carcinoma
- Thyroid carcinoma
- Acute renal failure secondary to dehydration
- Drug-induced liver injury
- Cardiovascular events
- Gallbladder-related disease

These AESIs are to be reported as described in Section 8.3.1 and Section 8.3.2. Information on AESIs of hypoglycemia, diabetic ketoacidosis, injection site reaction, pancreatitis, pancreatic carcinoma, thyroid carcinoma, drug-induced liver injury, and CV events should be reported in the appropriate eCRF. Participants with significant vomiting should be monitored for electrolytes. Refer to Section 6.5.3 for a discussion of gastrointestinal tolerability and mitigating strategies. Hepatic enzyme abnormality meeting the definition of PHL is also considered an AESI. Refer to Section 8.3.8 for the definition and reporting of AESIs of hepatic enzyme abnormality.

Refer to the IB for a discussion of potential risks.

8.3.7 Adverse Events Related to Liver Biopsy

Signs or symptoms suggestive of liver biopsy complication (eg, pain, bleeding [intraperitoneal hemorrhage, hematoma, hemobilia], etc) should be reported as AEs or SAEs, as applicable.

8.3.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Figure 2, Figure 3, and Appendix E for further instruction on cases of increases in liver biochemistry and evaluation for HL.

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture system, an automated email alert is sent to the designated AstraZeneca representative.

If the electronic data capture system is not available, then the investigator or other study site staff reports the SAE via secure method to the appropriate AstraZeneca representative.

When the electronic data capture system is temporarily not accessible, the AstraZeneca Study Representative should confirm that the investigator/site staff enters the SAE in the AstraZeneca electronic data capture system when access resumes.

For further guidance on the definition of an SAE, refer to Appendix B. The reference document for definition of expectedness/listedness is the IB.

8.3.10 Clinical Events for Adjudication

A CEA committee, blinded to the treatment of the participant, will independently adjudicate certain clinical AEs. The CEA committee will operate in accordance with the CEA Charter and Event Handling Manual for sites and site monitors.

The CEA committee will adjudicate events possibly related to the following:

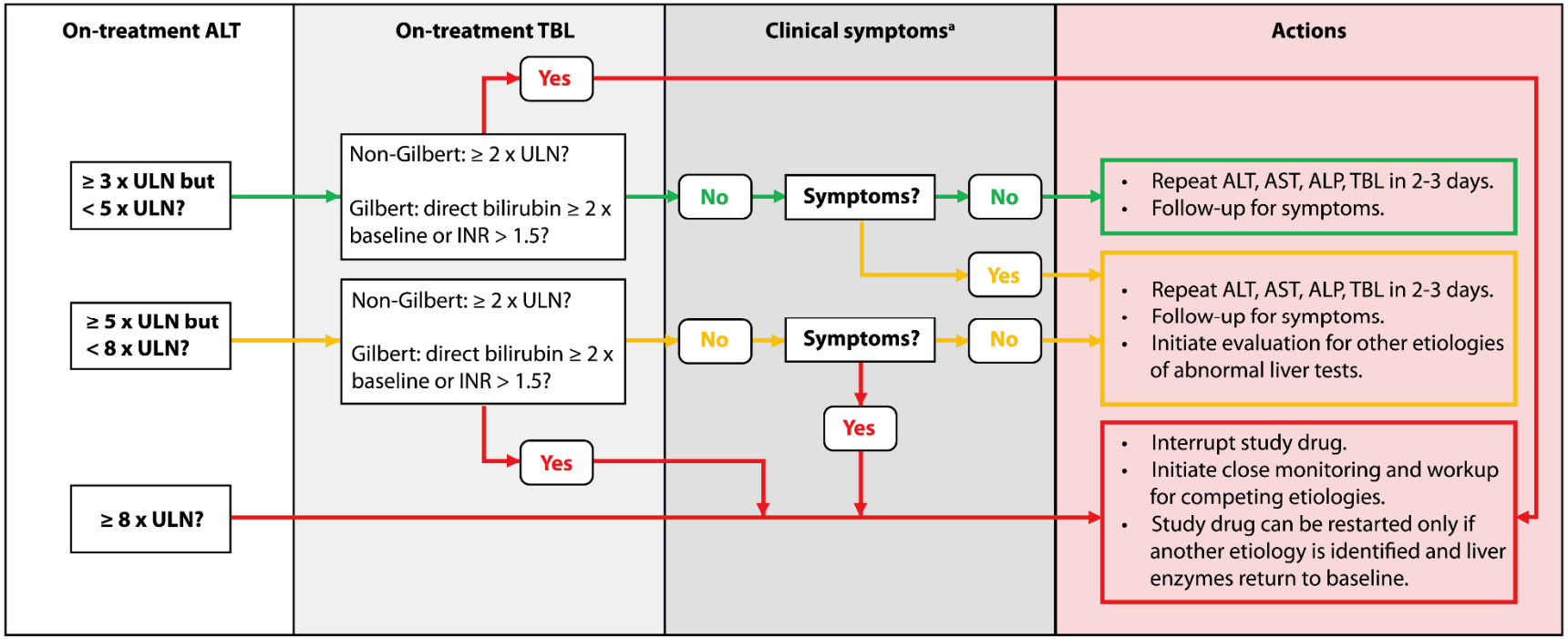
1 Events of hepatic decompensation include:
   (a) Clinically apparent ascites requiring treatment
   (b) Complication of ascites (eg, spontaneous bacterial peritonitis, diuretic-resistant ascites [refractory ascites], hepato-pleural effusion)
   (c) Hepatic encephalopathy of Grade 2 or above (according to the West Haven criteria as defined in Appendix G) requiring treatment
   (d) Portal hypertension-related upper gastrointestinal bleeding identified by endoscopy and requiring hospitalization, including events of bleeding from esophageal varices, gastric varices, and portal hypertensive gastropathy
   (e) Liver transplantation or qualification for liver transplantation, defined as a MELD score ≥ 15 on at least 2 consecutive occasions at least 4 weeks apart
2 Clinical cirrhosis
3 Events of suspected DILI
4 Hepatocellular carcinoma
5 All deaths (and CV deaths)
6 Cardiac ischemic events:
   (a) Myocardial infarction
   (b) Hospitalization for unstable angina
7 Cerebrovascular events:
   (a) Stroke
8 Hospitalization for heart failure
9 Diabetic ketoacidosis
10 Events of thyroid carcinoma, pancreatitis, and pancreatic carcinoma

For all Clinical Events identified for adjudication, the investigator will complete the appropriate modules of the eCRF and provide source documentation. In order to provide the independent adjudication committee with appropriate and adequate information for adjudication of the listed events, consult the CEA Charter and Event Handling Manual for Sites and Monitors.

Possible cases of DILI will be monitored and managed using the algorithm described in

Figure 2 and Figure 3, which is based on the IQ DILI Initiative consensus guideline (Regev et al 2019) as well as Appendix E, which will be used for the reporting of PHL cases.

Figure 2 Stopping Criteria and Dose Adaptations for Possible Hepatocellular DILI in Participants with Normal/Near Normal ALT at Baseline

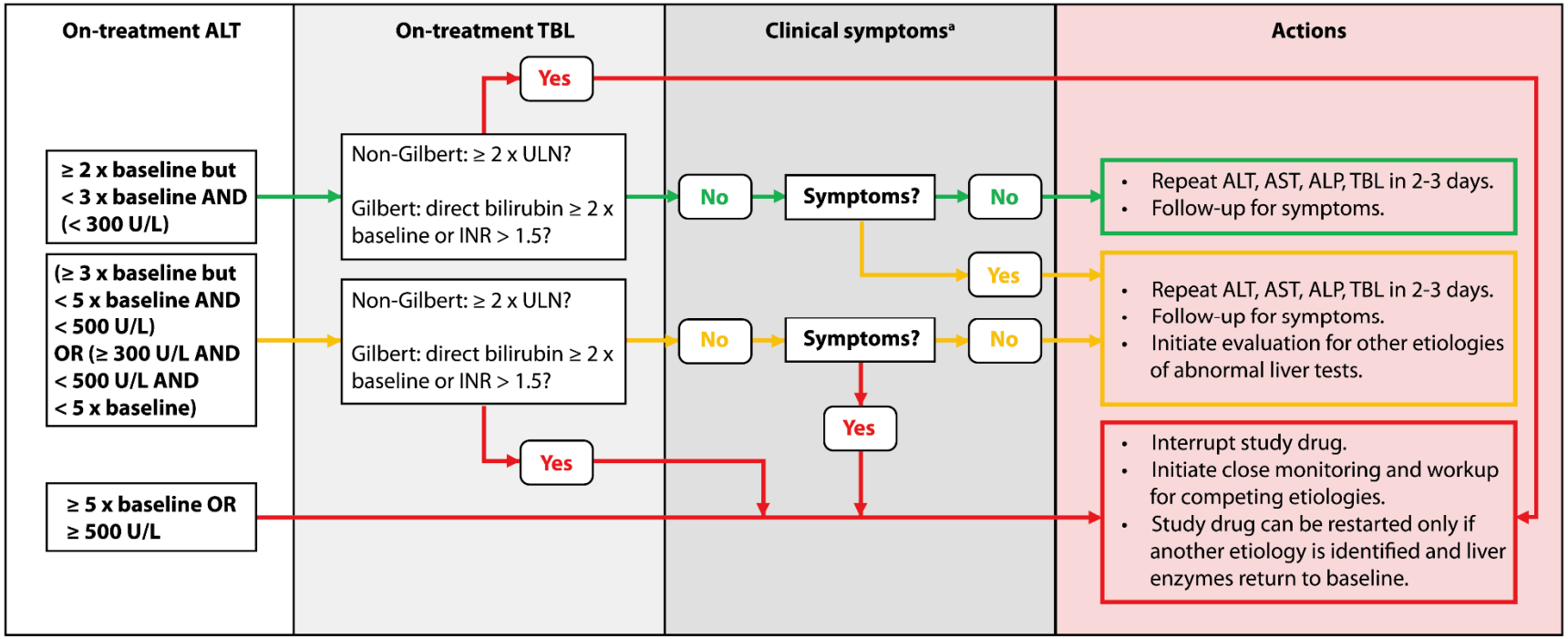


[a] Liver-related symptoms include: severe fatigue, nausea, vomiting, right upper quadrant pain.

Baseline pretreatment ALT is derived from the average of the last ALT measurement prior to randomization and the randomization visit (V2) based on central laboratory assessments. Elevated baseline is defined as ALT > 1.5 × ULN.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; INR, international normalized ratio; TBL, total bilirubin; ULN, upper limit of normal

Figure 3 Stopping Criteria and Dose Adaptations for Possible Hepatocellular DILI in Participants with Elevated ALT at Baseline



[a] Liver-related symptoms include: severe fatigue, nausea, vomiting, right upper quadrant pain.

Baseline pretreatment ALT is derived from the average of the last ALT measurement prior to randomization and the randomization visit (V2) based on central laboratory assessments. Elevated baseline is defined as ALT > 1.5 × ULN. If on treatment a participant has 2 or more consecutive ALT values at scheduled visits based on central laboratory assessments, each less than 50% of the baseline ALT and they are within 40% of each other (with percentage calculated based on the larger value as the denominator), then a new baseline should be set to be the minimum of the latest consecutive pair of values that are "stable" (ie, within 40% of each other).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; INR, international normalized ratio; TBL, total bilirubin; ULN, upper limit of normal

8.3.11 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

8.3.11.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.12 Medication Error, Drug Abuse, and Drug Misuse

8.3.12.1 Timelines

If an event of medication error, drug abuse, or drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up

Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (Section 8.3.9) and **within 30 days** for all other medication errors.

8.3.12.2 Medication Error

For the purposes of this clinical study, a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition of medication error can be found in Appendix B 4.

8.3.12.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition of drug abuse can be found in Appendix B 4.

8.3.12.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition of drug misuse can be found in Appendix B 4.

8.3.12.5 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP or AstraZeneca NIMP occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (Section 8.3.9) and **within 30 days** for all other overdoses.

8.3.13 Medical Device Deficiencies

As described in Section 6.1.2, third-party medical devices will be supplied under the study protocol.

In this study any deficiency observed with a third-party medical device will be collected and reported to the manufacturer.

A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

The AstraZeneca medical device complaint report will be used to collect the deficiency.

8.4 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples refer to Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.4.1 Pharmacokinetics

- Plasma samples will be collected for measurement of concentrations of cotadutide as specified in Section 1.3.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons. The timing

of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

- Plasma samples will be used to analyze the PK of cotadutide. Samples collected for analyses of cotadutide plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.4.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be collected at time points listed in Section 1.3 and assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated bioanalytical methods. Tiered analyses will be performed to include screening, confirmatory, and titer assay components. Assessment of cross-reactivity to GLP-1 and glucagon may be performed on samples that are confirmed positive for ADA.

ADA samples may also be further tested for characterization of the ADA response. Additional analyses may be conducted on anonymized, individual or pooled immunogenicity samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.4.3 Pharmacodynamics

8.5 Human Biological Sample Biomarkers

8.5.1 Collection of Mandatory Samples for Biomarker Analysis

Required samples for biomarker research (Section 8.1.5) will be collected from all participants

in this study as specified in the SoA (Section 1.3).

Analysis of biosamples may be performed for safety analytes or for biomarkers or analytes that may play a role in NASH and related conditions including but not limited to their association with disease progression and observed clinical responses to cotadutide. The results of this biomarker research may be reported either in the CSR or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies to generate hypotheses to be tested in future research.

8.5.2 Collection of Optional Biomarker Samples

Collection of optional samples for biomarker research is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement to optional consent. Optional blood samples will be collected, and analysis may be performed for safety analytes or for biomarkers thought to play a role in NASH and related conditions including, but not limited to, their association with disease progression and observed clinical responses to cotadutide. Optional biomarker samples will be collected according to local regulatory approval.

8.6 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA and is subject to agreement in the ICF addendum. A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study. Refer Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual. For storage and destruction of genetic samples refer to Appendix D.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

For the primary safety objective, analyses will compare cotadutide treatment to placebo. The exploratory efficacy analyses will test the null hypotheses of no treatment effect for cotadutide versus placebo in the FAS.

9.2 Sample Size Determination

Approximately 7440 participants were originally planned to be screened/enrolled to achieve 1860 randomly assigned to study intervention, including 300 in Part A. However, this study has prematurely stopped randomization as the cotadutide program has been discontinued. The sample size for this study includes approximately 55 randomized participants. The original

sample size calculations for Part A are detailed below.

In Part A, 300 participants were originally to be randomized in a 2:1:2:1 ratio. Approximately 100 participants were planned for each for each dose of cotadutide and 50 participants for each matching placebo group. This sample size was derived with respect to the comparison of each cotadutide group to the pooled placebo group for the proportion of participants with resolution of NASH without worsening of liver fibrosis at Week 48. The sample size would provide > 90% power for the test of each dose versus placebo to detect a difference of 20% in NASH resolution assuming a placebo response rate of 15%. The calculations assumed a 2-sided alpha level of 0.05.

The effects were assumed after any impacts from treatment discontinuation, early withdrawal, missing data imputation, etc. The assumed effect sizes for the histology-based endpoints took into account the PROXYMO interim analysis results as well as the published effects for a GLP-1 receptor agonist (Newsome et al 2021).

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study but are not randomly assigned/assigned in the study, are considered "screen failures."

9.3 Populations for Analyses

The following populations are defined:

Table 14 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants randomized into the study.
FAS	All participants who have been randomized to and received at least one dose of IP.
PP	Subset of FAS population with evaluable post-baseline biopsy after at least 36 weeks of treatment.
Safety	The Safety analysis set consists of all participants who have received at least one dose of IP. Erroneously treated participants (eg, those randomized to treatment A but actually given treatment B) are accounted for in the treatment group with the majority of estimated usage. In all cases, the dose level for analysis will correspond to the randomized dose.
PK	The PK population includes all participants who receive at least 1 dose of study intervention and have at least 1 complete intended PK sample containing detectable cotadutide concentrations.

FAS, full analysis set; ICF, informed consent form; IP, investigational product; PK, pharmacokinetic(s); PP, per protocol

9.4 Statistical Analyses

This section is a summary of the planned statistical analyses of the endpoints. A more technical and detailed description of the statistical analyses will be provided in the SAP.

9.4.1 General Considerations

The primary analyses will be of safety. No formal hypothesis testing will be performed. Treatments will be compared in tables using descriptive statistics.

Exploratory efficacy analyses will use nominal 2-sided 5% significance levels (equivalent to nominal 1-sided 2.5% significance levels) unless otherwise stated.

The primary estimand of interest for the histological endpoints will use 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 will also be used to handle the intercurrent events for continuous endpoints.

Participants will be analyzed according to their randomized IP assignment and dose, irrespective of the treatment they actually received. Analyses will be performed using the FAS and/or per protocol analysis sets, as appropriate (Table 14). The FAS will include all randomized and treated participants who received at least one dose of IP irrespective of their protocol adherence, addition or modification of background medications, discontinuation of study intervention or switches to alternative medications, and continued participation in the study.

9.4.2 Efficacy

The following exploratory endpoints will be analyzed descriptively versus placebo with 95% CIs at the nominal 2-sided alpha 5% level:

- Resolution of NASH at Week 48 without worsening of fibrosis
- Improvement in fibrosis at Week 48 without worsening of NASH
- Resolution of NASH and improvement in fibrosis at Week 48
- Improvement in fibrosis by at least one stage at Week 48
- Change from baseline in triglycerides, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, total cholesterol, and HbA1c through Week 48

Additional exploratory endpoints and their analyses will be detailed in the SAP.

The binary endpoint(s) will be analyzed using a Cochran-Mantel-Haenszel test with stratification by T2DM presence and F2/F3 fibrosis stages. The treatment effects will be summarized by the difference in proportions, 95% CI, and p-value. For the exploratory analysis of binary histological endpoints using FAS, participants with no liver outcome and missing histology data due to any reason may be imputed as non-responders.

Continuous endpoints (absolute change in body weight, change in HbA1c, percent change in triglycerides) will be analyzed using Analysis of Covariance models, adjusting for baseline value, presence of T2DM, and fibrosis stage (F2/F3). For the primary analyses of these endpoints, missing data will be imputed via multiple imputations.

9.4.3 Safety

Safety analyses will be performed using the safety analysis set. Safety data will be presented using descriptive statistics unless otherwise specified and will not be formally tested.

Safety events and findings will be summarized by treatment group. Erroneously treated participants (eg, those randomized to treatment A but actually given treatment B) are accounted for in the treatment group with the majority estimated usage. The majority estimated usage will be determined based on which treatment had more kits dispensed (not including kits returned unused). In the case of a tie, the randomized treatment will be used for safety analyses. In all cases, the dose group will be the same as randomized dose level.

Adverse Events

Adverse events will be coded using the most recent version of the MedDRA that will have been released for execution at AstraZeneca. AEs will be presented for each treatment group by SOC and/or Preferred Term covering number and percentage of participants reporting at least one event and number of events where appropriate. Exposure-adjusted incidence rates may be provided as appropriate. Only treatment-emergent AEs will be summarized.

An overview of AEs will present the number and percentage of participants with any AE, AEs with outcome of death, serious AEs, AEs leading to discontinuation of IP, and AEs leading to dose reduction of IP for each treatment group.

Separate AE tables will be provided taking into consideration the relationship as assessed by the investigator, maximum intensity, seriousness, death and events leading to discontinuation of IP as well as AESIs.

In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of participants in any treatment group.

Vital Signs

Vital sign parameters will be presented for each treatment group. Summary statistics for

continuous variables cover n, mean, SD, min, median, and max.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

A frequency table will be presented with the number of participants reporting at least one on-treatment abnormality.

Laboratory

Laboratory parameters will be presented for each treatment group. Summary statistics for continuous variables will cover n, mean, SD, min, median, and max. Frequency tables will cover number and percentage of participants in the respective category.

For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry and hematology parameters will be presented for observed values and change from baseline.

A frequency table will present number of participants reporting at least one treatment emergent change in laboratory parameters outside predefined criteria.

Elevation in liver parameters for assessment of HL will be reported appropriately if potential cases have been identified during the course of the study.

Electrocardiogram

ECG parameters will be presented for each treatment group. Summary statistics for continuous variables will cover n, mean, SD, min, median and max. Frequency tables will cover number and percentage of participants in the respective category. The (uncorrected) QT interval will be corrected according to the Fridericia's formula. Parameters to be tabulated are listed in Section 3.1.

For each scheduled post-baseline assessment, descriptive statistics for all ECG parameters will be presented for observed values and change from baseline. Additionally, summaries will be made of all ECG parameters fulfilling potentially clinically significant criteria during the treatment period.

9.4.4 Analysis of Pharmacokinetics and Immunogenicity

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of participants who develop detectable ADAs against cotadutide. The immunogenicity titer, and ADA cross-reactive to GLP-1 and glucagon will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK and safety will be evaluated, if data allow. Sparsely collected plasma concentrations will be descriptively summarized. Any issues considered to impact the PK data (such as, but not limited to participants not receiving complete/full intended cotadutide dose) may result in the

exclusion of concentration data from the PK analysis or exclusion from the PK summaries or descriptive statistics, the reason(s) for exclusion will be documented. The available concentration data for any participants excluded from the PK data summaries or descriptive statistics will be listed. If data are used in the population PK and the exposure-response analyses, the results will be reported in a separate report.

9.5 Interim Analyses

Not applicable.

9.6 Data Monitoring Committee

An independent DMC will be established to monitor data on an ongoing basis to ensure the safety of participants enrolled in this study and the integrity of the study. The DMC will meet periodically during the study to review the safety data and operate according to the procedures and processes described in full detail in the DMC charter.

For details on the DMC, refer to Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

Data Monitoring Committee

An independent DMC will be appointed and will report to AstraZeneca. The DMC will be responsible for safeguarding the interests of the participants in the study by assessing the safety of the study intervention during the study. The DMC will have access to the individual treatment codes and be able to merge these with the collected study data while the study is ongoing.

A DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with AZ. The DMC will ensure that the study meets high standards of ethics and patient safety.

Clinical Event Adjudication

The role of the CEA is to independently review, interpret and adjudicate the types of events experienced by the participants listed in Section 8.3.10. Events for adjudication will be identified preliminarily by the investigators, and also by AstraZeneca personnel, or in the CEA process as specified in the CEA charter. The CEA member(s) will not have access to individual treatment codes for any participant. The precise responsibilities and procedures applicable for CEA will be detailed in the CEA charter.

A 6 Dissemination of Clinical Study Data

For scientific reasons (as otherwise statistical analysis is not relevant), any results for this study (both technical and lay summaries) will be submitted to EU CTIS within a year from the global End of Study date in all participating countries.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management, Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and Protocol Deviations Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the required retention period (https://www.astrazenecapersonaldataretention.com/patients.html) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in GCP, ie, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is when the first participant is screened, which will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support

publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above

Adverse events for **malignant tumors** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of

intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough

information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication

- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes

- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

Where required, AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening, or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in healthcare and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary

withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main Clinical Study Protocol.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants at Visit 2. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study, the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative

component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study center. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, or general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

Specific guidance on managing liver anomalies can be found in Sections 7.1 and 8.3.10 of the Clinical Study Protocol.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law

Aspartate Aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study intervention irrespective of an increase in ALP.

Hy's Law

AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases eg, elevated ALP indicating

cholestasis, viral hepatitis, or another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met; where this is the case the investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results, the investigator will without delay:

- Determine whether the participant meets PHL criteria (refer to Section E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which of the tests available in the HL lab kit should be used.
  - Complete the 3 Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from

date PHL criteria was met. The AstraZeneca Global Clinical Head or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE, update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Intervention

This section is applicable to participants who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of PHL criteria being met, the investigator will determine if there has been a **significant change** in the participants' condition[#] compared with the last visit where PHL criteria were met[#]

- If there is no significant change, no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section E 4.2

E 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on-study intervention visit

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection, or liver disease?

If **No**: follow the process described in Section E 4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the participant's condition[#] compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change,[#] follow the process described in Section E 4.2 for reporting PHL as an SAE.

[#] **A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of

whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the Study Physician if there is any uncertainty.

E 8 Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive
[c] CD-transferrin is not available in China. Study teams should amend this list accordingly

Appendix F Alcohol Use Disorder Identification Test (AUDIT)

Subject Number:	Visit Number:	Assessment Date:

The Alcohol Use Disorders Identification Test: Interview Version

Read questions as written. Record answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks." Place the correct answer number in the box at the right.

1. How often do you have a drink containing alcohol? (0) Never [Skip to Qs 9-10] (1) Monthly or less (2) 2 to 4 times a month (3) 2 to 3 times a week (4) 4 or more times a week	6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
2. How many drinks containing alcohol do you haveon a typical day when you are drinking? (0) 1 or 2 (1) 3 or 4 (2) 5 or 6 (3) 7, 8, or 9 (4) 10 or more	7. How often during the last year have you had a feeling of guilt or remorse after drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
3. How often do you have six or more drinks on one occasion? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily *Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0*	8. How often during the last year have you been unable to remember what happened the night before because you had been drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily	9. Have you or someone else been injured as a result of your drinking? (0) No (2) Yes, but not in the last year (4) Yes, during the last year
5. How often during the last year have you failed to do what was normally expected from you because of drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily	10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down? (0) No (2) Yes, but not in the last year (4) Yes, during the last year
	Record total of specific items here *If total is greater than recommended cut-off, consult User's Manual.*

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Scoring the AUDIT Questionnaire

Scores for each question range from 0 to 4, with the first response for each question (eg, never) scoring 0, the second (eg, less than monthly) scoring 1, the third scoring 2, the fourth scoring 3, and the last response (eg, 4 or more times a week) scoring 4. For questions 9 and 10, which only have 3 responses, the scoring is 0, 2, and 4. A score of 8 or more is associated with harmful or hazardous drinking, a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.

Definition of a standard drink

In the AUDIT questions 2 and 3, it is assumed that a standard drink equivalent is 10 grams of alcohol. The alcohol content of a drink depends on the strength of the beverage and the volume of the container. The investigator should adjust the number of drinks in the response categories for these questions in order to fit the most common drink sizes and alcohol strength in their country.

Appendix G West Haven Criteria for Hepatic Encephalopathy

Grade	Description
I	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction
II	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior
III	Somnolence to semi-stupor Responsive to stimuli Confused Gross disorientation Bizarre behavior
IV	Coma

Appendix H Abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug antibody
AE	adverse event
AI	artificial intelligence
ALT	alanine aminotransferase/transaminase
ANA	antinuclear antibody
APRI	AST-to-platelet ratio index
AST	aspartate aminotransferase/transaminase
AUDIT	Alcohol Use Disorder Identification Test
BARD	BMI, AST/ALT ratio, diabetes
BMI	body mass index
BP	blood pressure
CAP	controlled attenuation parameter
CEA	clinical event(s) adjudication
CKD	chronic kidney disease
CRO	contract research organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTIS	Clinical Trial Information System
CV	cardiovascular
DBP	diastolic blood pressure
DES	data entry site
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
FAS	full analysis set
FAST	FibroScan-AST
FDA	United States Food and Drug Administration
FIB-4	fibrosis-4
GCP	good clinical practice
GGT	gamma glutamyl transferase

Abbreviation or special term	Explanation
GLP-1	glucagon-like peptide 1
HbA1c	hemoglobin A1c
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
HFF	hepatic fat fraction
HIV	human immunodeficiency virus
HL	Hy's Law
IB	Investigator's Brochure
IATA	International Airline Transportation Association
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
LDL	low-density lipoprotein
LSM	liver stiffness measurement
MACE	major adverse cardiovascular event
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
min	minimum
NAFLD	non-alcoholic fatty liver disease
NAS	non-alcoholic fatty liver disease activity score
NASH	non-alcoholic steatohepatitis
NFS	non-alcoholic fatty liver disease fibrosis score
PHL	potential Hy's Law
PK	pharmacokinetic(s)
QTcF	Fridericia-corrected QT interval
RTSM	randomization and trial supply management
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation or special term	Explanation
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SoA	schedule of activities
SOC	System Organ Class
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TIMP-1	tissue inhibitor of metalloproteinase type-1
ULN	upper limit of normal
WOCBP	women of childbearing potential

Appendix I Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

Clinical Study Protocol Version 2

Overall Rationale for the Amendment:

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. The principal reason for this amendment is to address feedback from the FDA on the study protocol in its entirety including revision of the study design of Part A to remove the 36-week extension period. The primary intent for the 36-week extension period of Part A was to collect additional comparative safety data, especially cardiovascular events; however, with only 300 participants, it is unlikely that a significant number of cardiovascular events would be observed during the extension period. The 36-week extension was also removed to enable full read out and closure of Part A prior to read out of Part B. This will further help delineate the Phase IIb portion from the Phase III portion of the trial. The amendment also includes other changes aimed at clearer articulation of inclusion/exclusion criteria and potential operational simplifications, both based on feedback from study investigators.

Substantial changes to the protocol are summarized below.

Section # and Name	Description of Change and Brief Rationale
Section 1.1 (Synopsis), Section 1.2 (Schema), Table 5 (Part A Schedule of Activities), Section 4.1.1 (Part A Overall Design), Section 4.1.3 (Adaptation Considerations and Dose Selection in Part B), Section 6.3.3.1 (Unblinding for Part A Analysis), Section 6.3.3.2 (Unblinding for Part B Analysis), Section 9.4.1 (General Considerations), Section 9.4.1.1 (Possible Adaptations for Part B), Section 9.5 (Interim Analysis)	• Removed the 36-week extension in Part A because it is unlikely that a significant number of cardiovascular events would be observed during the extension period. • Removed the interim analysis from the study because the Week 48 analysis of Part A will now be a complete analysis of the Part A data after database lock. Text on adaptive actions resulting from analysis of Part A has been moved from Section 9.5 (Interim Analysis) to Section 9.4.1.1 (Possible Adaptations for Part B). • Adjusted wording on blinding of Part A because of the elimination of the 36-week extension. After database lock, sites, participants, and sponsor will be unblinded.
Section 1.1 (Synopsis), Section 5.1 (Inclusion Criteria), Section 8.1.1 (Liver Biopsy-based Histopathology)	Updated the timeframe for historical biopsy in the inclusion criteria so that it is only defined from the time of randomization to provide clarity.
Section 1.1 (Synopsis), Section 4.1 (Overall Design), Section 9.2 (Sample Size Determination)	The estimated number of participants to be screened was increased from 3500 to 7440 to reflect updated estimate of the screen failure rate.

Section # and Name	Description of Change and Brief Rationale
Section 1.1 (Synopsis), Section 9.4.1 (General Considerations)	• The strategy for the primary estimand of histology endpoints was clarified to be a hybrid of the treatment policy and composite strategies. • The strategy for intercurrent events for liver outcomes was clarified.
Section 1.3.1 (Schedule of Activities: Screening), Table 6 (Part B Schedule of Activities), Section 3.2 (Objectives and Endpoints Part B), Section 4.2.3.3 Rationale for Exploratory Endpoints, Section 5.1 (Inclusion Criteria), Section 7.1 (Discontinuation of Study Intervention), Section 8.1.3 (MRE/MRI)	The substudy in Part B to assess endpoints using MRI, MRE, and abdominal ultrasound was removed to enhance operational feasibility of the study and focus on the primary objectives. The abdominal ultrasound is replaced by the collection of additional baseline data on gallbladder health in all study participants, which will provide a more thorough knowledge base than performing ultrasounds in a sub population.
Section 1.3.1 (Schedule of Activities: Screening), Section 8.2.5 (Clinical Safety Laboratory Assessments)	Removed assessment of blood alcohol at screening. Alcohol dependence will be based on urine ethanol drug screen and AUDIT questionnaire, which determines participant eligibility over the past 2 years, rather than a blood test, which only reflects recent alcohol consumption.
Section 1.3.1 (Schedule of Activities: Screening)	• Description of the timing of the biopsy and collection of tissue from a historical biopsy were edited to clarify that tissue must be sent for central evaluation at least 21 days from planned randomization to allow enough time for histopathology assessment. • Clarified that on-study biopsy tissue must be submitted to the central histopathology review laboratory at least 21 days prior to planned randomization.
Section 1.3.1 (Schedule of Activities: Screening), Table 5 (Part A Schedule of Activities), Table 6 (Part B Schedule of Activities), Section 6.2 (Preparation/Handling/Storage/Accountability)	Edited to allow training activities related to subcutaneous administration to be completed on Visit 2 (randomization day) to allow more flexibility to sites and participants.
Section 1.3.1 (Schedule of Activities: Screening), Table 5 (Part A Schedule of Activities), Table 6 (Part B Schedule of Activities), Section 3.1 (Objectives and Endpoints: Part A), Section 3.2 (Objectives and Endpoints: Part B), Section 4.2.3.3 (Rationale for Exploratory Endpoints); Section 8.1.8 (Exploratory Biomarker Assessments)	Reduced the list of exploratory biomarkers to be assessed to reduce the blood volume required for study participants. The study will still retain optional serum samples for exploratory purposes, and therefore additional biomarker analysis can be conducted post hoc.

Section # and Name	Description of Change and Brief Rationale
Section 1.3.1 (Schedule of Activities: Screening), Table 5 (Part A Schedule of Activities), Table 6 (Part B Schedule of Activities), Section 8.1.3 (Fibroscan)	• Clarified that FibroScan and FAST score assessment are only required at sites with software and probes and for participants who do not have a historical FibroScan within 90 days. • Added that FibroScan assessment must be conducted in a fasted state. • Clarified FibroScan visit windows.
Section 1.3.1 (Schedule of Activities: Screening)	Changed the requirement for discussion of alternative pre-biopsy screening strategy with sponsor to a recommendation to allow more flexibility.
Table 5 (Part A Schedule of Activities)	Clarified that participants who discontinue study intervention and have an early discontinuation visit in Part A should also have a follow-up visit 4 weeks later.
Table 5 (Part A Schedule of Activities), Table 6 (Part B Schedule of Activities)	Added a review of adherence to diet and lifestyle advice to Visit 9 and Visit 11 for both Part A and Part B to ensure consistency with Section 5.3.1 (Diet and Lifestyle Education).
Table 5 (Part A Schedule of Activities), Table 6 (Part B Schedule of Activities), Section 8.5.2 (Collection of Optional Biomarker Samples)	Removed optional biomarker plasma collection to reduce blood volume and burden on participants.
Table 5 (Part A Schedule of Activities), Table 6 (Part B Schedule of Activities)	Added text describing scheduling of Visit 2 (randomization) to clarify that the visit can occur after confirmation that the participant meets all eligibility criteria.
Table 5 (Part A Schedule of Activities), Table 6 (Part B Schedule of Activities), Section 7.1 (Discontinuation of Study Intervention)	Removed the requirement for conducting a biopsy at the early discontinuation visit for participants who discontinue study intervention; instead, participants will be encouraged to have the biopsy at Week 48 (Part A) or Week 84 (Part B) but can have the biopsy at early discontinuation if they are unwilling or unable to wait until Week 48 (Part A) or Week 84 (Part B).
Table 5 (Part A Schedule of Activities), Table 6 (Part B Schedule of Activities)	• Edited the footnote on ADA follow-up to note that monitoring is required only for participants with titer ≥ 30 at the Follow-Up visit for consistency with FDA recommendations. • Provided additional guidance for handling of ADA monitoring for participants who still meet the criteria 12 months after the last IP dose.
Table 6 (Part B Schedule of Activities)	Added confirmation of fasting at EOT in Part B to ensure collection of the optional biomarker sample in fasted state.
Table 6 (Part B Schedule of Activities)	Added 2 additional ECG timepoints to Part B (Visit 9 and Visit 11) for alignment with Part A.
Table 6 (Part B Schedule of Activities)	Removed the urine pregnancy test in Part B at Visit 12 and added assessment at V14.
Table 6 (Part B Schedule of Activities)	• Added assessment of calcitonin at EOT in Part B for consistency with Part A. • Removed assessment of calcitonin at visits between Week 84 and EOT to correct an administrative error.

Section # and Name	Description of Change and Brief Rationale
Table 6 (Part B Schedule of Activities)	Edited the schedule of activities to note that a follow-up visit should be conducted for all participants in Part B, regardless of whether their previous visit for EOT or E/D or whether they discontinued study intervention but remained in the study.
Section 3.1 (Objectives and Endpoints: Part A)	Added an exploratory objective and endpoint to Part A and Part B to assess improvements in other histological features of NASH including portal inflammation.
Section 4.4 (End of Study Definition)	Added FDA and EU definitions of the end of study to align with sponsor template.
Section 5.2 (Exclusion Criteria)	Added evidence of portal hypertension to the exclusion criterion on hepatic decompensation to provide further clarification on the definition.
Section 5.2 (Exclusion Criteria); Appendix G	Definition of alcohol unit was updated to use local regulations because the definition of a standard drink varies across countries/regions.
Section 5.2 (Exclusion Criteria)	To align with Table 13 (Prohibited Medications), edited the criterion on weight loss medications so that they are not allowed even with stable use.
Section 5.2 (Exclusion Criteria)	Added a total bilirubin cut-off for participants with Gilbert's syndrome to the exclusion criteria.
Section 5.4 (Screen Failures)	• Added more laboratory tests that can be retested without rescreening to reduce burden on investigators and participants. • Clarified that an on-study biopsy for participants being rescreened must occur at least 180 days from the date of the previous biopsy and only once the participant has met all other eligibility criteria and completed other screening requirements.
Section 6.5.2 (Prohibited Concomitant Medications)	• Added herbal preparations with any suspected hepatotoxicity to the list of prohibited concomitant medications. • Added that starting new herbal preparations or dietary supplements is not allowed once screening activities are initiated.
Section 6.5.4.2 (Therapies for Management of Type 2 Diabetes Mellitus)	Provided additional guidance on insulin dose to clarify that minimal change (≤ 20%) to the total daily insulin dose within the 90-day period prior to screening will not be considered exclusionary
Section 6.6 (Dose Modification)	• Clarified that participants should discontinue treatment either because they are unable to successfully uptitrate to 200 µg or because their dose needs to be reduced below 200 µg. • Added a sentence stating that the lowest dose of IP allowed for a participant to continue in the study is 200 µg to provide further clarification.
Section 6.7 (Missed Dose)	Clarified IP compliance and criteria for defining IP-related important protocol deviation.

Section # and Name	Description of Change and Brief Rationale
Section 6.8 (Treatment of Overdose) (previously Section 8.4), Section 8.3.9 (Reporting of Serious Adverse Events), Section 8.3.12 (Medication Error, Drug Abuse, and Drug Misuse), Appendix B4	Updated sections on overdose, drug abuse, and drug misuse and on reporting of serious adverse events to align with sponsor template language. Text on actions to take in the event of an overdose was added.
Section 6.8 (Treatment of Overdose)	The time frame for the definition of an overdose was changed from 24 hours to one calendar day to avoid reporting an overdose if the second dose is given slightly less than 24 hours after the first.
Section 7.1 (Discontinuation of Study Intervention)	Corrected the guidance on early discontinuation visits due to the removal of the extension period from Part A and clarified that the early discontinuation visit is to be conducted for participants who discontinue study intervention early.
Section 8.2.1 (Medical History)	Added collection of gallbladder disease history to Medical History because gallbladder-related disease was added as an adverse event of special interest.
Section 8.2.5 (Clinical Safety Laboratory Assessments)	• Added red cell distribution width and red blood cell morphology to reflect that these are part of the standard complete blood count panel. • Follicle-stimulating hormone was added to Section 8.2.5 (Clinical Safety Laboratory Assessments) to support assessment of menopausal status for inclusion criterion 5. • Added direct bilirubin to the list of additional laboratory assessments in participants with Gilbert's syndrome.
Section 8.3.6 (Adverse Events of Special Interest)	Added gallbladder-related disease to the list of AESIs because gallbladder disease has been associated with the use of GLP-1 receptor agonists.
Section 8.3.10 (Clinical Events for Adjudication)	• Added CV deaths parenthetically after all deaths for consistency with MACE endpoint. • Edited the wording on the clinical event for adjudication related to heart failure. This adjudication endpoint was streamlined to hospitalization for heart failure as this includes all types of heart failure. • Edited a footnote in Figure 2 and Figure 3 to clarify the definition of baseline pretreatment ALT for management of possible drug-induced liver injury. • Added a cross reference to Appendix E (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law) for clarification.
Section 8.8 (Mobile Software Applications[s])	Removed the section on software applications because the study will no longer use a digital support system.

Section # and Name	Description of Change and Brief Rationale
Section 9.3 (Populations for Analyses), Section 9.4.3 (Safety)	Changed the definition of the Safety Population to majority of estimated usage to minimize potential bias in estimated rates of AEs based on exposure, while relying on objective and programmable criteria. Participants receiving the wrong treatment will be analyzed according to the actual treatment (majority treatment received) and randomized dose level (to avoid bias in assigning participants with tolerability issues prior to reaching a 400 µg dose to the 300 µg analysis arm).
Section 9.4.2.2 (Secondary Endpoint[s])	• Primary analysis of progression to cirrhosis will use multiple imputation (placebo washout) to provide more realistic estimates of cirrhosis progression rates by making imputations in both arms based on rates observed in the placebo arm. Because progression to cirrhosis may not be very common (especially compared to the degree of missing data), results using non-responder imputation for missing data would be difficult to interpret for this endpoint, while multiple imputation will better estimate the progression rates. • Clarified that binary endpoints will utilize a composite strategy for intercurrent events of liver outcomes.
Section 9.4.2.3 (Multiplicity Plan)	Multiplicity strategy for Part B was changed to allow for the possibility of reaching statistical significance in 600 µg secondary endpoint analyses without necessarily reaching significance for the 300 µg primary endpoint analyses, while still controlling the familywise Type I error.
Appendix A1 (Regulatory and Ethical Considerations), Appendix A6 (Dissemination of Clinical Study Data)	Updated sections on regulatory reporting requirements for serious breaches and dissemination of clinical study data to align with sponsor template language.

Nonsubstantial changes to the protocol are summarized below.

Section # and Name	Description of Change and Brief Rationale
Section 1.1 (Synopsis)	The number of evaluable participants was removed for clarity because it is the same as the number of randomized participants.
Section 1.1 (Synopsis), Section 4.1 (Overall Design)	Corrected the description of the study population to include the upper limit of the age range.
Section 1.1 (Synopsis), Section 3.1 (Objectives and Endpoints: Part A), Section 3.2 (Objectives and Endpoints: Part B)	Minor clarifications to the safety endpoints to align with planned analyses.

Section # and Name	Description of Change and Brief Rationale
Section 1.3 (Schedule of Activities: Screening), Table 5 (Part A Schedule of Activities), Table 6 (Part B Schedule of Activities), Section 8.2.4 (Electrocardiograms)	• ECG-related footnote was added to the schedule of activities for the treatment period of Part B for consistency with the schedule of activities for the treatment period of Part A. • The rest period was updated to 10 minutes in the footnotes and in Section 8.2.4 (Electrocardiograms) to correct an administrative error. • Greater detail regarding triplicate ECG procedures in Part A was added. • Guidance for ECG device malfunction was added.
Table 5 (Part A Schedule of Activities)	Clarification to note that V11 is also the EOT visit for Part A.
Section 2.1 (Study Rationale)	• Changed the length of the PROXYMO study treatment period from 52 to 19 weeks to correct an administrative error. • Changed ALT to AST to correct a typographical error.
Table 5 (Part A Schedule of Activities), Table 6 (Part B Schedule of Activities), Section 4.2.3.3 (Rationale for Exploratory Endpoints), Section 8.1 (Efficacy Assessments)	Added controlled attenuation parameter to the schedule of activities and the description of efficacy assessments to align with the endpoint related to FibroScan for Part A and Part B.
Section 3.1 (Objectives and Endpoints: Part A), Section 3.2 (Objectives and Endpoints: Part B), Section 4.2.3.3 (Rationale for Exploratory Endpoints)	Added C-Peptide to the exploratory biomarker endpoints to correct an administrative error.
Section 3.3 (Estimands)	Added a description of the estimands to Section 3 (Objectives and Endpoints) to align with sponsor template.
Section 4.1.2 (Part B Overall Design)	Clarified that participants will remain on study intervention until the end of treatment visit, not the common study end date.
Section 5.1 (Inclusion Criteria)	• Clarified that there are no contraceptive requirements for male participants. • Original protocol stated that women must use one highly effective form of birth control. Clarified that women must use *at least* one highly effective method of birth control.
Section 5.2 (Exclusion Criteria)	Added the albumin cut-off value in units (g/L) used by the central laboratory.
Section 6.1.1 (Investigational Products)	Additions were made to the description of the investigational products to improve clarity on number of doses and instructions for use.
Section 6.1.2 (Medical Devices)	Updated the ECG device model.
Section 6.2 (Preparation/Handling/Storage/ Accountability)	• Updated the location of the guidance for final disposition of unused study intervention to correct an administrative error. • Removed sharps containers from list of supplies provided to participants that need to be returned. Clarified that sharps containers are provided to participants for safe needle disposal. • Added cooling bags to the list of items supplied by the sponsor.

Section # and Name	Description of Change and Brief Rationale
Section 6.5.3 (Management of Nausea and Vomiting)	Added the class of medication (anti-histamine) for cyclizine for consistency with other medications listed.
Section 7.2 (Participant Withdrawal from the Study)	• For clarity, removed text on early discontinuation that was inconsistent with other sections of the protocol.
Section 8.1.1 (Liver Biopsy-based Histopathology)	• Added the early discontinuation visit as a timepoint for biopsy for consistency with the Schedule of Activities.
Section 8.1.2 (Artificial Intelligence-based Histopathology)	• Added literature references for AI histopathology read. • Removed reference to the Histopathology Manual in Section 8.1.2 (Artificial Intelligence-based Histopathology) because the manual does not have information on artificial intelligence-based read.
Section 8.2.3 (Vital Signs)	Corrected the timing of the initial blood pressure from baseline to screening and clarified that the selection of the arm to use for readings through the study should be based on the systolic blood pressure.
Appendix A6 (Dissemination of Clinical Study Data)	Edited for clarity and consistency with terminology used elsewhere in the protocol.

11 REFERENCES

Ambery et al 2018
Ambery P, Parker VE, Stumvoll M, Posch MG, Heise T, Plum-Moerschel L, et al. MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised, controlled, double-blind, ascending dose and phase 2a study. Lancet. 2018;391(10140):2607-18.

Angulo 2007
Angulo P. GI epidemiology: Non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2007;25(8):883-9.

Angulo et al 2015
Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, associates with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology. 2015;149(2):389-97.

Armstrong et al 2016
Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016;387(10019):679-90.

Bellentani et al 2010
Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. Dig Dis. 2010;28(1):155-61.

Boland et al 2020
Boland ML, Laker RC, Mather K, Nawrocki A, Oldham S, Boland BB, et al. Resolution of NASH and hepatic fibrosis by the GLP-1R/GcgR dual-agonist cotadutide via modulating mitochondrial function and lipogenesis. Nat Metab. 2020;2(5):413-31.

Bosch et al 2021
Bosche J, Chung C, Carrasco-Zevallos OM, Harrison SA, Abdelmalek MF, et al. A machine learning approach to liver histological evaluation predicts clinically significant portal hypertension in NASH cirrhosis. Hepatol. 2021;74(6):3146-60.

Cholankeril et al 2017
Cholankeril G, Patel R, Khurana S, Satapathy SK. Hepatocellular carcinoma in non-alcoholic steatohepatitis: Current knowledge and implications for management. World J Hepatol. 2017;9(11):533-43.

Dulai et al 2017
Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in non-alcoholic fatty liver disease: Systematic review and meta-analysis.

Hepatology. 2017;65(5):1557-65.

Estes et al 2018
Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology. 2018;67(1):123-133.

Inker et al 2021
Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y. New creatinine- and cystatin c-based equations to estimate GFR without race. N Eng J Med. 2021;385(19):1737-49.

Harrison et al 2019
Harrison SA, Bashir MR, Guy CD, Zhou R, Moylan CA, Frias JP, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2019;394(10213):2012-24.

Marra et al 2013
Marra F1, Lotersztajn S. Pathophysiology of NASH: perspectives for a targeted treatment. Curr Pharm Des. 2013;19(29):5250-69.

Mishra and Younossi 2012
Mishra A, Younossi ZM. Epidemiology and natural history of non-alcoholic fatty liver disease. J Clin Exp Hepatol. 2012;2(2):135-44.

Nahra et al 2021
Nahra R, Wang T, Gadde KM, Oscarsson J, Stumvoll M, Jermutus L, et al. Effects of cotadutide on metabolic and hepatic parameters in adults with overweight or obesity and type 2 diabetes: A 54-week randomized phase 2b study. Diabetes Care. 2021;44(6):1433-42.

Nalbantoglu and Brunt 2014
Nalbantoglu I, Brunt EM. Role of liver biopsy in nonalcoholic fatty liver disease. World J Gastroenterol. 2014;20(27):9026-37.

Neuschwander-Tetri 2017
Neuschwander-Tetri. Non-alcoholic fatty liver disease. BMC Med. 2017;15:45.

Newsome et al 2021
Newsome PH, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med. 2021;384(12):1113-24.

Pais et al 2016
Pais R, Barritt AS 4th, Calmus Y, Scatton O, Runge T, et al. NAFLD and liver transplantation:

Current burden and expected challenges. J Hepatol. 2016;65(6):1245-1257.

Petit et al 2017
Petit JM, Cercueil JP, Loffroy R, Denimal D, Bouillet B, Fourmont C, et al. Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes: The Lira-NAFLD study. J Clin Endocrinol Metab. 2017;102(2):407-15.

Regev et al 2019
Regev A, Palmer M, Avigan MI, Dimick-Santos L, Treem WR, Marcinak JF, et al. Consensus: guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis. Aliment Pharmacol Ther. 2019;49:702-13.

Taylor-Weiner et al 2021
Taylor-Weiner A, Pokkalla H, Han L, Jia C, Huss R, et al. A machine learning approach enables quantitative measurement of liver histology and disease monitoring in NASH. Hepatol. 2021;74(1):133-47.

Wong et al 2014
Wong RJ1, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology. 2014;59(6):2188-95.

Younossi et al 2016
Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84.

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