Clinical Study Protocol	
Study Intervention	AZD4831 (mitiperstat)
Study Code	D6581C00001
Version	2.0
Date	20 March 2023

A Phase IIa, Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety, Tolerability, and Pharmacodynamics of AZD4831 (mitiperstat) in Participants with Non-cirrhotic Non-alcoholic Steatohepatitis (NASH) with Fibrosis (COSMOS)

Sponsor Name: AstraZeneca AB

Legal Registered Address: SE-15185 Södertälje, Sweden

Regulatory Agency Identifier Number(s):

EU CT: 2022-500594-13-00

IND: 158550

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: D6581C00001

Amendment Number: 1

Study Intervention: AZD4831 (mitiperstat)

Study Phase: Phase IIa

Short Title: A Phase IIa Study to Assess Safety, Tolerability, and Pharmacodynamics of AZD4831 (mitiperstat) in Adult Participants with Non-cirrhotic NASH with Fibrosis

(COSMOS)

Study Physician Name and Contact Information will be provided separately

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	20 March 2023
Original Protocol	10 May 2022

Amendment 1: 20 March 2023

Overall Rationale for the Amendment:

The main reasons for this amendment include:

1 Extension of the Screening period to 8 weeks to allow sufficient time for biopsy scheduling and results.
2 Clarifications to allow shortening of the Screening period for participants with historical biopsies and elevated ALT.
3 Inclusion of participants with fibrosis stage F1.
4 Addition of study stopping criteria.
5 Removal of exclusion for women of childbearing potential from the study.
6 Revision of text to align with updated EU CTR guidelines.
7 Removal of exclusions/restrictions for CYP3A4 perpetrators.
8 Addition of guidelines for handling of skin reactions.
9 Minor revision of several sections for clarification, typographical errors, and harmonization across all amendments.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Throughout CSP	**Added** '(mitiperstat)' to study intervention name	Addition of international non-proprietary name	Non-substantial
Title page, full title and short title; and Section 1.1 (Synopsis), full title and short title	**Added** 'COSMOS' to study name	Addition	Non-substantial
Section 1.1 (Synopsis); Section 1.2, Figure 1 (Study Design); Section	**Revised** Screening period from 6 weeks (42 days) to 8 weeks (56 days);	Screening period lengthened to allow	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.2, Table 1 (Study Endpoint Assessment); Section 1.3, Table 2 (Schedule of Activities); and Section 4.1 (Overall Design)	**Revised** total study duration from approximately 22 weeks to approximately 24 weeks	additional time for biopsy scheduling and results	
Section 1.1 (Synopsis) and Section 4.1 (Overall Design	**Added** 'Participants, including participants who are rescreened, can be randomized anytime within the screening period outlined in the SoA (Table 2) once all inclusion/exclusion criteria have been fulfilled. For participants who have a historical biopsy and elevated alanine aminotransferase (ALT), the screening period can be shortened.'	Addition to allow Screening period to be shortened for participants who do not require a fresh biopsy	Non-substantial
Section 1.3, Table 2 (Schedule of Activities)	**Removed** 'Drugs of abuse and alcohol screening (Section 8.2.5)' and 'Exploratory fasting biomarker sampling (optional)' from Visit 3	Reduction of samples taken to streamline screening period and reduce patient burden	Non-substantial
Section 1.3, Table 2 (Schedule of Activities)	**Added** footnote '[a] Participants, including participants who are rescreened, can be randomized anytime within the screening period outlined in the SoA once all inclusion criteria have been fulfilled.'	Addition to allow Screening period to be shortened for participants who do not require a fresh biopsy	Non-substantial
Section 1.3, Table 2 (Schedule of Activities)	**Added** footnote '[b] Participants with historical biopsy and meeting all inclusion criteria are not required to have Visit 2. All participants must have Visit 1 and 3 prior to randomization.'	Addition to allow Screening period to be shortened for participants who do not require a fresh biopsy	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.3, Table 2 (Schedule of Activities)	**Removed** from footnote c 'other' **Added** 'Visit 1'	Clarification	Non-substantial
Section 5.4 (Screen Failures)	**Added** 'Participants who are rescreened do not need to complete the full 8-week screening period, if all inclusion/exclusion criteria have been fulfilled. However, they must complete Visit 1 and Visit 3, following Table 2.'	Addition to allow Screening period to be shortened for participants who do not require a fresh biopsy	Non-substantial
Section 1.1 (Overall Design); Section 2.1 (Study Rationale); Section 2.3.3 (Conclusion); Section 4.1 (Overall Design); Section 4.2 (Scientific Rationale for Study Design); Section 5.1 (Inclusion Criteria, Criterion 2b); Section 8.5.1 (Liver Biopsy)	**Added** 'F1'	Addition to expand potential participant population	Substantial
Section 1.1 (Synopsis), Section 1.2, Table 1 (Study Endpoint Assessment); Section 4.1 (Overall Design); and Section 9.6 (Data Monitoring Committee)	**Added** 'and study stopping criteria'	Clarification to the remit of the Data Review Committee	Substantial
Section 7.4 (Study Stopping Criteria)	**Added** Section 7.4, Study Stopping Criteria	Addition	Substantial
Section 1.3, Table 2 (Schedule of Activities)	**Removed** row 'FSH'	Revised to allow women of childbearing potential into the study	Substantial
Section 5.1 (Inclusion Criteria, Criterion 7)	**Removed** 'of non-childbearing potential'	Revised to allow women of childbearing potential into the study	Substantial
Section 5.1 (Inclusion Criteria, Criterion 8)	**Removed** 'men or'	Revised to allow women of childbearing potential into the study	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 5.1 (Inclusion Criteria, Criterion 8a)	**Removed** '(a) Male participants: • Male participants must be surgically sterile or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides) during treatment and until the end of relevant systemic exposure in the male participant, plus a further 90-day period. Male study participants must not donate or bank sperm during this same time period.'	Revised to allow women of childbearing potential into the study	Substantial
Section 5.1 (Inclusion Criteria, Criterion 8b)	**Removed** '(b) For a non-pregnant woman of childbearing potential partner, contraception recommendations should also be considered. Acceptable methods of contraception include birth control pills, injections, implants, or patches, intrauterine devices, and tubal ligation/occlusion. A barrier method is not necessary if the female partner is sterilized.'	Clarification to allow women of childbearing potential into the study	Substantial
Section 5.1 (Inclusion Criteria, Criterion 8c)	**Removed** 'and must be of non-child-bearing potential'	Revised to allow women of childbearing potential into the study	Substantial
Section 5.1 (Inclusion Criteria, Criterion 8c)	**Added** 'Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use an acceptable method of birth control, from enrolment throughout the study and	Revised to allow women of childbearing potential into the study	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	until at least 4 weeks after last dose of study intervention. Acceptable methods of contraception include birth control pills, injections, implants or patches, intrauterine devices, and tubal ligation/occlusion. The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea. Female condom and male condom should not be used together.'		
Section 5.1 (Inclusion Criteria, Criterion 8c)	**Removed** 'Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy [but not tubal ligation]), 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	Revised to allow women of childbearing potential into the study	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	exogenous hormonal treatment and 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.'		
Section 8.2.5, Table 8 (Other Clinical Safety Labs--Screening Only)	**Removed** 'FHS (female participants only)'	Revised to allow women of childbearing potential into the study	Substantial
Section 1.3, Table 2 (Schedule of Activities)	**Added** row 'Urine pregnancy test' at Visit 1	Revised to allow women of childbearing potential into the study	Substantial
Section 8.2.5, Table 7 (Laboratory Safety Variables)	**Added** 'Pregnancy test (for WOCBP only)'	Revised to allow women of childbearing potential into the study	Substantial
Section 8.3.9.1 (Maternal Exposure)	**Removed** 'Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the IP should be discontinued immediately and the pregnancy reported to AstraZeneca.' **Added '**Should a pregnancy occur, the IP should be discontinued immediately and the pregnancy reported to AstraZeneca.'	Revised to allow women of childbearing potential into the study	Substantial
Section 1.3, Table 2 (Schedule of Activities)	**Removed** row 'COVID-19 enquiry'	Clarification	Non-substantial
Section 5.2 (Exclusion Criteria; Criterion 15)	**Added '**if clinically indicated, based on investigator discretion.**'**	Addition	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 8.2.5, Table 8 (Other Clinical Safety Labs-Screening Only)	**Added** superscript 'c' for 'COVID-19 testing [c]' **Added** footnote '[c] If clinically indicated, based on investigator discretion'	Addition	Non-substantial
Section 1.3, Table 2 (Schedule of Activities)	**Removed** 'height only taken at Screening Visit 1)'	Clarification	Non-substantial
Section 1.3, Table 2 (Schedule of Activities)	**Added** row 'HbA1c testing (Section 8.2.5)' **Added** footnote '[m] HbA1c results needed to determine eligibility.'	Clarification	Non-substantial
Section 8.2.5, Table 7 (Laboratory Safety Variables)	**Added** 'HbA1c'	Clarification	Non-substantial
Section 1.3, Table 2 (Schedule of Activities)	**Added** footnote '[e] If positive for HIV at Visit 1, a reflex test will be performed on the remaining sample. Further confirmation is available with optional HIV RNA test, available in retest kit. If positive for hepatitis C at Visit 1, a hepatitis C RNA test will be triggered to confirm the result.'	Clarification	Non-substantial
Section 1.3, Table 2 (Schedule of Activities)	**Added** footnote '[f] Urine pregnancy test required for WOCBP only. If there is a suspicion of pregnancy, urine pregnancy test should be repeated prior to first dosing.'	Addition	Substantial
Section 1.3, Table 2 (Schedule of Activities)	**Added** footnote '[k] Visit 3 clinical safety laboratory evaluations (chemistry, hematology, and urinalysis) are only required for participants who require a fresh liver biopsy.'	Clarification	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.3, Table 2 (Schedule of Activities)	**Removed** from footnote l 'based on investigator discretion'	Clarification	Substantial
Section 4.4 (End of Study Definition)	**Removed** 'A participant is considered to have completed the study if he/she has completed all phases of the study including the final follow-up Visit 9, regardless of the number of doses of study medication they have received. Participants who have died during the study are also considered to have completed the study. The end of the study is defined as the date of the last expected visit of the last participant in the study globally. Guidelines for the dissemination of study results are provided in Appendix D 5.'	Revision of text to align with updated EU CTR guidelines	Substantial
Section 4.4 (End of Study Definition)	**Added** 'For the purpose of Clinical Trial Transparency (CTT) 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 subject for any protocol related activity. Food and Drug Administration requirements defines two completion dates: Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final	Revision of text to align with updated EU CTR guidelines	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	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 they have completed all phases of the study including the last visit.'		
Section 5.1 (Inclusion Criteria; Criteria 3, 5, and 6) and Section 5.2 (Exclusion Criteria; Criterion 20)	**Removed** 'prior to screening' **Added** 'prior to randomization'	Clarification	Non-substantial
Section 5.1 (Inclusion Criteria; Criterion 3)	**Removed** 'screening' **Added** 'Visit 1'	Clarification	Non-substantial
Section 5.1 (Inclusion Criteria; Criterion 4)	**Removed** 'Increased serum ALT level (> ULN [41 U/L for men and 31 U/L for women] but < 300 U/L) at screening, with historical local serum	Revised to harmonize across local amendments	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	ALT levels > ULN on ≥ 1 occasion in the 6 months prior to screening.' **Added** 'Two increased serum ALT measurements (ALT > ULN); one historical local ALT within 6 months prior to screening and one at screening.'		
Section 5.2 (Exclusion Criteria, Criterion 2)	**Added** 'or hepatitis B core antibody'	Clarification	Non-substantial
Section 8.2.5, Table 8 (Other Clinical Safety Labs-Screening Only)	**Added** 'Hepatitis B core antibody'	Clarification	Non-substantial
Section 5.2 (Exclusion Criteria; Criterion 12)	**Removed** 'allergy/hypersensitivity' **Added** 'drug allergies or hypersensitivity'	Clarification	Non-substantial
Section 5.2 (Exclusion Criteria, Criterion 13)	**Removed** 'Participants with hyperthyroidism, uncontrolled hypothyroidism (including but not limited to TSH ≥ 10 mIU/mL), or any clinically significant thyroid disease as judged by the investigator.' **Added** 'Participants with hyperthyroidism, uncontrolled hypothyroidism, or any clinically significant thyroid disease as judged by the investigator. Patients with TSH ≥ ULN should be excluded.'	Clarification	Substantial
Section 5.2 (Exclusion Criteria; Criterion 19)	**Removed** 'History of substance dependence or positive screen for drugs of abuse at screening.' **Added** 'Positive screen for drugs of abuse at screening or admission to the study site prior to the	Clarification	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	administration of the study intervention. Note: participants who test positive for drugs (ie, opioids) that are prescribed for appropriate medical use are eligible to participate in the study.'		
Section 5.2 (Exclusion Criteria; Criterion 22)	**Removed** 'Strong CYP3A4 inducers or inhibitors within 28 days prior randomization (Table 5).'	The co-administration of itraconazole (strong CYP3A4 inhibitor) with AZD4831 (mitiperstat) (Clinical DDI study D6580C00013) resulted in higher exposure of AZD4831 (mitiperstat) by approximately 30%	Substantial
Section 5.3.1 (Meals and Dietary Restrictions)	**Removed** 'Participants must refrain from consumption of grapefruit juice from the start of study intervention until the final dose.'	The co-administration of itraconazole (strong CYP3A4 inhibitor) with AZD4831 (mitiperstat) (Clinical DDI study D6580C00013) resulted in higher exposure of AZD4831 (mitiperstat) by approximately 30%	Substantial
Section 6.5 (Concomitant Therapy)	**Removed** 'Cytochrome P450-related restricted medications are described in Table 5. Table 5 is not a complete list of potent CYP3A4 inhibitors/inducers. Refer to concomitant medications summary of product characteristics for further information and clarification.'	The co-administration of itraconazole (strong CYP3A4 inhibitor) with AZD4831 (mitiperstat) (Clinical DDI study D6580C00013) resulted in higher exposure of AZD4831 (mitiperstat) by approximately 30%	Substantial
Section 6.5 (Concomitant Therapy, Table 5)	**Removed** Table 5, Cytochrome P450 -related Restricted Medications Table numbering updated	The co-administration of itraconazole (strong CYP3A4 inhibitor) with AZD4831 (mitiperstat) (Clinical DDI study D6580C00013) resulted in higher exposure of	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		AZD4831 (mitiperstat) by approximately 30%	
Section 5.2 (Exclusion Criteria, Criterion 29f)	**Removed** '25 µmol/L' **Added** 'ULN'	Clarification	Substantial
Section 5.2 (Exclusion Criteria, Criterion 29g)	**Removed** '100000/mm^3' **Added** '150000/mm^3'	Clarification	Substantial
Section 5.2 (Exclusion Criteria; Criterion 30)	**Removed** 'seated' **Added** 'supine'	Correction	Non-substantial
Section 5.2 (Exclusion Criteria; Criterion 32)	**Removed** 'Day' **Added** 'Week'	Typographical error	Non-substantial
Section 6.5.1 (Rescue Medicine)	**Removed** section. The text in this section has been added to section 8.3.6.1	Sponsor does not consider this study to include rescue medicines. The protocol has been amended to suggest treatment for maculopapular rash is in line with standard treatment guidelines.	Non-substantial
Section 8.2.3 (Vital Signs)	**Removed** '3 measurements' **Added** '2 measurements'	Correction	Non-substantial
Section 8.2.5, Table 8 (Other Clinical Safety Labs-Screening Only)	**Added** footnote '[b] For European countries, alcohol urine test will be used.'	Clarification	Non-substantial
Section 8.3.6.1 (Skin Reactions, Including Maculopapular Rash) and Appendix E 5 (Guide to Skin Reaction Assessment)	**Removed** 'Upon investigator discretion, a clinical dermatologist can be consulted and a skin biopsy considered.' **Added** 'Patients should be referred to a dermatologist if they experience a skin reaction or rash that is considered severe, serious, persists ≥ 7 days, continues worsening after discontinuing the investigational agent, or if the investigator deems it otherwise necessary. It would be recommended that the dermatologist determine whether the individual	Clarification to further monitor, characterize and treat if necessary potential skin reactions	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	subject will benefit with additional treatment and recommended that a biopsy is performed if deemed necessary by the dermatologist in these scenarios.'		
Appendix E 5 (Guide to Skin Reaction Assessment)	**Added** 'Photos taken by the investigator and participant should avoid identifying features like the face, use adequate lighting, and capture both a close-up photo(s) of the affected skin and photo(s) from farther away to give context to the size of the affected area and the location of the skin reaction/rash. Face, tattoos, piercings and other identifiers must not be seen in the photo(s) to avoid identification of the participant (participant can cover them when making photo, or these can be masked/edited afterwards by investigator).'	Clarification	Non-substantial
Appendix E 5 (Guide to Skin Reaction Assessment)	**Added** 'Participant must not send any photo(s) to investigator via SMS, e-mail or in any other way in order to keep the data privacy and anonymity. Investigator may take a photo of participant's photo(s) showed on digital device (phone, tablet, etc). Alternatively, participant can print out photo(s) at the site visit and give them to the site staff for scanning.'	Clarification	Non-substantial
Section 8.3.10 (Medication Error, Drug Abuse, and Drug Misuse) and	**Added** sub-section headings in Section 8.3.10	Revision of text to align with updated EU CTR guidelines	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix E 4 (Medication Error, Drug Abuse, and Drug Misuse)	**Revised** text with minor clarifications in Section 8.3.10 and Appendix E 4 to align with EU CTR guidelines		
Section 8.5 (Human Biological Samples)	**Removed** 'Pharmacokinetic 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.' **Added** 'after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses'	Clarification	Non-substantial
Section 8.5.1 (Liver Biopsy)	**Removed** 'procedure are described in the Histopathology Manual' **Added** 'should follow local procedures'	Correction	Non-substantial
Section 8.6.1.1 (Collection of Mandatory Sample for Genetic Analysis)	**Removed** 'PNPLA2' **Added** 'PNPLA3'	Typographical error	Non-substantial
Section 8.6.1.1 (Collection of Mandatory Sample for Genetic Analysis)	**Added** 'or entire gene sequencing' and 'and NASH associated genes'	Clarification	Non-substantial
Section 9.3.1 (Full Analysis Set)	**Removed** 'the secondary pharmacodynamics variables as well as for the exploratory pharmacodynamics variables' **Added** 'all pharmacodynamics variables'	Clarification of the analysis set (FAS) for all pharmacodynamic variables	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 9.4.1 (General Considerations)	**Removed** 'Baseline will be defined as the last non-missing value on or before the day of first dose and on or before dose the day of randomization (whatever occurs first), individually for each participant and endpoint. The baseline value for safety analyses is the last non-missing value prior to administration of the first dose of IP.' **Added** 'For analyses both on the FAS and on the SAS, baseline is defined as the last non-missing value prior to first dose including unscheduled assessments that occurs prior to first dose.'	Clarification to align definition for FAS and SAS and have a more clear description	Non-substantial
Section 9.4.2.1 (Primary Endpoint)	**Removed** 'data will also be analyzed as relative differences, that is (value at time t – value at baseline)/(value at baseline), in a similar mixed effects model but without log transformation of data.' **Added** 'data will also be analyzed as individual percental change, that is (value at time t – value at baseline)/(value at baseline)100%, in a similar mixed effects model but without log transformation of data.'	Clarification to present results in percent scale rather than as relative differences	Non-substantial
Section 9.4.2.1 (Primary Endpoint) and Section 9.4.2.2 (Secondary Endpoint)	**Removed** 'Participant that fulfills all of the inclusion and none of the exclusion criteria' **Added** 'FAS'	Clarification of the analysis set (FAS) for all pharmacodynamic variables	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix D 6 (Data Quality Assurance)	**Added** clarifying text about details found in the Monitoring Plan and the AstraZeneca Global retention and Disposal (GRAD) Schedule	Revision of text to align with updated EU CTR guidelines	Non-substantial
Appendix F 1 (Introduction)	**Added** 'and in possible cholestatic DILI'	Clarification to harmonize across local amendments	Substantial
Appendix F 8 (Recommended Stopping Criteria)	**Added** 'Table F10 Stopping Criteria for Possible Cholestatic DILI'	Clarification to harmonize across local amendments	Substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase IIa, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of AZD4831 (mitiperstat) in Participants with Non-cirrhotic Non-alcoholic Steatohepatitis (NASH) with Fibrosis (COSMOS)

Short Title: A Phase IIa Study to Assess Safety, Tolerability, and Pharmacodynamics of AZD4831 (mitiperstat) in Adult Participants with Non-cirrhotic NASH with Fibrosis (COSMOS)

Rationale: The primary objective of this study is to evaluate safety and tolerability of AZD4831 (mitiperstat) and pharmacodynamics in participants with non-cirrhotic NASH with fibrosis.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effect of AZD4831 (mitiperstat) on circulating markers of hepatic injury and apoptosis or necrosis compared with placebo	Change from baseline and over placebo to Week 12: • ALT
Secondary	
To assess the effect of AZD4831 (mitiperstat) on circulating biomarkers of fibrosis compared with placebo	Change from baseline and over placebo to Week 12: • Pro-C3
To assess the PK of AZD4831 (mitiperstat)	Plasma concentration of AZD4831 (mitiperstat) will be summarized by timepoints. If PK data permit, a population PK model may be developed and potentially coupled with separate PD models; the derived PK parameters and the modeling may be provided in a separate PK and population PK/PD report.
Safety	
To assess safety and tolerability of AZD4831 (mitiperstat) compared with placebo in participants with non-cirrhotic NASH with fibrosis	Safety and tolerability, including hepatic safety, will be evaluated in terms of AEs (including AESIs related to skin reactions, including maculopapular rash, and infection) and clinical and laboratory assessments.

AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; NASH, non-alcoholic steatohepatitis; PD, pharmacodynamic(s); PK, pharmacokinetic(s); Pro-C3, released N-terminal propeptide of type III collagen

Exploratory objectives and endpoints are provided in Section 3.

Overall Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study including a maximum of approximately 90 randomized adult participants with biopsy-proven non-cirrhotic non-alcoholic steatohepatitis (NASH) with fibrosis (NAS ≥ 4, fibrosis stages F1, F2, F3). The study will be conducted at approximately 48 sites across approximately 9 countries.

During screening, the participants will be checked for eligibility and enrolled in the study. Following an 8-week screening period, approximately 90 participants will be randomized at Visit 4 in a 1:1 ratio to once daily dosing of 5 mg AZD4831 (mitiperstat) or placebo. Participants, including participants who are rescreened, can be randomized anytime within the screening period outlined in the SoA (Table 2) once all inclusion/exclusion criteria have been fulfilled. For participants who have a historical biopsy and elevated alanine aminotransferase (ALT), the screening period can be shortened.

All participants will be treated once daily with 5 mg AZD4831 (mitiperstat) or placebo for 12 weeks. The safety, tolerability, and pharmacodynamics will be evaluated at 12 weeks.

This is the first clinical study to test AZD4831 (mitiperstat) in participants with non-cirrhotic NASH with fibrosis.

Disclosure Statement: This is a parallel group treatment study with 2 arms that is participant and investigator blinded.

Number of Participants:

Approximately 300 participants will be screened/enrolled to achieve approximately 90 participants randomly assigned to study intervention or placebo.

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”, unless otherwise specified by the protocol.

Intervention Groups and Duration:

Participants will be randomized to once daily dosing of 5 mg AZD4831 (mitiperstat) or placebo. Dosing should be supervised and documented by study staff when study intervention is administered in the clinic.

The study will comprise 3 periods totaling approximately 24 weeks:

- A screening period of up to 8 weeks

- A total treatment period of 12 weeks
- A safety follow-up period of 4 weeks

Data Review Committee: An unblinded safety data review committee consisting of AstraZeneca personnel and an external dermatologist will be set up for ongoing, periodic safety monitoring, with a focus on skin reactions and study stopping criteria.

Statistical Methods

The primary pharmacodynamic endpoint of this study is change from baseline to Week 12 in alanine aminotransferase (ALT), and it will be assessed through a treatment policy estimand. This approach will assess the effect of the treatment policy of AZD4831 (mitiperstat) and placebo regardless of discontinuation of study medication. The main analysis will be using a mixed effects linear model with participant as random effect, treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline as covariate, including all participants in the full analysis set (FAS). Data will be log-transformed before analyses, and results will be back-transformed to describe relative change versus placebo in value at end of treatment relative to baseline.

The null hypothesis of no decrease in ALT comparing AZD4831 (mitiperstat) to placebo will be tested versus the alternative hypothesis of a decrease in ALT in favor of AZD4831 (mitiperstat) to placebo using a one-sided test at 5% significance level.

The secondary endpoint Pro-C3 will be analyzed in the same way as ALT.

The study has been powered to have at least 80% power to detect a 25% decrease in ALT level at end of treatment relative to baseline for AZD4831 (mitiperstat) treated versus placebo treated in a one-sided test at 5% significance level, based on the FAS population. ALT measurements will be log-transformed before analysis. Under the assumption of a standard deviation of 0.50 for change from baseline in log-transformed ALT, and allowing for 10% missing data, 45 participants per arm would render the desired power.

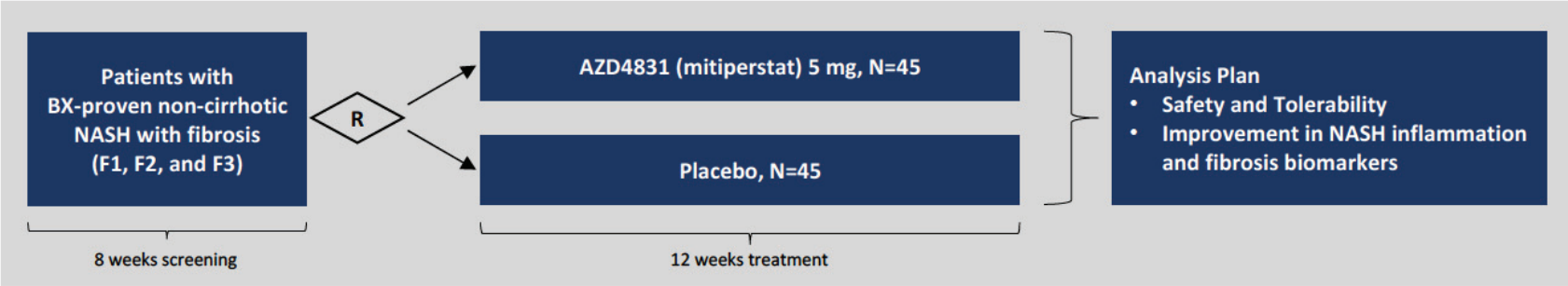
Safety analyses will be performed using the safety analysis set, which includes all participants who receive at least 1 dose of randomized AZD4831 (mitiperstat) or placebo. Safety data will be presented using descriptive statistics unless otherwise specified and will not be formally tested.

No multiplicity adjustment for alpha is planned.

All personnel involved with the conduct of the study will remain blinded until database lock at 12 weeks and protocol violations have been identified and documented. Analyses will be performed by AstraZeneca or its representatives.

1.2 Schema

Figure 1 Study Design



BX, biopsy; NASH, non-alcoholic steatohepatitis; R, randomization

Table 1 Study Endpoint Assessment

	Screening	R	12-week Treatment Period				FUP
Visit	V1 to V3	V4	V5	V6	V7	V8	V9
Weeks from randomization	Week -8 to -1	Week 0	Week 2	Week 4	Week 8	Week 12	Week 16
Endpoints		Safety, PK, PD	CCI	CCI	CCI	Safety, PK, PD	Safety, PK

An unblinded DRC consisting of AstraZeneca personnel and an external dermatologist will be set up for ongoing, periodic safety monitoring focused on skin reactions and study stopping criteria.
DRC, data review committee; R, randomization; FUP, follow up; PK, pharmacokinetics; PD, pharmacodynamics; V, visit

1.3 Schedule of Activities

Table 2 Schedule of Activities

Assessment and sampling time points may be adjusted based on emerging data.	**Screening[a]**			**Treatment**					**Final Follow-up**
	Visit 1	**Visit 2 [b,c]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8/EDV**	**Visit 9**
	Week -8 to -1			**Week 0**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**
				Day 1	**Day 15 (± 2 d)**	**Day 29 (± 2d)**	**Day 57 (± 2 d)**	**Day 85 (± 2 d)**	**Day 113 (± 5 d)**
Informed consent, including consent for genetic testing [d]	X								
Enrollment in RTSM	X								
Optional informed consent for Genomics Initiative research (Section 8.7, Appendix A)	X								
Inclusion/exclusion criteria (Section 4.4)	X		X						
Liver Biopsy (Section 8.5.1)		X [b,c]							
Hepatitis B and C and HIV screening (Section 8.2.5) [e]	X								
Urine pregnancy test (Section 8.2.5) [f]	X								
COVID-19 tests (Section 8.2.5)	X								
Demographic data	X								
Medical history	X								
Concomitant medication	X		X	X	X	X	X	X	X
Drugs of abuse and alcohol screening (Section 8.2.5)	X								
AUDIT questionnaire (Appendix B)	X								
Randomization				X					

Table 2 Schedule of Activities

Assessment and sampling time points may be adjusted based on emerging data.	Screening [a]			Treatment					Final Follow-up
	Visit 1	Visit 2 [b,c]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8/EDV	Visit 9
	Week -8 to -1			Week 0	Week 2	Week 4	Week 8	Week 12	Week 16
				Day 1	Day 15 (± 2 d)	Day 29 (± 2d)	Day 57 (± 2 d)	Day 85 (± 2 d)	Day 113 (± 5 d)
Study intervention administration in clinic [g]				X		X		X	
Study intervention dispensed for at home administration				X		X	X		
Safety and tolerability:									
Collection of AEs and SAEs [h]	X	X	X	X	X	X	X	X	X
BP, pulse rate (supine), and body temperature (Section 8.2.3)	X		X	X	X	X	X	X	X
Orthostatic Test (Section 8.2.3.1) [i]				X				X	
Weight and height (Section 8.2.3)	X (BMI)		X (weight)						X (weight)
12-lead ECG (Section 8.2.4)	X		X			X			X
Clinical safety laboratory evaluations, (chemistry, hematology, and urinalysis) (Section 8.2.5) [j]	X		X [k]	X	X	X	X	X	X
CCI [redacted]	X CCI [redacted]			X				X	
Physical examination (Section 8.2.2)	X		X						

Table 2 Schedule of Activities

Assessment and sampling time points may be adjusted based on emerging data.	Screening [a]			Treatment					Final Follow-up
	Visit 1	Visit 2 [b,c]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8/EDV	Visit 9
	Week -8 to -1			Week 0	Week 2	Week 4	Week 8	Week 12	Week 16
				Day 1	Day 15 (± 2 d)	Day 29 (± 2d)	Day 57 (± 2 d)	Day 85 (± 2 d)	Day 113 (± 5 d)
Brief physical exam (including skin) (Section 8.2.2)						X		X	X
ANCA testing (Section 8.2.5) [l]			X [l]						
HbA1c testing (Section 8.2.5) [m]	X								
Blood sample for genetic analysis (Section 8.6.1.1) [e]				X [n]					
Pharmacokinetics:									
Plasma for AZD4831 (mitiperstat) PK (Section 8.5.2)				X (predose)		X [o]		X	X
Pharmacodynamics:									
Fasting blood, plasma, and urine sampling for biomarkers (Section 8.5.3)			X	X (predose)		X		X	
Optional Exploratory Samples:									
Exploratory fasting biomarker sampling (optional) (Section 8.6.2) [j]				X				X	
Genomics Initiative optional, exploratory genetic sample (Section 8.7, Appendix A)				X					

[a] Participants, including participants who are rescreened, can be randomized anytime within the screening period outlined in the SoA once all inclusion criteria have been fulfilled.

[b] Participants with historical biopsy and meeting all inclusion criteria are not required to have Visit 2. All participants must have Visit 1 and 3 prior to randomization.

[c] Visit 2 and the fresh liver biopsy screening are only required if there is no histologically confirmed NASH as diagnosed by liver biopsy within 12 months of provision of written informed consent. For participants without a historical biopsy, the screening liver biopsy will be scheduled after all Visit 1 screening procedures and once it has been confirmed that the participant meets all other inclusion/exclusion criteria and safety laboratory assessments are available.
[d] Consent and sample collection for mandatory genetic testing will only be conducted in countries where genetic testing is allowed in this study.
[e] If positive for HIV at Visit 1, a reflex test will be performed on the remaining sample. Further confirmation is available with optional HIV RNA test, available in retest kit. If positive for hepatitis C at Visit 1, a hepatitis C RNA test will be triggered to confirm the result.
[f] Urine pregnancy test required for WOCBP only. If there is a suspicion of pregnancy, urine pregnancy test should be repeated prior to first dosing.
[g] Participants will receive study intervention at the site on Day 1, Day 29, and Day 85 and at home once daily on other days. Study intervention will be administered after PK sampling. At Visit 4 and Visit 6, study intervention will be administered from a newly dispensed bottle. At Visit 8, study intervention will be administered from the previously dispensed bottle (brought from home).
[h] AEs will be collected from the time of first dose (the only exception is related to the predose orthostatic test at Visit 4: if orthostatic hypotension is confirmed, it should be reported as an AE, and symptoms related to the measurement of orthostatic vitals if present should also be reported as an AE). SAEs will be collected from signing of ICF.
[i] Orthostatic BP will be measured at Visit 4 and at Visit 8 prior to any required blood draw and study intervention and 1-2 hours post dose at Visit 4. Orthostatic BP will be measured 1 and 3 minutes after the participant stands.
[j] Blood draws for clinical safety, CCI and exploratory fasting biomarker sampling will be drawn predose (where applicable).
[k] Visit 3 clinical safety laboratory evaluations (chemistry, hematology, and urinalysis) are only required for participants who require a fresh liver biopsy.
[l] The ANCA sample collected at baseline is to only be tested upon requirement ie, CCI An additional sample should be collected if clinically indicated.
[m] HbA1c results needed to determine eligibility.
[n] If for any reason the sample is not drawn at Visit 4, it may be taken at any visit until the last study visit.
[o] In a subset of participants (approximately 20%), 2 additional postdose samples will be collected at Visit 6. Visit 6 sample collection times are: predose, and 0.5 to 1.5 h and 1.5 to 3 h, with a minimum of 1 hour between the postdose sampling occasions. Once approximately 20% of participants have been tested, no further participants would need this additional post dose sampling.

AE, adverse event; ANCA, antineutrophil cytoplasmic antibody; AUDIT, Alcohol Use Disorder Identification Test; BP, blood pressure; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; EDV, early discontinuation visit; HbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; ICF, informed consent form; NASH, non-alcoholic steatohepatitis; PCR, polymerase chain reaction; PK, pharmacokinetic(s); RNA, ribonucleic acid; RTSM, randomization and trial supply management; SAE, serious adverse event; SoA, schedule of activities; CCI

2 INTRODUCTION

AZD4831 (mitiperstat) is a highly potent MPOi that is being developed for the management of cardiovascular and metabolic disease. AZD4831 (mitiperstat) is hypothesized to delay disease progression and potentially reverse disease in NASH with fibrosis through direct disease-modifying effects.

2.1 Study Rationale

This Phase IIa study will evaluate the safety and pharmacodynamics of 5 mg AZD4831 (mitiperstat) in adults with biopsy-proven non-cirrhotic NASH with fibrosis stage F1, F2, or F3.

MPOi AZD4831 (mitiperstat) is a low molecular weight, selective, and irreversible inhibitor of MPO that has been associated with improvement in liver inflammation and fibrosis in an animal model of NASH.

2.2 Background

2.2.1 Disease Background

NASH is part of the spectrum of liver diseases known as NAFLD, ranging from simple steatosis or non-alcoholic fatty liver to NASH. NAFLD is the most common cause of chronic liver disease in Western industrialized countries, and it has an estimated prevalence of approximately 6% to 35% worldwide (Bellentani 2017, Younossi et al 2016). NASH is the progressive form of the disease with a prevalence of approximately 2% to 3% of the general population. NASH can lead to cirrhosis and its complications, hepatocellular carcinoma, and end stage liver disease (Bellentani et al 2010). NASH is expected to become the leading reason for liver transplantation over the next decade and is an important etiology driving the burden of hepatocellular carcinoma (Cholankeril et al 2017, Wong et al 2014, Pais et al 2016).

NASH 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% and 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).

NASH is defined histologically as a multicomponent condition composed of hepatic steatosis,

inflammation, and hepatocyte ballooning in varying proportions. NASH differs from steatosis alone by the presence of hepatic cell inflammation and injury in response to lipotoxic intermediates that are accumulated and metabolized in the steatotic liver. 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, with lifestyle modifications being the mainstay of treatment. Many patients do not achieve or maintain dietary goals and weight loss. Consequently, the 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 (Estes et al 2018).

2.2.2 MPO and AZD4831 (mitiperstat) Background

A detailed description of the chemistry, pharmacology, pharmacodynamics, and safety of AZD4831 (mitiperstat) is provided in the IB.

MPO is a highly abundant protein mainly present in azurophilic granules of neutrophils, constituting 5% of the dry weight of the cells. In addition to neutrophils, there are also data suggesting the presence of MPO in monocytes and macrophages. MPO can be secreted and is unique in its ability to generate reactive chlorinating species such as hypochlorous acid, the active component of bleach, which possesses potent bactericidal and viricidal activities. In addition, hypochlorous acid reacts with electron-rich moieties of a large range of biomolecules (Nicholls and Hazen 2005).

MPO is deposited and active in the livers of patients with NASH (Rensen et al 2009, Pulli et al 2015, Pulli et al 2017). Neutrophils, the principal cell type expressing MPO, are elevated in patients with NASH and a high neutrophil to lymphocyte ratio is associated with advanced fibrosis (Alkhouri et al 2012). MPO has been identified as part of a proapoptotic and profibrotic pathway of progression in NASH via activation of inflammatory myeloid cells, hepatocytes, and hepatic stellate cells, with nonclinical studies indicating that MPO knockout reduces NASH-induced fibrosis (Pulli et al 2015, Rensen et al 2012). As such, MPO has been identified as a potential therapeutic target to ameliorate this disease.

In a diet-induced mouse model of NASH, the MPOi AZD4831 (mitiperstat) at a dose providing a plasma exposure predicted to achieve approximately CCI [redacted] (estimated based on PK-pharmacodynamics modeling using data

from study CCI), demonstrated significant improvement in histological scoring of liver inflammation and fibrosis while not affecting steatosis (study CCI data on file: Study report to be finalized by pre-IND submission). It is hypothesized that AZD4831 (mitiperstat) will similarly reduce inflammation and fibrosis in patients with NASH, thereby limiting progression of the disease and leading to NASH resolution and fibrosis reversal.

AZD4831 (mitiperstat) is a potent inhibitor of extracellular MPO in the micro- and macro-vasculature but has minimal effect on intracellular MPO activity, thus is expected to have a low risk of decreasing host-defense against infections.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD4831 (mitiperstat) may be found in the IB.

2.3.1 Risk Assessment

Identified and potential risks of AZD4831 (mitiperstat) along with mitigation strategies are shown in Table 3.

Table 3 Risk Assessment

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
AZD4831 (mitiperstat) - Identified Risk		
Maculopapular rash	Generalized maculopapular rash has been observed in healthy volunteers in completed global SAD/MAD studies at single doses of 45 mg and above and at repeated doses of 15 mg and above, at 7-10 days post dose. In the Phase IIa study in participants with HFpEF, one participant (of 27) had generalized maculopapular rash CTCAE Grade 3 at 5 mg AZD4831 (mitiperstat) occurring 5 days after up-titration from 2.5 to 5 mg. In a single-blind multiple-ascending dose study in healthy Japanese and Chinese participants, maculopapular rash CTCAE Grade 1 was reported in one Japanese participant (of 6) on 5 mg AZD4831 (mitiperstat), and maculopapular rash Grade 2 was reported in one Chinese participant (of 6) on 5 mg AZD4831 (mitiperstat) and in in 3 Japanese participants (of 6) on 10 mg AZD4831 (mitiperstat). See IB Section 6.3 for further information.	• Exclusion of participants with ongoing allergy/hypersensitivity reaction to drugs (Section 5.2) • Specific discontinuation criteria (Section 7.1) • AESI with special data collection/eCRF. (Section 8.3.6) • DRC oversight (Section 9.6)

Table 3 Risk Assessment

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
AZD4831 (mitiperstat) - Potential Risks of Clinical Significance		
Host-defense impairment (infections, including pneumonia)	The MPO in neutrophils generate ROS to fight infecting microorganisms so there is a theoretical risk is that treatment with an MPO inhibitor could impair host-defense mechanisms. Humans with total or partial MPO deficiency generally do not have an increased susceptibility to infections, but the incidence of Candida infections may be increased. An increased incidence of infection has not been seen in healthy volunteers/clinical study participants with AZD4831 (mitiperstat). See IB Section 6.2 for further information.	• AESI (Section 8.3.6) • AE monitoring for infections and relevant labs (CBC)
CCI	In the nonclinical safety studies in rats and dogs, inhibition of CCI caused reversible CCI These effects have also been observed nonclinically and clinically with other compounds of the same class and the magnitude of this effect is related to the degree of selectivity CCI . Clinically relevant changes in CCI have not been seen in limited clinical data with AZD4831 (mitiperstat). See IB Section 6.2 for further information.	• Monitoring CCI (Section 8.2.5) • CCI • Specific discontinuation criteria (Section 7.1)
CCI	CCI AZD4831 (mitiperstat) molecule and is known CCI o consistent findings on CCI has not been seen in healthy volunteers/clinical study participants with AZD4831 (mitiperstat). See IB Section 6.2 for further information.	• Monitoring CCI (Section 8.2.5)
CCI reduction and CCI increase	In secondary pharmacology studies, AZD4831 (mitiperstat) was shown to be an inhibitor of CCI Inhibition of this receptor is known to decrease CCI and cause CCI . Clinically relevant changes in CCI have not been seen in clinical trial participants on AZD4831 (mitiperstat). See IB Section 6.2 for further information.	• Monitoring CCI (Section 8.2.3)

Table 3 Risk Assessment

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Anemia and inflammation	One high-dose CCI dog developed severe clinical symptoms on CCI of dosing and did not recover sufficiently to allow further dosing. The dog was euthanized on CCI showed CCI. The cause of these findings is unknown. No other dogs in any studies with AZD4831 (mitiperstat) showed similar symptoms or CCI. Clinically relevant CCI have not been seen in healthy volunteers/clinical study participants with AZD4831 (mitiperstat). See IB Section 6.2 for further information.	• Routine CCI monitoring (Section 8.2.5)
CCI	A CCI finding was found in transgenic CCI mice in the CCI dose range finding study. CCI findings included increased CCI. Pathology showed CCI and CCI, increased CCI and CCI showed CCI findings were observed at CCI Clinically relevant changes in kidney function have not been seen in clinical trials. See IB Section 6.2 for further information.	• CCI (Section 5.2) • Routine CCI (Section 8.2.5)
Other		
COVID-19 pandemic risks	There is currently an outbreak of respiratory disease (COVID-19) caused by a novel SARS-CoV-2, for which the WHO declared a pandemic situation on 12 March 2020. While there is a theoretical risk that treatment with an MPO inhibitor could impair host-defense mechanisms, an increased incidence of infection has not been seen in limited clinical data with AZD4831 (mitiperstat). Therefore, the risk to participants exposed to SARS-CoV-2 or to those who suffer from COVID-19 is expected to be similar to the background population with the same comorbidities as those in the study, in particular non-cirrhotic NASH with fibrosis. The risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).	• Participants with signs or confirmation of significant infection are excluded from the study (Section 5.2) • Further risk mitigation measures are detailed in Appendix C

Table 3 Risk Assessment

Risk 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).	• Each investigator or designee that obtains a liver biopsy must be experienced and qualified to perform the procedure • Patients with cirrhosis, hepatic decompensation, and/or coagulopathy excluded (Section 5.2) • Relevant laboratory parameters checked prior to the procedure (eg, INR and platelet count) (Section 5.2)
Blood draws	Routine blood draws have a well-established risk profile.	• The risk is mitigated by following institutional standards.

AE, adverse event; AESI, adverse event of special interest; CBC, complete blood count; COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; DRC, Data Review Committee; eCRF, electronic case report form; CCI [redacted] B, Investigator's Brochure; INR, International normalized ratio; MAD, multiple ascending dose; MPO, myeloperoxidase; NASH, non-alcoholic steatohepatitis; NOAEL, no observed adverse effect level; CCI [redacted]; SAD, single ascending dose; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CCI [redacted] WHO, World Health Organization

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 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.

NASH is a condition with rising prevalence associated with poor quality of life and adverse prognosis; therefore, information acquired from this study could be of benefit to patients in the future by providing an improved understanding of the pathological processes that drive NASH progression, which may ultimately lead to new treatment opportunities for patients with NASH.

2.3.3 Conclusion

The study design aims to minimize potential risks to participants based on the protocol inclusion and exclusion criteria, safety monitoring, and other measures (Table 3). Taking into account the measures to minimize risk to participants in this study, the potential and identified risks associated with AZD4831 (mitiperstat) are justified by the anticipated benefits that may be afforded to participants with non-cirrhotic NASH with stage F1-F3 fibrosis.

3 OBJECTIVES AND ENDPOINTS

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effect of AZD4831 (mitiperstat) on circulating markers of hepatic injury and apoptosis or necrosis compared with placebo	Change from baseline and over placebo to Week 12: • ALT
Secondary	
To assess the effect of AZD4831 (mitiperstat) on circulating biomarkers of fibrosis compared with placebo	Change from baseline and over placebo to Week 12: • Pro-C3
To assess the PK of AZD4831 (mitiperstat)	Plasma concentration of AZD4831 (mitiperstat) will be summarized by timepoints. If PK data permit, a population PK model may be developed and potentially coupled with separate PD models; the derived PK parameters and the modeling will be provided in a separate PK and population PK/PD report.
Safety	
To assess safety and tolerability of AZD4831 (mitiperstat) compared with placebo in participants with non-cirrhotic NASH with fibrosis.	Safety and tolerability, including hepatic safety, will be evaluated in terms of AEs (including AESIs related to skin reactions, including maculopapular rash, and infection) and clinical and laboratory assessments.
Exploratory	
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
CCI	

AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; CCI ratio, diabetes; BMI, body-mass index; CCI CCI NASH, non-alcoholic steatohepatitis; CCI PD, pharmacodynamic(s); PK, pharmacokinetic(s); Pro-C3, released N-terminal propeptide of type III collagen; CCI

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study including a maximum of approximately 90 randomized adult participants with biopsy-proven non-cirrhotic NASH with fibrosis (NAS ≥ 4, fibrosis stages F1, F2, F3). The study will be conducted at approximately 48 sites across approximately 9 countries.

During screening, the participants will be checked for eligibility and enrolled in the study. Following an 8-week screening period, approximately 90 participants will be randomized at Visit 4 in a 1:1 ratio to once daily dosing of 5 mg AZD4831 (mitiperstat) or placebo. Participants, including participants who are rescreened, can be randomized anytime within the screening period outlined in the SoA (Table 2) once all inclusion/exclusion criteria have been fulfilled. For participants who have a historical biopsy and elevated ALT, the screening period can be shortened.

All participants will be treated once daily with 5 mg AZD4831 (mitiperstat) or placebo for 12 weeks. The safety, tolerability, and pharmacodynamics will be evaluated at 12 weeks.

An unblinded safety DRC consisting of AstraZeneca personnel and an external dermatologist will be set up for ongoing, periodic safety monitoring, with a focus on skin reactions and study stopping criteria. Additional details will be contained in the safety DRC charter.

Participants will be in the study for up to 24 weeks, including a screening period of up to 8 weeks, a 12-week treatment period, and a 4-week safety follow-up period.

4.2 Scientific Rationale for Study Design

This is the first study to test AZD4831 (mitiperstat) in participants with non-cirrhotic NASH with fibrosis.

This is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study. 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 participants with non-cirrhotic NASH with liver fibrosis. Participants with biopsy-proven non-cirrhotic NASH with fibrosis (NAS ≥ 4 with a component score of ≥ 1 for steatosis, lobular inflammation, and ballooning, as well as liver fibrosis stage F1, F2, F3) will be enrolled. Participants with stage F4 fibrosis (cirrhosis, compensated and decompensated) will not be included.

The study will evaluate safety, tolerability, PK, and pharmacodynamic effects of 1 dose level of AZD4831 (mitiperstat) versus placebo, administered once daily for a total of 12 weeks. The control group will receive matching placebo; there are no approved pharmacological

treatments for NASH that could be used as a comparator. All participants will be treated according to local guidelines on standard of care treatment, focusing on treatment of NASH symptoms and comorbidities.

The primary endpoint is change from baseline to Week 12 in log-transformed ALT, an indicator of hepatocellular injury. The secondary endpoints are Pro-C3 (measured to assess extracellular matrix formation) and PK. The study will also assess the safety and tolerability of AZD4831 (mitiperstat), including hepatic safety, at 12 weeks compared with placebo, with special focus on the incidence of AESIs related to skin reactions (including maculopapular rash) and infection, vital signs, clinical laboratory parameters, and ECG.

The exploratory endpoints include additional non-invasive assessments of CCI which is a composite measure of CCI Additional markers CCI will be measured. CCI will be measured to assess CCI will be measured to assess CCI . Other tools that leverage CCI s an index of NASH disease activity and fibrosis. Various non-invasive indices such as CCI , and CCI 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.

4.3 Justification for Dose

To date, 4 Phase I clinical studies have been completed in which a total of 36 healthy volunteers have been exposed to AZD4831 (mitiperstat) at doses of 5 to 405 mg as single doses and 53 healthy volunteers at doses 2.5 to 45 mg as multiple doses. In healthy volunteers, AZD4831 (mitiperstat) was generally well tolerated with the exception of generalized maculopapular rash seen around 7 to 10 days after the first dose: in the single ascending dose study (D6580C00001), 1 out of 6 receiving 45 mg, 1 out of 6 receiving 135 mg, and 2 out of 6 receiving 405 mg; in the MAD study (D6580C00004), 2 out of 8 receiving 15 mg and 2 out of 5 receiving 45 mg.

In a single-blind MAD study in Japanese and Chinese healthy volunteers (Study D6580C00008), maculopapular rash was reported in 5 of 24 Japanese and Chinese healthy volunteers who received AZD4831 (mitiperstat). Maculopapular rash CTCAE Grade 1 was reported in one of 6 Japanese healthy volunteers on 5 mg AZD4831 (mitiperstat), and maculopapular rash Grade 2 was reported in 1 of 6 Chinese healthy volunteers on 5 mg AZD9831 and in 3 of 6 Japanese healthy volunteers on 10 mg AZD4831 (mitiperstat).

A Phase IIa study intended to assess target engagement, safety, and tolerability of AZD4831

(mitiperstat) in participants with HFpEF was prematurely terminated during the COVID-19 pandemic after meeting predefined target engagement, safety, and tolerability criteria (Study D6580C00003). One participant out of 27 receiving 5 mg AZD4831 (mitiperstat) was discontinued from study treatment due to CTCAE Grade 3 generalized maculopapular rash.

The dose selection for this study is based on data from the Phase I MAD study (healthy volunteers), the Phase II study (HFpEF), and data from the MAD study in Japanese and Chinese healthy volunteers. One dose level is being investigated (5 mg) based on expected pharmacodynamics and safety. The 5 mg dose is predicted to result in approximately 60% MPO inhibition and is the upper safety dose since no rash was observed at doses below 15 mg AZD4831 (mitiperstat) in the Phase I MAD study (healthy volunteers), in 1 of 27 participants at 5 mg AZD4831 (mitiperstat) in the Phase IIa study (HFpEF), and in 2 of 12 healthy volunteers on 5 mg AZD4831 (mitiperstat) in the Japanese and Chinese MAD study. Doses of 2.5 and 5 mg are currently being investigated in an ongoing Phase IIb/III study (D6580C00010) in heart failure with left ventricular ejection fraction > 40%.

4.4 End of Study Definition

For the purpose of Clinical Trial Transparency (CTT) 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 subject for any protocol related activity.

Food and Drug Administration requirements defines two 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 they have completed all phases of the study including the last visit.

5 STUDY POPULATION

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

Each participant should meet all the inclusion criteria and none of the exclusion criteria to be assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Participants who do not meet the entry requirements are screen failures (Section 5.4).

In this protocol, "enrolled" participants are defined as those who sign informed consent. "Randomized" participants are defined as those who undergo randomization and receive a randomization number.

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 at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Participants with histologically confirmed NASH as diagnosed by liver biopsy within 12 months of provision of written informed consent fulfilling all of the following histological criteria and in accordance with the NASH CRN NAFLD Activity Score (NAS).

   (a) NAS ≥4 with a score of at least 1 in each of the 3 histological components (ie, steatosis, lobular inflammation, and ballooning)

   (b) Presence of fibrosis stage F1, F2, or F3

   Participants without a historical biopsy that meets the above histological criteria should be willing to undergo a liver biopsy at screening, result of which subsequently fulfills the criteria.

3 Hemoglobin A1c ≤ 9.5% (inclusive) at Visit 1 if T2DM present, managed by a stable medication (ie, no major dose adjustments in prior 3 months to randomization).

4 Two increased serum ALT measurements (ALT > ULN); one historical local ALT within 6 months prior to screening and one at screening.

5 Participants with or without diabetes. If participants are on GLP-1 receptor agonists, SGLT2 inhibitors, or pioglitazone, the medication has to be stable for at least 6 months prior to randomization.

6 Stable weight for at least 3 months prior to randomization. Stable weight is defined as ≤ 5% change.

Reproduction

7 Male and/or female. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

(a) Criterion not applicable to this CSP version.

(b) Criterion not applicable to this CSP version.

(c) Female participants:

- Female participants must not be pregnant or lactating.
- Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use an acceptable method of birth control, from enrolment throughout the study and until at least 4 weeks after last dose of study intervention. Acceptable methods of contraception include birth control pills, injections, implants or patches, intrauterine devices, and tubal ligation/occlusion. The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea. Female condom and male condom should not be used together.

Informed Consent

9 Capable of giving signed informed consent as described in Appendix D 3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol (including use of sample for genetic testing where allowed).

10 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 will be 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 Any positive results for HIV infection or positive results for hepatitis B surface antigen or hepatitis B core antibody or hepatitis C antibody test.

3 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).

4 History of cirrhosis and/or hepatic decompensation, including ascites, hepatic encephalopathy, or variceal bleeding.

5 Prior or planned liver transplantation.

6 Clinically significant cardiovascular or cerebrovascular disease within the past 3 months, 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 6 months or who are due to undergo these procedures at the time of screening.

7 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.

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

9 History of any life-threatening cardiac dysrhythmia (continuous or paroxysmal) or uncontrolled ventricular rate in participants with atrial fibrillation or atrial flutter or sinus node dysfunction with clinically significant pause or second to third degree AV-block untreated with pacemaker.

10 History of malignant neoplasms within 5 years prior to screening, except for adequately treated basal cell, squamous cell skin cancer, or in situ cervical cancer.

11 Prolonged QT interval (Fridericia-corrected QT interval > 470 ms) on ECG at screening (Visit 1), known congenital long QT syndrome, or family history of cardiac sudden death at age < 40 years.

12 History or ongoing drug allergies or hypersensitivity reactions to drugs (including but not limited to rash, angioedema, acute urticaria).

13 Participants with hyperthyroidism, uncontrolled hypothyroidism, or any clinically significant thyroid disease as judged by the investigator. Patients with TSH ≥ ULN should be excluded.

14 History of psychosis or bipolar disorder. History of major depressive disorder within the past year with the participant being clinically unstable, or any history of suicide attempt or history of suicidal ideation within the past year at the discretion of the investigator.

15 Participants with a positive SARS-CoV-2 infection test at screening (Visit 1), if clinically indicated, based on investigator discretion.

16 Participants with a significant COVID-19 illness within 6 months of enrollment:

(a) Participants with a diagnosis of COVID-19 pneumonia based on radiological assessment.

(b) Participants with diagnosis of COVID-19 with significant findings from pulmonary imaging tests.

(c) Participants with a diagnosis of COVID-19 requiring hospitalization and/or oxygen supplementation therapy.

17 History of excessive alcohol consumption, defined as an average weekly intake of > 21 drinks/week for males or > 14 drinks/week for females. One drink is equivalent to 14 g alcohol.

18 Evidence of alcohol dependence as assessed by the AUDIT questionnaire at screening (Appendix B).

19 Positive screen for drugs of abuse at screening or admission to the study site prior to the administration of the study intervention. Note: participants who test positive for drugs (ie, opioids) that are prescribed for appropriate medical use are eligible to participate in the study.

20 Recent (within 3 months of randomization) use of drugs approved for weight loss (eg, orlistat, bupropion/naltrexone, phentermine-topiramate, phentermine, lorcaserin), as well as those drugs used off-label.

21 Participants planning to make significant lifestyle changes to their diet or exercise regimen during the conduct of the study.

Prior/Concomitant Therapy

22 Criterion not applicable to this CSP version.

23 High dose vitamin E (> 400 IU) unless on a stable dose within 6 months of screening.

Prior/Concurrent Clinical Study Experience

24 Participation in another clinical study with an IP administered in the last 3 months or 5 half-lives of the therapy (whichever is longer) at the time of screening.

25 Participation in a clinical study testing anti-obesity medications within 12 months of screening.

26 Recent (within 6 months of screening) use of therapies associated with development of NAFLD (eg, systemic corticosteroids, methotrexate, tamoxifen, amiodarone, or long-term use of tetracyclines) (Table 5).

27 Recent (within 6 months of screening) use of obeticholic acid or other therapy under investigation for NASH (Table 5).

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

Diagnostic Assessments

29 Abnormal laboratory values including any of the following:

(a) AST or ALT > 5 × ULN.

(b) ALP ≥ 1.5 × ULN, unless not of hepatic origin.

(c) Impaired renal function defined as estimated glomerular filtration rate ≤ 30 mL/minute/1.73 m^2 at screening (estimated according to chronic kidney disease epidemiology collaboration) (Inker et al 2021).

(d) Albumin < 35 g/L.

(e) International normalized ratio > 1.3.

(f) TBL > ULN in the absence of known Gilbert's disease.

(g) Platelets < 150000/mm^3.

(h) MELD score ≥ 12.

(i) Any other clinically significant abnormalities in clinical chemistry, hematology, or urinalysis results as judged by the investigator.

30 Severely uncontrolled hypertension defined systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg on the average of 2 supine measurements after being at rest for at least 10 minutes at screening or randomization.

31 Heart rate > 110 bpm or < 50 bpm at randomization.

32 Any clinically significant abnormalities in rhythm, conduction, or morphology of the resting ECG, as considered by the investigator at the screening visit (Visit 1) and/or on Week −1.

Other Exclusions

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

34 Vulnerable participants, eg, kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

35 Judgment by the investigator that the participant should not participate in the study if they have any ongoing or recent (ie, during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions, and requirements.

36 Previous randomization in the present study.

Participants may be rescreened once if the reason for screen failure was transient (including but not limited to study-supplied equipment failure or unforeseen personal events that mandate missed screening visits) (Section 5.4). Rescreened participants should be assigned the same participant number as for the initial screening. Individuals who do not meet a specific criterion may have this parameter retested if the investigator determines there is a reason to believe that this was caused by a temporary/transient reason.

5.3 Lifestyle Considerations

No restrictions on lifestyle are required.

5.3.1 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 Table 2.

Study intervention can be taken with or without food.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized into the study. 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 (screen failure) may be rescreened once at the investigator's discretion. Participants that previously withdrew from the study are not permitted to be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening, and all enrollment assessments and procedures (including signing ICF) should be performed again, except the biopsy. Participants who are rescreened do not need to complete the full 8-week screening period, if all inclusion/exclusion criteria have been fulfilled. However, they must complete Visit 1 and Visit 3, following Table 2. Individuals who do not meet a specific criteria may have this parameter retested if the investigator determines there is a reason to believe that this was caused by a temporary/transient reason.

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) (including marketed product(s) and 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 AZD4831 (mitiperstat) or matching placebo.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Table 4 Investigational Products

Study Intervention Name	AZD4831 (mitiperstat)	Matching placebo
Dosage level(s)	5 mg	N/A

Table 4 Investigational Products

Study Intervention Name	AZD4831 (mitiperstat)	Matching placebo
Dosage formulation	Plain, round, biconvex, white, film-coated tablet	Plain, round, biconvex, white, film-coated tablet placebo
Route of administration	Oral	Oral
Dosing instructions	Once daily	Once daily
Use	Experimental	Placebo-comparator
IMP and NIMP	IMP	IMP
Packaging and labeling	Investigational Product will be provided in bottles. Labels of bottles with AZD4831 (mitiperstat) 5 mg will have white background and black description. Each bottle will be labeled in accordance with Annex VI to CTR 536/2014 and per country regulatory requirements.	Investigational Product will be provided in bottles. Labels of bottles with AZD4831 (mitiperstat) PTM 5 mg will have white background and black description. Each bottle will be labeled in accordance with Annex VI to CTR 536/2014 and per country regulatory requirements.
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca

CTR, clinical trial regulation; IMP, investigational medicinal product; N/A, not applicable; NIMP, non-investigational medicinal product; PTM, Placebo to Match

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 enrolled 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 Study medication will be dispensed to participants in a bottle with a white label. Participants will be instructed to take one tablet per day. Each bottle contains 35 tablets, and the participant will receive enough bottles to last until the next resupply visit.

5 The AstraZeneca representative or delegate is responsible for confirming the investigator or delegate has recorded the quantities of returned and unused tablets at a participant level before the study intervention is destroyed.

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

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants will be blinded with respect to active or placebo treatment.

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. This computerized randomization procedure will ascertain allocation concealment and will assign the participants 1:1 to AZD4831 (mitiperstat) (5 mg) or placebo. The randomization codes will be computer generated and loaded into the IRT/RTSM database. Before the study is initiated, the log-in information and directions for the IRT/RTSM will be provided to each site.

The study will be blinded to both participants and investigators/site staff as well as to the sponsor (designated sponsor personnel will be unblinded as part of the DRC as described in Section 9.6). The IRT/RTSM will provide to the investigator(s) the kit identification number to be allocated to the participant at the dispensation visit. Study intervention will be dispensed at the study visits summarized in Table 2. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

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 the 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.

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 (eg, antidote available), 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.

The randomization list should be sent to the personnel analyzing the PK samples. PK samples will be analyzed by the bioanalytical laboratory performing the bioanalyses only for participants on active treatment, as referenced in Section 8.5.2.1. To allow for the appropriate selection of samples, the bioanalytical laboratory will, therefore, have access to the treatment codes but will not share the codes with the sponsor or others involved in the study until the blinding is broken for the study.

6.4 Study Intervention Compliance

Study intervention will be administered in clinic on the day of randomization (Day 1, Visit 4), Day 29 (Visit 6), and Day 85 (Visit 8). Participants will self-administer study intervention at home on other days.

At Visit 8, a new bottle will not be dispensed at the site, and the participant will receive study intervention from the bottle they have brought from home. When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision, after checking treatment was not taken at home before coming to the study site. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. Participants will be provided with a dosing card to record the dose intake information (date and time) for each dose.

A record of the number of AZD4831 (mitiperstat)/placebo tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays 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 evaluated by the investigator/sponsor and recorded along with:

- Decision to keep taking or abstain from the medication
- Reason for use

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

COVID-19 vaccines received during the study and prior to study entry are to be recorded; the type of vaccine is also to be recorded.

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Anti-thyroid medications are restricted in this study; these include propylthiouracil, methimazole, and carbimazole.

NASH-related prohibited and restricted medications are described in Table 5.

Table 5 NASH-related Prohibited and Restricted Medications

Medication/Intervention	Additional Usage Information (including limits for duration permitted and special situations in which it's allowed)
Restricted	
Herbal preparations or dietary supplements marketed for control of body weight or appetite	Concurrent or prior use within 1 week prior to the start of screening and during the study.
Systemic corticosteroids by oral, intravenous, intraarticular, or intramuscular route	Within 6 months prior to screening and during the study unless prescribed for a very brief period of less than 7 days.
Vitamin E (high doses >400 IU)	Concurrent use, unless on a stable dose for at least 6 months prior to screening and no changes made during study. Vitamin E must not have been initiated after the liver biopsy was performed.
Pioglitazone or other PPAR-γ agonists	Concurrent use, unless on a stable dose for at least 6 months prior to screening, and no changes made during study.
Prohibited	
Therapies associated with development of NAFLD such as methotrexate, tamoxifen, amiodarone, or long-term use of tetracyclines	Within 6 months of screening until the end of the study. In the case of tetracyclines, these drugs are restricted during the study unless prescribed for a very brief period of less than 7 days.
Therapies in classes under investigation for the treatment of NASH (except for SGLT2 inhibitors and PPAR-γ agonists), such as obeticholic acid	Within 6 months of screening until the end of the study.
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 the last 3 months prior to the start of screening and during the study.

NAFLD, non-alcoholic fatty liver disease; NASH non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; SGLT2, sodium glucose co-transporter 2

6.6 Dose Modification

No dose modifications are allowed during the study.

6.7 Intervention After the End of the Study

There is no planned 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 permanently discontinue study intervention prior to Week 12 will have an EDV as described in Table 2. If study intervention is permanently discontinued, the participant should remain in the study, ie, continue to participate in scheduled study visits and evaluations.

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

At each visit, participants will be instructed to contact the investigator immediately if rash or skin reaction has developed. If maculopapular rash CTCAE Grade 1, 2, or 3 has developed, the participant must be permanently discontinued from study intervention and AstraZeneca medical staff must be informed.

- CTCAE Grade 1: Macules/papules covering < 10% body surface area with or without symptoms (eg, pruritus, burning, tightness)
- CTCAE Grade 2: Macules/papules covering 10% to 30% body surface area, with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental activities of daily living (refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc); rash covering > 30% body surface area with or without mild symptoms
- CTCAE Grade 3: Macules/papules covering > 30% body surface area, with moderate or severe symptoms; limiting self-care activities of daily living (refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)

If the participant develops a rash or skin reaction that is not considered a maculopapular rash but is a generalized rash/skin reaction or is considered to be an SAE, the participant must be permanently discontinued from the study intervention and AstraZeneca medical staff should

be informed.

Further information and rash/skin reaction evaluation guidance is provided in Appendix E 5.

Participants may also be discontinued from the study intervention in the following situations:

- Participant decision - The participant is at any time free to discontinue treatment, without prejudice to further treatment
- Lost to follow-up
- Pregnancy in a female participant
- AE or other safety reasons as judged by the investigator and/or sponsor, where continued treatment may put the participant at undue risk
- Development of uncontrolled and clinically significant CCI as judged by the investigator
- Severe non-compliance with the CSP
- Elevations in liver tests corresponding to possible DILI (Appendix F 8 for details)

Data to be collected at the time of intervention discontinuation and follow-up and any further evaluations that need to be completed are noted in Table 2.

7.1.1 Temporary Discontinuation

Every attempt should be made to maintain participants on the study intervention during the course of the study. If the study intervention has been interrupted, it should be re-introduced as soon as, in the opinion of the investigator, the participant is able to re-start study treatment.

Note related to AESI skin reactions (including maculopapular rash): In the event of maculopapular rash CTCAE Grade 1, 2, or 3, or any other generalized rash/skin reaction or serious rash/skin reaction, study intervention should be permanently discontinued. At each visit, participants will be instructed to stop the study intervention and contact the investigator immediately if rash or skin reaction has developed. After the participant has been seen by the study doctor or designee and the skin reaction is not considered a maculopapular rash CTCAE Grade 1, 2, or 3, or any other generalized rash/skin reaction or serious rash/skin reaction, the study treatment can be restarted.

7.1.2 Rechallenge

Participants who have temporarily discontinued study intervention can resume treatment as soon as, in the opinion of the investigator, the participant is able to re-start study treatment and the participant wishes to resume. No minimum time period is necessary before treatment can resume.

If a participant develops maculopapular rash CTCAE Grades 1, 2, or 3 or any other generalized rash/skin reaction or serious rash/skin reaction, study intervention should be permanently discontinued.

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. 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).
- At the time of withdrawal from the study, if possible, an EDV should be conducted, as shown in Table 2 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
    - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- 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.
- The reason for participant withdrawal should be recorded in the eCRF.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or 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 or not 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 have withdrawn from the study.
- Site personnel, or delegated third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get IP. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

7.4 Study Stopping Criteria

In the event of any of the following criteria being met, the clinical trial would be stopped if confirmed with the DRC.

- Any one death considered related to AZD4831 (mitiperstat) by the DRC.
- A difference of 2 patients experiencing SAEs considered related to AZD4831 (mitiperstat) by the DRC as compared to placebo.
- One Hy's Law case on AZD4831 (mitiperstat) (That is: AST or ALT ≥ 3× ULN **together with** Total Bilirubin ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases).
- Five patients who experience the following categories of rash/skin reaction leading to permanent discontinuation: CTCAE Grade 2 maculopapular rash, CTCAE Grade 3 maculopapular rash, other generalized rash/skin reaction not considered maculopapular, or other rash/skin reaction not considered maculopapular that is considered as an SAE; these would also need to be considered related to AZD4831 (mitiperstat) by the DRC.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in Table 2. 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 Table 2, is essential and required for study conduct.
- 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.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 2.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 300 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

ALT will be used as a surrogate non-invasive biomarker of hepatocellular injury (Table 8). The primary endpoint is change in ALT from baseline and over placebo to Week 12.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in Table 2. AEs based on examinations and tests are described in Section 8.3.5.

8.2.1 Medical History

Complete medical history will include history and current medical conditions past or present cardiovascular 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.

The AUDIT questionnaire to assess alcohol use habits will be completed at screening only (Table 2). The AUDIT questionnaire should be administered by the investigator using the latest version, downloaded from https://auditscreen.org. A sample is provided in Appendix B. The results will be used for determining participant eligibility (Section 4.4).

8.2.2 Physical Examinations

- A complete physical examination will include assessments of the following: general appearance; respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems.
- A brief physical examination will include, at a minimum, assessments of general appearance and skin, abdomen, musculoskeletal, cardiovascular, and respiratory systems.

Physical examination will be performed at timepoints as specified in Table 2.

8.2.3 Vital Signs

Vital signs (supine BP [average of 2 measurements], pulse rate, height, weight, and body temperature) will be performed in-clinic at timepoints as specified in Table 2. Vital sign assessments are to be collected using equipment supplied by the investigator.

At Visits 4 and Visit 8, the vital signs BP measurements can be used for the predose supine measurements for the orthostatic test, if taken after being supine for at least 10 minutes and as long as the standing BP measurements are taken after these supine measurements at the time intervals described below for the orthostatic BP measurement.

The measurements should be done before any blood sampling. The measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

8.2.3.1 Orthostatic Blood Pressure Measurements and Follow-up of Confirmed Orthostatic Hypotension

Orthostatic BP measurements will be obtained using a standard sphygmomanometer after scheduled supine measurements (1 and 3 minutes after the participant stands) and prior to any required blood draw:

- At baseline (Visit 4, Day 1), orthostatic BP should be measured predose and 1 to 2 hours post-dose.
- At Week 12 (Visit 8) orthostatic BP should be measured predose.

To minimize chances of orthostatic hypotension related to volume depletion, participants should be well hydrated when they come to the clinic for study visits. Supine BP measures will be collected after participants have been lying down for at least 10 minutes. To ensure that a stable supine BP is obtained, at least 2 systolic and 2 diastolic BP measurements will be obtained. If the replicate measurements differ by no more than 10 mmHg and 5 mmHg, respectively, the supine BP will be considered stable. The mean value of each replicate (mean systolic and mean diastolic value) will represent the baseline BP for that visit. After stable BP

is achieved, the participant will stand, and BP measurements will be taken at 1 and 3 minutes after the participant stands. If the BP measurements do not meet the criteria for orthostatic hypotension, no additional measurement is needed. If the BP measurement meets the criteria shown in Table 6, investigators will repeat the supine and standing measurements up to 2 additional times. The exception is for participants with orthostatic hypotension symptoms: In this situation, the orthostatic hypotension AE should be reported based on a single orthostatic test sequence.

When evaluating orthostatic vitals, record any symptoms of dizziness or light headedness. Record on the AE page in the eCRF. At Visit 4, if orthostatic hypotension is confirmed predose and postdose, the orthostatic hypotension AE should be reported twice (predose and postdose). The same applies to symptoms related to the measurement of orthostatic vitals: if present predose and postdose, it should also be reported as an AE twice (predose and postdose).

Table 6 Orthostatic Blood Pressure Criteria and Management

Decrease in BP Indicative of Orthostatic Hypotension	Actions
≥ 20 mmHg systolic or ≥ 10 mmHg diastolic	Repeat the BP measurements (supine and standing) up to 2 additional times, unless orthostatic hypotension is present in association with symptoms related to the measurement of orthostatic vitals: in such a case the test doesn't need to be repeated and the orthostatic hypotension AE and symptoms related to the measurement of orthostatic vitals AE should be reported based on a single sequence. If either the 1-minute or 3-minute standing BP meets the orthostatic (postural) hypotension criteria, then the sequence is considered indicative of orthostatic hypotension. If 2 of 2 or 2 of 3 sequences are positive, then orthostatic hypotension is confirmed, and an AE of orthostatic hypotension will be reported.

AE, adverse event; BP, blood pressure

For participants with orthostatic hypotension, individualized treatment should be prescribed at the investigator's discretion following local guidelines, including pharmacological (eg, down titration of nitrates) or non-pharmacological (eg, hydration) treatments.

8.2.4 Electrocardiograms

Single 12-lead ECG will be obtained after the participant has been resting in a supine position for at least 10 minutes, at the visits outlined in Table 2. A digital ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals will be used. Interpretation of the clinical safety digital ECG findings will be reviewed and confirmed by the investigator and recorded in the eCRF.

8.2.5 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken as the visits indicated in Table 2.

AEs based on laboratory tests should be recorded and reported as described in Section 8.3.5.

Additional safety samples, including antineutrophil cytoplasmic antibodies samples, may be collected if clinically indicated at the discretion of the investigator. The date and time of collection will be recorded on the appropriate eCRF.

The clinical chemistry, hematology, and urinalysis will be performed at a central laboratory.

Table 7 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	
Hemoglobin	Leukocyte differential count (absolute count and percent differential)
Leukocyte count	Platelet count
Hematocrit	MCV
MCHC	MCH
RDW	Reticulocyte
HbA1c	
Clinical Chemistry (serum)	
Creatinine	Albumin
Bilirubin, total	Potassium
Bilirubin, direct	Calcium, total
Bilirubin, unconjugated, ie, indirect (total – direct)	Sodium
ALP	Creatine kinase
AST	Glucose
ALT	Chloride
CCI [redacted]	Bicarbonate
CCI [redacted]	Phosphorus
CCI [redacted]	Magnesium
CCI [redacted]	
Urine	
Hb/Erythrocytes/Blood	Glucose
Protein/Albumin	Pregnancy test (for WOCBP only)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; HbA1c, hemoglobin A1c; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution width; CCI [redacted] WOCBP, women of childbearing potential.

Note, in case a participant shows an AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, refer to Appendix F "Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law," for further instructions.

Table 8 Other Clinical Safety Labs--Screening Only

Panel Name	Markers
Serology	• HIV I and II • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C antibody
Immunology [a]	• c-ANCA • p-ANCA
Substance use	• Blood alcohol (screening only; whole blood) [b] • Drugs of abuse, standard panel (screening only; urine)
Other	• COVID-19 (local assessment) [c]

[a] The ANCA sample collected at baseline is to only be tested upon requirement ie, CCI [redacted] based on investigator discretion. An additional sample should be collected if clinically indicated.
[b] For European countries, alcohol urine test will be used.
[c] If clinically indicated, based on investigator discretion.
c-ANCA, cytoplasmic staining antineutrophil cytoplasmic antibodies; p-ANCA, perinuclear-anti-neutrophil cytoplasmic antibodies

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 E.

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 or SAE.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

Adverse events will be collected from time of first dose throughout the treatment period and including the follow-up period. The only exception is related to the predose orthostatic test at

Visit 4: If orthostatic hypotension is confirmed, it should be reported as an AE, and symptoms related to the measurement of orthostatic vitals if present should also be reported as an AE.

Serious adverse events will be recorded from the time of signing of the informed consent form.

If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product 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 Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the participant's last AE assessment in 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.

AE Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Maximum CTCAE grade for maculopapular rash
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- 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
- In case of fatality:

  - Probable cause of death
  - Date of death
  - Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention 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 IP?"

For SAEs, causal relationship should also be assessed for other medication. 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 E to the CSP.

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 measurements 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:

- Skin reactions, including maculopapular rash
- Infections

These AESIs are to be reported as described in Section 8.3.1 and Section 8.3.2.

8.3.6.1 Skin Reactions, Including Maculopapular Rash

If the rash is considered maculopapular, it will be evaluated using CTCAE Grades 1-3 for rash maculopapular; if not considered maculopapular, severity will be captured as mild/moderate/severe, along with data element components generally used for CTCAE grading of other skin reactions, given that CTCAE grading is specific to the particular type of skin lesion. For all rashes, various aspects of the rash will be documented, including start/end date, morphology of lesions (maculopapular vs other morphologies), body surface area impacted, anatomical site(s), symptoms, effect on participant (including ADL impacted), concomitant medications, medication administered, and specific rash diagnosis, if available. Photos (overview and detailed) should be taken.

Refer Appendix E 5 for further guidance in rash assessment and reporting.

At all visits, participants will be instructed to contact the investigator immediately if rash or skin reaction has developed at any time point during the study.

Participants who develop skin reactions, including rash, will be asked to return to the clinic for an additional visit that will include a full physical exam and collection of blood samples for safety, hs-CRP, and PK. If a participant is discontinued from IP and proceeds to the EDV, an exploratory biomarker sample and blood and urine samples for metabolite analysis will also be collected. The genetic sample should also be collected at the EDV if not previously collected from the participant. It is suggested to start with treatment for maculopapular rash,

per local standard treatment guidelines (which may include, but not be limited to, a topical steroid and/or oral antihistamine). The treatment should be individualized per participant and based on investigator discretion. The participant can be provided with a treatment for the skin rash, according to clinical management standard.

Patients should be referred to a dermatologist if they experience a skin reaction or rash that is considered severe, serious, persists ≥ 7 days, continues worsening after discontinuing the investigational agent, or if the investigator deems it otherwise necessary. It would be recommended that the dermatologist determine whether the individual subject will benefit with additional treatment and recommended that a biopsy is performed if deemed necessary by the dermatologist in these scenarios.

Blood samples should be drawn prior to treatment, if possible, and without delaying treatment.

8.3.6.2 Infection

Infections will be considered AESI in this study. Local laboratory testing for microorganisms per local guidelines is requested for serious infections (those that meet SAE criteria) and results documented.

8.3.7 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. Refer to Appendix F for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.8 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not 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 EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the investigator/study site staff how to proceed.

Further guidance on the definition of a SAE is provided in Appendix E.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

8.3.9 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.

8.3.9.1 Maternal Exposure

Should a pregnancy occur, the IP should be discontinued immediately and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention 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 8.3.8) 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.

8.3.10 Medication Error, Drug Abuse, and Drug Misuse

8.3.10.1 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 **one 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 **one** (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 event of medication error, drug abuse or misuse (Section 8.3.8) and **within 30 days** for all other events.

8.3.10.2 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 and examples of medication error can be found in Appendix E 4.

8.3.10.3 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 and examples of drug abuse can be found in Appendix E 4.

8.3.10.4 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 and examples of drug misuse can be found in Appendix E 4.

8.4 Overdose

For this study, any dose of study intervention greater than those specified in this protocol within the same day will be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/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 8.3.8) and **within 30 days** for all other overdoses.

8.5 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. Further details on Handling of Human Biological Samples are provided in Appendix G.

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.

- Pharmacokinetic samples may be disposed of or anonymized by pooling, after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses. 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.

8.5.1 Liver Biopsy

Liver biopsy samples taken at baseline (either historical [collected within 12 months of screening] or taken during the screening period) will be assessed locally by a qualified pathologist. Details of the liver biopsy should follow local procedures.

Participants must have histologically confirmed NASH as diagnosed by liver biopsy (historical or screening) fulfilling the following histological criteria:

- NAS ≥ 4 with a score of at least 1 in each of the 3 histological components (ie, steatosis, lobular inflammation, and ballooning)
- Presence of fibrosis stage F1, F2 or F3

8.5.2 Pharmacokinetics

- Blood samples will be collected for measurement of concentrations of AZD4831 (mitiperstat) in plasma as specified in Table 2.
- Pharmacokinetic samples will be collected predose; thus, participants should be reminded not to take their study medication at home on the day of their clinic visit as they will receive study medication in clinic on these days. Therefore, study medication administration at Visit 4, Visit 6, and Visit 8 will be in clinic.
- 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.
- Plasma samples will be used to analyze the PK of AZD4831 (mitiperstat). Samples collected for analyses of AZD4831 (mitiperstat) plasma concentration may also be used to evaluate safety or pharmacodynamics aspects related to concerns arising during or after the study.
- Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.
- Dosing cards will be given to the participants at the randomization visit and the participants will be asked to fill in the dose intake information (date and time) at home.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5.2.1 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be analyzed by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method and only for participants on active treatment. Only samples from participants on active treatment will be analyzed (Section 6.3), unless there is a need to confirm that correct treatment has been given to study participants. 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 until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will not be reported in the

CSR, but in a separate Bioanalytical Report. Pharmacokinetic concentrations may be assessed during the study for evaluation of the exposure levels.

8.5.3 Pharmacodynamics

Samples for pharmacodynamic assessments will be collected according to the Laboratory Manual at timepoints described in Table 2. Non-invasive biomarker assessments are described in Section 8.6.1.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

Samples for biomarker research are required and will be collected from all participants in this study as specified in Table 2.

Table 8 presents protocol-defined non-invasive biomarker assessments that are part of the primary, secondary, or exploratory objectives.

Table 8 Non-invasive Biomarker Assessments

Assessment	Biomarker
CCI	ALT CCI
CCI	CCI Pro-C3, CCI
CCI	
CCI	

Table 8 Non-invasive Biomarker Assessments

Assessment	Biomarker
CCI	

ALT, alanine aminotransferase; CCI

CCI

Pro-C3, released N-terminal propeptide of type III collagen; CCI

8.6.1.1 Collection of Mandatory Sample for Genetic Analysis

A blood sample will be collected for mandatory genetic analysis by AstraZeneca or designated organization(s) for participants at sites located in countries that have authorized genetic analysis in this study. This sample will be used to prepare DNA to assess the genotype of certain genes that may be associated with:

- how the investigational drug is metabolized by the participant's body
- the development of skin reactions
- progression of NAFLD (eg, PNPLA3, HSD17B13, TM6SF2, MBOAT7, GCKR)

Genotyping or entire gene sequencing will include, but will not be limited to, an assessment of the human leukocyte antigen genes and NASH associated genes. The sample will only be used for these purposes as outlined.

The blood sample for genetic research will be obtained from the participants at Visit 4.

If for any reason the sample is not drawn at Visit 4, it may be taken at any visit until the last study visit. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.6.2 Optional Collection of Human Biological Samples for Future Use

Collection of fasting plasma, serum, and urine samples for future biomarker research is also part of this study as specified in Table 2 and is subject to agreement to optional consent.

Plasma, serum, and urine samples will be collected for the future exploratory analysis of biomarkers that may respond to treatment with AZD4831 (mitiperstat) or that predict response to treatment with AZD4831 (mitiperstat). Distinct from the mandatory collection of exploratory samples, these samples may be used to analyze exploratory biomarkers not

defined in the CSP and may include multiplex analysis using biomarker panels.

Samples will be collected, handled, labeled, stored, and shipped as detailed in the Laboratory Manual. Storage, re-use, and destruction of exploratory samples are described in Section 8.5 and Appendix F.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in Table 2 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. Appendix A 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. Information on storage and destruction of genetic samples is provided in Appendix A.

8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary hypothesis of the study is that once daily dosing of 5 mg AZD4831 (mitiperstat) will result in a significant decrease versus once daily dosing of placebo in ALT at end of treatment relative to ALT at baseline in a NASH patient population. The safety hypothesis is that once daily dosing of 5 mg AZD4831 (mitiperstat) will be safe and tolerable in a NASH patient population.

Statistical hypotheses for secondary endpoints are described in Section 9.4, and further details will be provided in the SAP.

No multiplicity adjustment for alpha is planned.

9.2 Sample Size Determination

The study has been powered to have at least 80% power to detect a 25% decrease in ALT level at end of treatment relative to baseline for AZD4831 (mitiperstat) treated versus placebo treated in a one-sided test at 5% significance level, based on the FAS population. Alanine aminotransferase measurements will be log-transformed before analysis. Under the assumption of a standard deviation of 0.50 for change from baseline in log-transformed ALT,

and allowing for 10% missing data, 45 participants per arm would render the desired power.

9.3 Populations for Analyses

9.3.1 Full Analysis Set

All participants who have been randomized to the study intervention will be included in the FAS irrespective of their protocol adherence and continued participation in the study. Participants will be analyzed according to their randomized study intervention irrespective of whether or not they have prematurely discontinued and irrespective of the treatment they actually received. Participants who withdraw consent to participate in the study are included up to the date of their study termination. The FAS will be considered the primary analysis set for all pharmacodynamics variables.

9.3.2 Safety Analysis Set

All participants who received at least 1 dose of randomized AZD4831 (mitiperstat) or placebo will be included in the safety analysis set. Throughout the safety results sections, erroneously treated participants (eg, those randomized to AZD4831 (mitiperstat) but actually given placebo) will be accounted for in the actual treatment group. A participant who had received any dose of the experimental study intervention will be classified as in the experimental IP group.

9.3.3 PK Analysis Set

The PK analysis set will consist of all participants in the FAS who have received at least one dose of AZD4831 (mitiperstat) and who have at least one PK sample post dose.

9.4 Statistical Analyses

The SAP will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1 General Considerations

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violations have been identified and documented. Analyses will be performed by AstraZeneca or its representatives.

Nominal significance will be 5% and all tests will be one-sided. All confidence intervals will be 2-sided and 95%.

No multiplicity adjustment for alpha is planned.

For analyses both on the FAS and on the SAS, baseline is defined as the last non-missing value prior to first dose including unscheduled assessments that occurs prior to first dose.

All summary statistics will be presented in total, divided by fibrosis stage, and divided by T2DM status.

9.4.2 Pharmacodynamics

9.4.2.1 Primary Endpoint

The primary pharmacodynamic endpoint for this study is change from baseline to Week 12 in log-transformed ALT.

The null hypothesis of no decrease in ALT comparing AZD4831 (mitiperstat) to placebo will be tested versus the alternative hypothesis of a decrease in ALT in favor of AZD4831 (mitiperstat) to placebo using a one-sided test at 5% significance level, assessed through a treatment policy estimand. The endpoint will be analyzed in a mixed effects linear model with participant as random effect, treatment, visit and treatment-by-visit interaction as fixed effects, and baseline as covariate. Data will be log-transformed before analyses, and results will be back-transformed to describe relative change versus placebo in value at end of treatment relative to baseline. Furthermore, data will also be analyzed as individual percental change, that is (value at time t – value at baseline)/(value at baseline)100%, in a similar mixed effects model but without log transformation of data.

- **Treatment:** Treatment with 5 mg AZD4831 (mitiperstat) compared to placebo, administered in addition to optimal background therapy for co-morbidities
- **Population:** FAS
- **Endpoint:** Change from baseline in log-transformed ALT
- **Intercurrent events:** Intercurrent events will be ignored (treatment policy strategy) and potential missing data imputed
- **Population-level summary:** Relative change versus placebo in value at end of treatment relative to baseline

Any missing baseline ALT values will be imputed based on existing baseline values of FAS participants using PROC MI MCMC, disregarding the treatment group. For postbaseline missing ALT values, a distinction in the imputation will be made between non-monotone and monotone missing data. Monotone missing data are defined as missing data that constitute the end participant follow-up, while non-monotone missing data means that there are observations made after the missing time point. Any non-monotone missing data will be replaced using PROC MI MCMC while monotone missing data will use PROC MI regression. The imputation model will include timepoint, baseline value, and treatment group. More details will be described in the SAP.

9.4.2.2 Secondary Endpoint

For Pro-C3 the null hypothesis of no decrease comparing AZD4831 (mitiperstat) to placebo will be tested versus the alternative hypothesis of a decrease in favor of AZD4831 (mitiperstat) to placebo in the same way as for ALT. Missing observations will be imputed using the same method as for missing ALT observations.

Estimand for Pro-C3:

- **Treatment:** Treatment with 5 mg AZD4831 (mitiperstat) compared to placebo, administered in addition to optimal background therapy for co-morbidities
- **Population:** FAS
- **Endpoint:** Change from baseline in log-transformed Pro-C3
- **Intercurrent events:** Intercurrent events will be ignored (treatment policy strategy) and potential missing data imputed
- **Population-level summary:** Relative change versus placebo in value at end of treatment relative to baseline

Furthermore, all pharmacodynamics data collected will be listed for each participant and summarized descriptively (including, but not limited to, mean, SD, minimum, median, maximum, geometric mean, geometric coefficient of variation) by treatment and time point/visit. Figures of the mean response (absolute change from baseline, and value relative to baseline where appropriate) will be used to visualize the average response over time.

It is important to distinguish between non-adherence with, or withdrawal from, randomized treatment and discontinuation from the trial. A randomized participant can withdraw from the study but not from the analysis. The potential impact of intercurrent events (events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation [eg, discontinuation of treatment, switching treatment, severe adverse and clinical events, lost to follow-up, or withdrawn consent]) apart from rash leading stop of study treatment, potential intercurrent events are anticipated to have even distribution between the treatment arms.

9.4.2.3 Exploratory Endpoints

Analysis of exploratory endpoints will be described in the SAP.

9.4.3 Safety

The safety endpoint for this study is safety and tolerability, including hepatic safety, during treatment with AZD4831 (mitiperstat) (5 mg) compared with placebo. Safety analyses will be performed using the safety analysis set. Safety data will be presented using descriptive statistics unless otherwise specified.

Adverse Events

Adverse events will be coded using the most recent version of the MedDRA that will have been released for execution at AstraZeneca. Adverse events will be presented for each treatment group by System Organ Class and/or Preferred Term covering number and percentage of participants reporting at least one event and number of events where appropriate. An overview of AEs will present for each treatment group the included number and percentage of participants with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP. Separate AE tables will be provided taking into consideration seriousness, death, and events leading to discontinuation of IP. An additional table will present number and percentage of participants with most common AEs. Most common (eg, frequency of > x%, ≥ x%) will be defined in the SAP. In accordance with the requirements of the FDA, a separate table will present nonserious AEs occurring in more than 5% of participants in any treatment group. Key participant information will be presented for participants with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP. An AE listing for the safety analysis set will cover details for each individual AE. Adverse events of special interest related to skin reactions, including maculopapular rash, and infection will be presented. Full details of AE analyses will be provided in the SAP.

Vital Signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, min, Q1, median, Q3, and max. For each scheduled postbaseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline. Details of vital sign analyses will be provided in the SAP.

Laboratory

Laboratory parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, min, Q1, median, Q3, and max. For each scheduled postbaseline visit, descriptive statistics for all clinical chemistry and hematology parameters will be presented for observed values and change from baseline. A frequency table presents number of participants reporting at least one treatment emergent change in selected laboratory parameters. Details of laboratory analyses will be provided in the SAP.

Electrocardiogram

Electrocardiogram evaluation will be summarized and presented by treatment group for baseline and for each scheduled postbaseline assessment. More details of ECG analyses will be provided in the SAP.

9.4.4 Analysis of Pharmacokinetic Data

Plasma concentrations of AZD4831 (mitiperstat) will be summarized by timepoints and

presented in the CSR. If PK data permit, a population PK model may be developed, possibly with the support of PK data from other studies, using nonlinear mixed effects regression analysis in the NONMEM program. Furthermore, if data allows, the population PK model may be coupled with separate pharmacodynamics models. All PK/pharmacodynamics modeling will be described in a separate data analysis plan. Moreover, the derived PK parameters and the results of any such modeling will be provided in a separate PK and population PK/pharmacodynamics report (as an appendix to the CSR or as a stand-alone report).

9.5 Interim Analysis—Not Applicable

9.6 Data Monitoring Committee

There will be no data monitoring committee in this study. An unblinded safety DRC consisting of AstraZeneca personnel and an external dermatologist will be set up for ongoing, periodic safety monitoring, with a focus on skin reactions and study stopping criteria. Additional details will be contained in the safety DRC charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Optional Genomics Initiative Sample

A 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 health care and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) 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.

A 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 Criterion

- 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 in 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 4 randomization. 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 4, 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 D.

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, 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 B 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.	

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.

Appendix C COVID-19

C 1 Background to COVID-19

There is currently an outbreak of respiratory disease (COVID-19) caused by a novel SARS-CoV-2 that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe causing the WHO to declare a pandemic situation on 12 March 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect participants, site staff, and society as a whole.

Both EMA and FDA as well as national health authorities in Europe have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect participants participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline.

C 2 Risk Assessment for COVID-19 Pandemic

While there is a theoretical risk that treatment with a myeloperoxidase inhibitor could impair host-defense mechanisms, an increased incidence of infection has not been seen in limited clinical data with AZD4831 (mitiperstat). Therefore, the risk to participants exposed to SARS-CoV-2 or to those who suffer from COVID-19 is expected to be similar to the background population with the same co-morbidities as those in the study, in particular non-cirrhotic non-alcoholic steatohepatitis (NASH) with fibrosis. The risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

AstraZeneca has no data on the co-administration of AZD4831 (mitiperstat) and COVID-19 vaccines being approved. Potential AZD4831 (mitiperstat) vaccine interactions affecting patient safety or IMP and vaccine efficacy are therefore unclear.

Measures to mitigate the additional risks caused by COVID-19 are:

- This study is going to start enrolling only when the sponsor deems it is safe to start the study. In addition, the study will not start until the local confinement measures or other

safety restrictions linked to the COVID-19 pandemic imposed by the local authorities are compatible with safe conduct of the study.

- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Participants will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnea, sore throat, and fatigue throughout the study during the pandemic. Once clinical signs of infection are reported by participants, the investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, adverse events and concomitant medications will be obtained via phone calls. The decision to continue with dosing the participant with the study drugs in the event of him/her showing symptoms of COVID-19 infection will be per investigator's discretion.
- The probability of virus transmission will be controlled as much as possible by:
  - Advice for participant to adhere to local requirements for reduction of the public exposure while ambulatory.
  - Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on investigator's discretion.
  - Physical distancing and person-to-person contact restrictions will be applied during site visits.
  - Where physical distancing is not possible, personal protective equipment will be used by study participants (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the investigators and site staff and guided by local requirements.
  - Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.
- If site visits are not possible due to local restrictions, home nursing visits may be considered after discussion with and approval by the sponsor. Study intervention may be delivered direct to participant if appropriate and via sponsor approved courier service.

C 3 Restrictions Related to COVID-19

During the COVID-19 pandemic, participants are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory. If applicable, prior to screening (Visit 1), potential participants should be called to confirm they are not experiencing any COVID-19 symptoms and signs and are asked not to attend the site in case of suspected infection. If appropriate, participants will be referred to the local health care system. Physical distancing and person-to-person contact restrictions will be applied and explained to participants while staying at the study site. Where physical distancing is not possible, study

participants will be asked to use surgical face masks and/or gloves if deemed appropriate by the investigator and site staff and guided by local requirements.

C 4 Data Quality Assurance Related to COVID-19

Monitoring visits at site will be limited to a minimum required as deemed appropriate during COVID-19 pandemic, per local regulations.

In addition, where possible, other measures for carrying out protocol related activities, such as but not limited to home nursing, may be employed as required.

Appendix D Regulatory, Ethical, and Study Oversight Considerations

D 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 Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (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 contract research organization, 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 serious adverse event (SAE) is essential so that legal obligations and ethical responsibilities towards 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 and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to the sponsor 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 subject or the reliability and robustness of the data generated in the clinical trial.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately but no later than 24 hours of when he or she becomes aware of it.
- In certain regions/countries, the sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
    - The sponsor 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, the sponsor is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (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 the sponsor or delegated party, through the contacts (e-mail address or telephone number) provided by the sponsor

D 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.

D 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.

D 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 ICF.
- 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.

D 5 Dissemination of Clinical Study Data

Due to scientific reasons, results (both technical and lay summaries) for this trial will be disclosed to EU Clinical Trial Information System within a year from global End of Trial Date in all participating countries, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on AstraZeneca Clinical Trials and 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.

D 6 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, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and 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.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring 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, Contract Research Organizations).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) 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 25 years after study completion unless local regulations or institutional policies require a longer retention period, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. 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.

D 7 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 source data verification plan.

D 8 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 the first site open, 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.

D 9 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 E Adverse Events Definitions and Additional Safety Information

E 1 Definition of Adverse Events

An adverse event (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.

E 2 Definition of Serious Adverse Events

A serious adverse event (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.

AEs for **malignant tumors** reported during a study should generally be assessed as **SAEs**. 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-SAE**. 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 an SAE, 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 E 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 E 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 E 2.

E 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.

E 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 investigational medicinal product (IMP) or AstraZeneca non-investigational medicinal product (NIMP) 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 refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding interactive response technology [IRT]/ randomization and trial supply management [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

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 Data Entry Site (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 regards 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

E 5 Guide to Skin Reaction Assessment

This Appendix describes the process to be followed to appropriately identify, assess, and report cases of skin reactions. Skin reactions, including maculopapular rash, will be considered AEs of special interest in this study. To ensure that data are collected systematically, any skin reaction will be recorded on a special eCRF page. All skin reactions should be recorded and reported as AEs or SAEs.

If the rash is considered maculopapular, it will be evaluated using Common Terminology Criteria for Adverse Events (CTCAE) Grades 1 to 3 for rash maculopapular; if not considered maculopapular, severity will be captured as mild/moderate/severe, along with data element components generally used for CTCAE grading of other skin reactions, given that CTCAE grading is specific to the particular type of skin lesion. For all rashes, various aspects of the rash will be documented, including start/end date, morphology of lesions (maculopapular vs other morphologies), body surface area impacted, anatomical site(s), symptoms, effect on participant (including activities of daily living [ADL] impacted), concomitant medications, medication administered, and specific rash diagnosis, if available.

If maculopapular rash Grade 1, 2, or 3 has developed, participant must be permanently discontinued from IP, and AstraZeneca medical staff should be informed.

If the participant develops a rash or skin reaction that is not considered a maculopapular rash, the participant must permanently discontinue if the rash/skin reaction is considered an SAE or is a generalized rash/skin reaction. AstraZeneca medical staff should be informed.

At all visits, participants will be instructed to contact the investigator immediately if rash has developed at any time point during the study. Participants will be recommended to make an acceptable quality self-photo of skin affected with rash.

Participants who develop skin reactions, including rash, will be asked to return to the clinic for an additional visit that will include a full physical examination and blood samples for safety, high-sensitivity C-reactive protein (hs-CRP), and pharmacokinetics (PK). If a participant is discontinued from investigational product and proceeds to the early discontinuation visit (EDV), exploratory biomarker sample and blood and urine samples for exploratory metabolite analysis will also be collected. The mandatory genetic sample per Section 8.6.1 should also be collected at the EDV if not previously collected from the participant. Initiation of treatment for maculopapular rash is suggested, in line with local standard treatment guidelines which could include, but not limited to, a topical steroid and/or oral antihistamine. The treatment should be individualized per participant and based on investigator discretion. The participant can be provided with a treatment for the skin rash, according to clinical management standard.

Patients should be referred to a dermatologist if they experience a skin reaction or rash that is considered severe, serious, persists ≥ 7 days, continues worsening after discontinuing the investigational agent, or if the investigator deems it otherwise necessary. It would be recommended that the dermatologist determine whether the individual subject will benefit with additional treatment and recommended that a biopsy is performed if deemed necessary by the dermatologist in these scenarios.

Blood samples should be drawn prior to treatment, if possible, and without delaying treatment.

The investigator should make quality photo(s) of participant's skin affected with rash, that will allow the evaluation of rash according to the guidance given in this section. Photos taken by the investigator and participant should avoid identifying features like the face, use adequate lighting, and capture both a close-up photo(s) of the affected skin and photo(s) from farther away to give context to the size of the affected area and the location of the skin reaction/rash. Face, tattoos, piercings, and other identifiers must not be seen in the photo(s) to avoid identification of the participant (participant can cover them when making photo, or these can be masked/edited afterwards by investigator).

Participant must not send any photo(s) to investigator via SMS, e-mail, or in any other way in order to keep the data privacy and anonymity. Investigator may take a photo of participant's photo(s) showed on digital device (phone, tablet, etc). Alternatively, participant can print out photo(s) at the site visit and give them to the site staff for scanning.

The Common Terminology Criteria for AEs is a descriptive terminology that can be used for AE reporting.

In general, CTCAE Guidelines describe the Grades of AE severity from 1 to 5:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*

Grade 3: Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

***Instrumental ADL** refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

****Self-care ADL** refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note: for <u>Maculopapular rash, only 3 CTC Grades exist:</u>

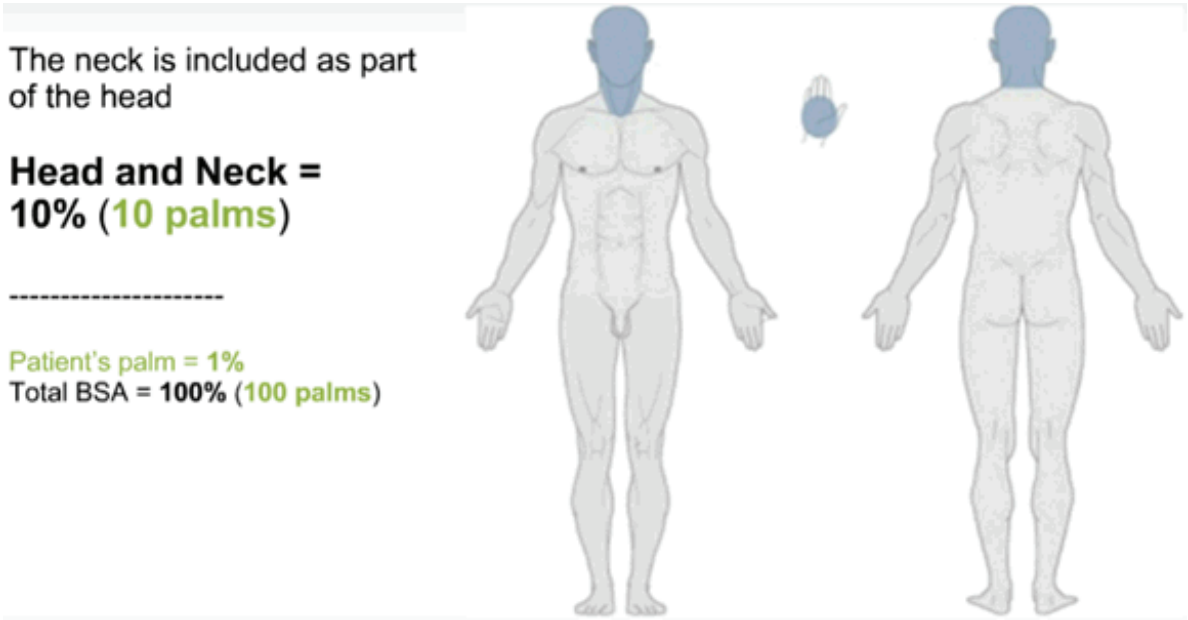
Maculo-Papular Rash	
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous AEs, frequently affecting the upper trunk, spreading centripetally, and associated with pruritis.	
Grade 1	Macules/papules covering < 10% Body Surface Area with or without symptoms (eg, pruritus, burning, tightness)
Grade 2	Macules/papules covering 10 - 30% Body Surface Area, with or without symptoms (eg, pruritus, burning, tightness); limiting Instrumental Activities of Daily Living*; rash covering > 30% Body Surface Area with or without mild symptoms
Grade 3	Macules/papules covering > 30% Body Surface Area, with moderate or severe symptoms; limiting Self-care Activities of Daily Living **

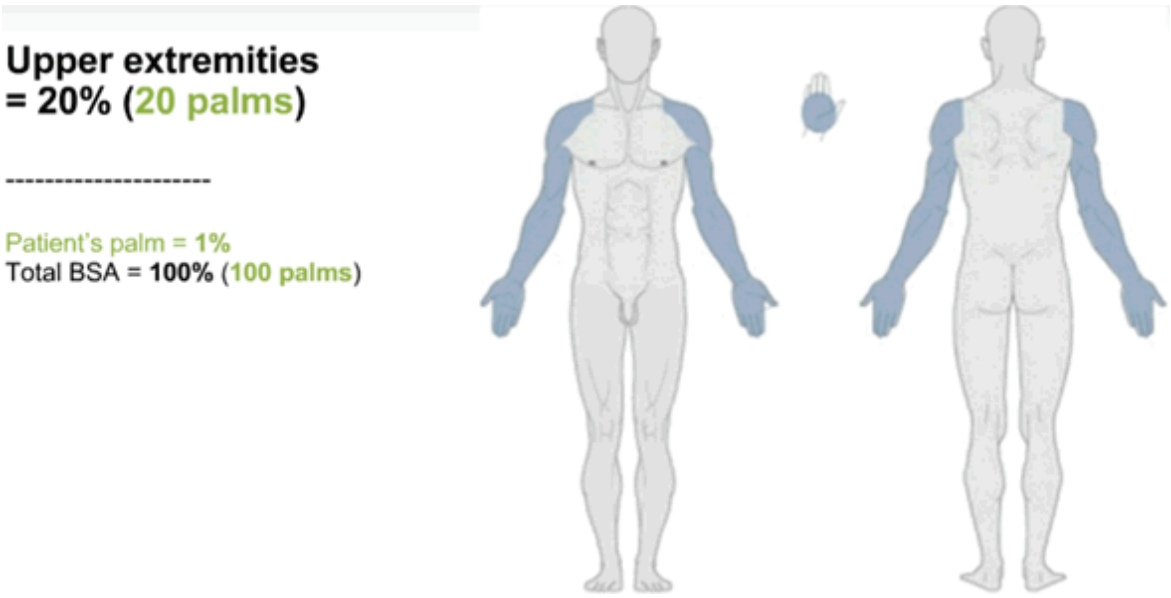
CTCAE v5.0
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

To assess the Body Surface Area affected by rash, follow the algorithm described below:

Area	Number of palms	Percent area
Whole body	100	100%
Head and Neck	10	10%
Upper extremities	20	20%
Trunk	30	30%
Lower extremities	40	40%

The participant's palm is defined as "1", representing 1% of total Body Surface Area. Total Body Surface Area = 100% (100 palms).

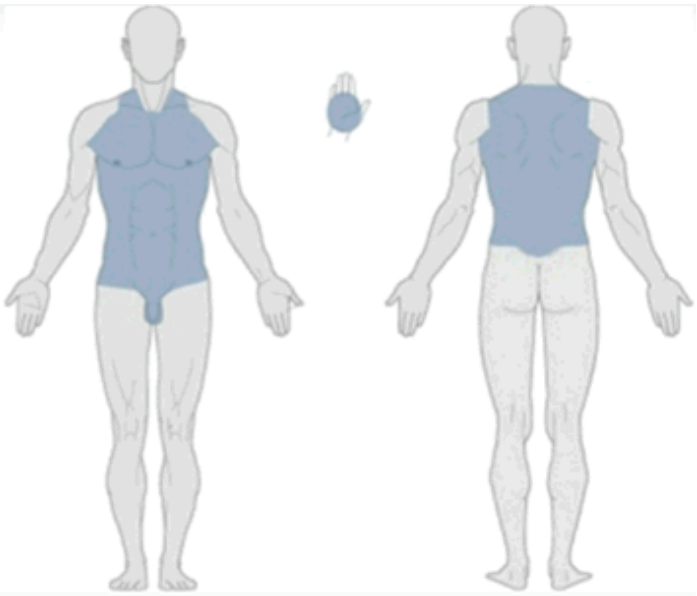




The axillae and genitals are included with the trunk

Trunk (axillae and groin) = 30% (30 palms)

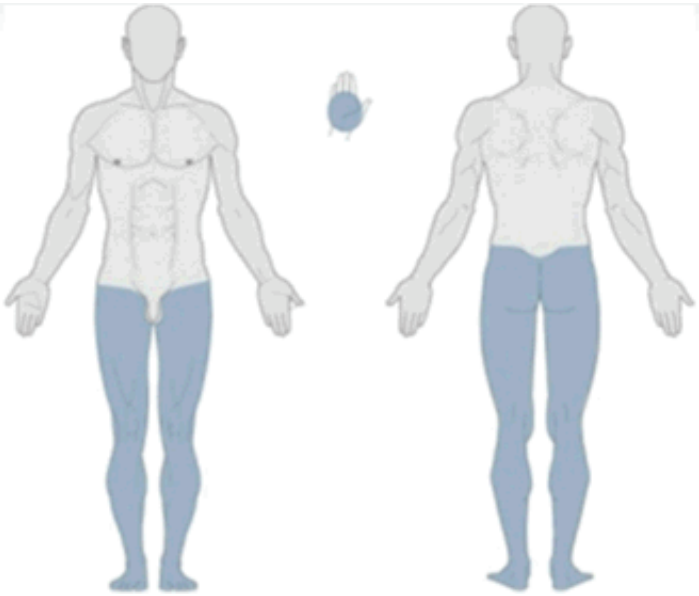
Patient's palm = **1%**
Total BSA = **100%** (100 palms)



The inguinal canal separates the trunk and legs anteriorly

Lower extremities (buttocks included) = **40%** (40 palms)

Patient's palm = **1%**
Total BSA = **100%** (100 palms)



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

F 1 Introduction

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

Specific guidance on stopping criteria and dose adaptations in possible hepatocellular drug-induced liver injury (DILI) and in possible cholestatic DILI can be found in Appendix F 8 of the CSP.

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 alanine aminotransferase (ALT) from a central laboratory and/or elevated total bilirubin (TBL) from a local laboratory.

The investigator will also review adverse event (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 serious adverse events (SAEs) and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Definitions

Potential Hy's Law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication 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, 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.

F 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

Central Laboratories Being Used:

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 (definition in Section F 2) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

F 4 Follow-up

F 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 CSP.

F 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 a 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. Complete 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.

F 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 Lead 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.

F 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 F 4.2.

[#] **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.

F 7 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 & IgG anti-CMV
	IgM & IgG anti-HSV
	IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
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

F 8 Recommended Stopping Criteria

Table F9 Recommended Stopping Criteria and Dose Adaptations for Possible Hepatocellular DILI in Phase II-III NASH Clinical Trials in Participants with Normal or Elevated Baseline ALT (> 1.5 × ULN)[a]

Treatment Emergent ALT Elevations	TBL Values at Time of Treatment Emergent ALT Elevation	Presence of Liver-related Symptoms[b]	Action
NASH Participants with Near Normal ALT at Baseline[c]			
≥ 3 × ULN but < 5 × ULN	< 2 × ULN Participants with Gilbert's syndrome: direct bilirubin < 2 × baseline AND INR ≤ 1.5	Absent	Repeat ALT, AST, ALP, TBL in 2-3 days. Follow-up for symptoms.
		Present	Repeat ALT, AST, ALP, TBL in 2-3 days. Follow-up for symptoms. Initiate evaluation for other etiologies of abnormal liver tests.
	TBL ≥ 2 × ULN Participants with Gilbert's syndrome: direct bilirubin ≥ 2 × baseline or INR > 1.5	Irrespective of symptoms	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified, and liver enzymes return to baseline.
≥ 5 × ULN but < 8 × ULN	< 2 × ULN Participants with Gilbert's syndrome: direct bilirubin < 2 × baseline AND INR ≤ 1.5	Absent	Repeat ALT, AST, ALP, TBL in 2-3 days. Follow-up for symptoms. Initiate evaluation for other etiologies of abnormal liver tests.
		Present	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified, and liver enzymes return to baseline.
	TBL ≥ 2 × ULN Participants with Gilbert's syndrome: direct bilirubin ≥ 2 × baseline or INR > 1.5	Irrespective of symptoms	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified, and liver enzymes return to baseline.
≥ 8 × ULN	Irrespective of TBL	Irrespective of symptoms	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified, and liver enzymes return to baseline.
NASH Participants with Elevated ALT at Baseline[c]			
≥ 2 × baseline but < 3 × baseline AND (< 300 U/L)	< 2 × ULN Participants with Gilbert's syndrome: direct bilirubin < 2 × baseline AND INR ≤ 1.5	Absent	Repeat ALT, AST, ALP, TBL in 2-3 days. Follow-up for symptoms.
		Present	Repeat ALT, AST, ALP, TBL in 2-3 days. Follow-up for symptoms.

Table F9 Recommended Stopping Criteria and Dose Adaptations for Possible Hepatocellular DILI in Phase II-III NASH Clinical Trials in Participants with Normal or Elevated Baseline ALT (> 1.5 × ULN)[a]

Treatment Emergent ALT Elevations	TBL Values at Time of Treatment Emergent ALT Elevation	Presence of Liver-related Symptoms[b]	Action
			Initiate evaluation for other etiologies of abnormal liver tests.
	TBL ≥ 2 × ULN Participants with Gilbert's syndrome: direct bilirubin ≥ 2 × baseline or INR > 1.5	Irrespective of symptoms	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified, and liver enzymes return to baseline.
(≥ 3 × baseline but < 5 × baseline AND < 500 U/L) or (≥ 300 U/L AND < 500 U/L AND < 5 × baseline)	< 2 × ULN Participants with Gilbert's syndrome: direct bilirubin < 2 × baseline AND INR ≤ 1.5	Absent	Repeat ALT, AST, ALP, TBL in 2-3 days. Follow-up for symptoms. Initiate evaluation for other etiologies of abnormal liver tests.
		Present	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified, and liver enzymes return to baseline.
	TBL ≥ 2 × ULN Participants with Gilbert's syndrome: direct bilirubin ≥ 2 × baseline or INR > 1.5	Irrespective of symptoms	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified, and liver enzymes return to baseline.
≥ 5 × baseline or ≤ 500 U/L	Irrespective of TBL	Irrespective of symptoms	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified, and liver enzymes return to baseline.

[a] Adapted from: (Regev et al 2019)
[b] Liver-related symptoms include: severe fatigue, nausea, vomiting, right upper quadrant pain
[c] Baseline ALT is derived from an average of 2 pretreatment ALT measurements at least 2 weeks apart. Elevated baseline is defined as ALT ≥ 1.5 × ULN. If on treatment a participant has 2 or more consecutive ALT values, at least 2 weeks apart, each less than 50% of the baseline ALT with any 2 consecutive values being 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).

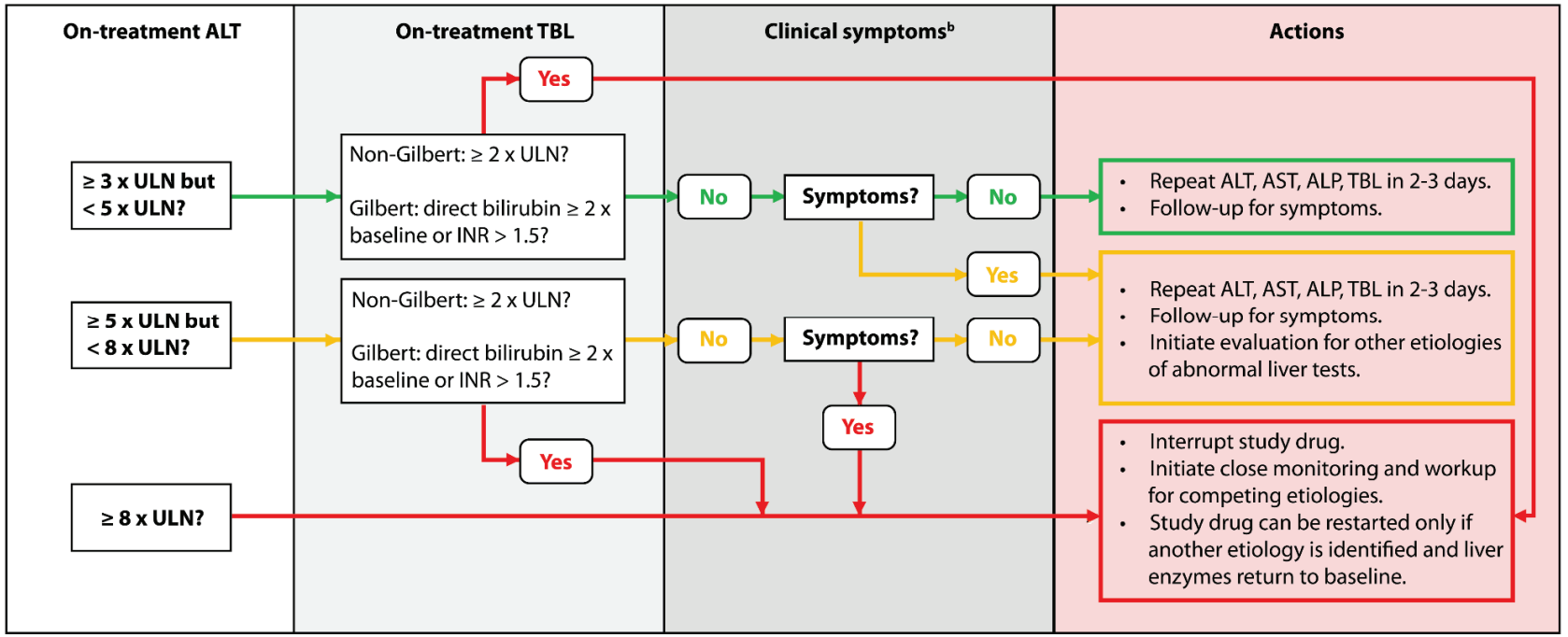
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; INR, international normalized ratio; NASH, non-alcoholic steatohepatitis; TBL, total bilirubin; ULN, upper limit of normal

Table F10 Stopping Criteria for Possible Cholestatic DILI

Criteria	Action
• ALP ≥ 2 ULN and DBL ≥ 2 ULN (if subject has Gilbert's syndrome) or • ALP ≥ 2 ULN and TBL ≥ 2 ULN • ALP ≥ 2 ULN and TBL/DBL ≥ 2 ULN and INR > 1.5 • ALP ≥ 2 ULN and TBL/DBL ≥ 2 ULN and symptoms of clinical hepatitis	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified, and laboratory and clinical symptoms have resolved.

Liver-related symptoms include: severe fatigue, nausea, vomiting, right upper quadrant pain

Figure F2 **Recommended Stopping Criteria and Dose Adaptations for Possible Hepatocellular DILI in Participants with Normal/Near Normal ALT at Baseline**

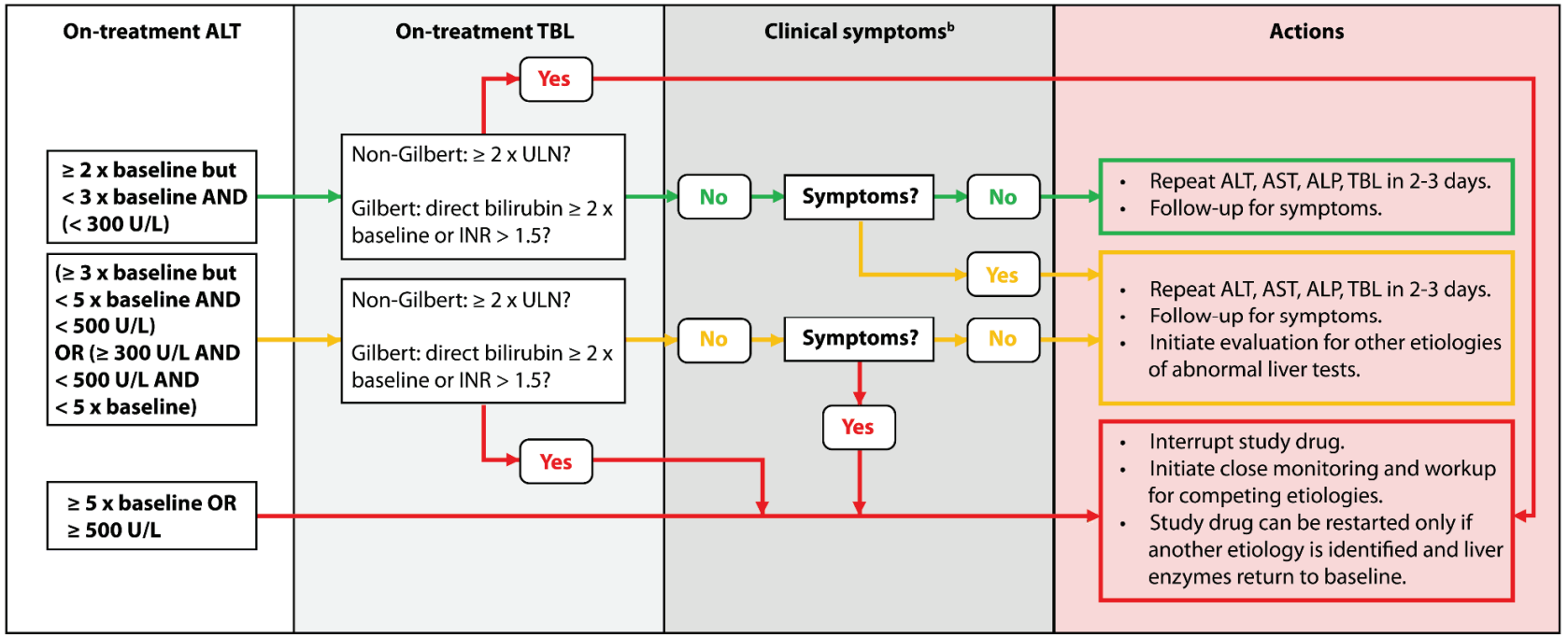


[a] Liver-related symptoms include: severe fatigue, nausea, vomiting, right upper quadrant pain

Baseline ALT is derived from an average of 2 pretreatment ALT measurements at least 2 weeks apart. Elevated baseline is defined as ALT > 1.5 × ULN. If on treatment a participant has 2 or more consecutive ALT values, at least 2 weeks apart, each less than 50% of the baseline ALT with any 2 consecutive values being 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

Figure F3 Recommended 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 ALT is derived from an average of 2 pretreatment ALT measurements at least 2 weeks apart. Elevated baseline is defined as ALT > 1.5 × ULN. If on treatment a participant has 2 or more consecutive ALT values, at least 2 weeks apart, each less than 50% of the baseline ALT with any 2 consecutive values being 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

Appendix G Handling of Human Biological Samples

G 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 Biobank Team during the entire sample life cycle.

G 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, 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 that 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 that the action documented, and the study site is notified.

G 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 H Abbreviations

Abbreviation or special term	Explanation
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
CCI	[redacted]
AST	aspartate aminotransferase/transaminase
AUDIT	Alcohol Use Disorder Identification Test
AV	atrioventricular
CCI	[redacted]
BMI	body-mass index
BP	blood pressure
bpm	beats per minute
CCI	[redacted]
[redacted]	[redacted]
COVID-19	coronavirus disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DRC	Data Review Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EDV	early discontinuation visit
CCI	[redacted]
FAS	full analysis set
FDA	United States Food and Drug Administration
CCI	[redacted]
GCP	Good Clinical Practice
CCI	[redacted]

Abbreviation or special term	Explanation
HbA1c	hemoglobin A1c
HFpEF	heart failure with preserved ejection fraction
HIV	human immunodeficiency virus
Hs-CRP	high-sensitivity C-reactive protein
IATA	International Airline Transportation Associations
IB	Investigator's Brochure
ICF	informed consent form
IEC	independent ethics committee
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
MAD	Multiple Ascending Dose
MCMC	Markov chain Monte Carlo
MELD	model for end-stage liver disease
MI	multiple imputation
MPO	myeloperoxidase
MPOi	myeloperoxidase inhibitor
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
NIMP	non-investigational medicinal product
CCI	[redacted]
PHL	potential Hy's Law
CCI	[redacted]
PK	pharmacokinetic(s)
CCI	[redacted]
Pro-C3	released N-terminal propeptide of type III collagen
CCI	[redacted]
[redacted]	[redacted]
PROC	The PROC step consists of a group of SAS statements that call and execute a procedure
RTSM	randomization and trial supply management
SAE	serious adverse event

Abbreviation or special term	Explanation
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
CCI	[redacted]
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
CCI	[redacted]
ULN	upper limit of normal

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