
Clinical Study Protocol

Study Intervention	AZD2389
Study Code	D7930C00002
Version	4.0
Date	17 April 2025

A Phase 2a, Randomised, Single-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics and Explore the Pharmacodynamic Effects of AZD2389 in Participants with Liver Fibrosis and Compensated Cirrhosis (BORANA)

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Regulatory Agency Identifier Number(s):

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IND Number 165806

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

Version Scope: Global

Brief Title: A study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of AZD2389 in participants with liver fibrosis and compensated cirrhosis.

Study Phase: Phase 2a

Study Clinical Lead Name and Contact Information will be provided separately.

Study Clinical Lead is responsible for the clinical integrity of the study (for example, the study physician or scientist).

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
CSP Version 4.0	17 April 2025
CSP Version 3.0	24 February 2025
CSP Version 2.0	18 December 2024
CSP Version 1.0	19 September 2024

CSP Version 4.0 (17-April-2025)

Overall Rationale for the Modification:

The primary purpose of this amendment is to include recommendations made by the Food and Drug Administration after of review of Clinical Study Protocol Version 3, and to implement changes for consistency.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 5.2: Exclusion Criteria (13 and 32)	Duration of stable dose of GLP-1 medication has been revised from at least 3 months to > 6 months	Change is made to include recommendation made by FDA.
Section 7: Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	Following text has been added in Section 7: Specifically, stopping rules can be found in Appendix A10	Inclusion of study stopping criteria based on CTCAEs has been added as per FDA recommendation
Section 7.1.1: Platelet Count Stopping Criteria	The criterion for discontinuation of the study intervention based on participant's platelet count drops has been revised from $< 75 \times 10^9/L$ to $< 100 \times 10^9/L$.	Change is made to include recommendation made by FDA.
Section 7.1.2: Hepatic Decompensation Stopping Criteria	Added Section 7.1.2 for addition of a criterion for discontinuation of study intervention if the participant develops evidence of hepatic decompensation.	To ensure participants' safety.
Section 7.1.5: AE Stopping Criteria	Added Section 7.1.5 for adverse event stopping criteria for discontinuation of study intervention in case of CTCAE Grade 3 or higher that is attributed to study intervention OR CTCAE Grade 4 or higher regardless of attribution to study intervention.	To ensure participants' safety.
Table 5: Laboratory Safety Variables	U-creatinine has been added to the Laboratory Safety Variables.	To ensure participants' safety.
Section 8: Study Assessments and Procedures, Section 8.2.2: Imaging – FibroScan, Section 1.3: Schedule of Activities-	Following text has been added in Section 8, Section 8.2.2, and footnote d in Table 1: A single retest is permitted where screening values that are in close proximity to eligibility criteria lead to	To reduce screen failures due to test variability that is inherent to the test.

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Table 1 Schedule of Activities – Screening	exclusion. This must be performed within the screening window.	
Appendix A10: Study Stopping Criteria	Appendix A10 study stopping criteria has been added.	To ensure participants' safety.

Abbreviations: AE = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; FDA = Food and Drug Administration; GLP-1 = glucagon-like peptide-1

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 7.1.3: Liver Chemistry Stopping Criteria, Section 7.1.4: QTc Stopping Criteria, Section 7.1.6: Rechallenge, Appendix A11: Publication Policy	Sections numbering has been updated.	For consistency in numbering.
Section 7.1.1: Platelet Count Stopping Criteria	The subsection heading is updated to add text "Stopping Criteria".	For consistency with headings of the other subsections.
Sections 8.1.7: Alcohol and Drugs of Abuse. Section 8.10: Health Economics OR Medical Resource Utilisation and Health Economics	Spelling of utilize/ utilized to utilise/ utilisation has been updated.	For consistency in UK spelling.
Appendix G: Protocol Amendment History	Summary of CSP Version 3.0 modifications (Amendment 2) is moved to Appendix G.	Updated in align with current AstraZeneca CSP template requirements/guidelines.

Abbreviations: CSP = Clinical Study Protocol

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
AASLD	American Association for the Study of Liver Diseases
Ae	Amount of Drug Excreted in Urine
AE	Adverse Event
ALD	Alcohol-related Liver Disease
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Transaminase
AST	Aspartate Aminotransferase/Transaminase
AUCinf	Area Under the Concentration-time Curve Extrapolated to Infinity
AUClast	Area Under the Concentration-time Curve to the Last Measurable Concentration
AUCtau	Area Under the Concentration-time Curve Over a Dosing Interval
AUDIT	Alcohol Use Disorders Identification Test
AxMP	Auxilliary Medicinal Product
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BP	Blood Pressure
CCI	
CCl ₄	Carbon Tetrachloride
CFR	Code of Federal Regulations
CK	Cytokeratin
CLD	Chronic Liver Disease
CL/F	Apparent Clearance
CLR	Renal Clearance
Cmax	Maximum Concentration
COA	Clinical Outcome Assessment
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CCI	
CYP	Cytochrome P450
DPP	Dipeptidyl Peptidase
DES	Data Entry Site

Abbreviation or special term	Explanation
DILI	Drug-induced Liver Injury
DUS	Disease Under Study
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
E/D	Early Discontinuation
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
EEA	European Economic Area
CCI	
EU	European Union
EU CT	EU Clinical Trial
EudraCT	EU Drug Regulating Authorities Clinical Trials Database
FAP	Fibroblast Activating Protein
FDA	Food and Drug Administration
Fe	Fraction of Drug Excreted in Urine
CCI	
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GLP-1	Glucagon-like Peptide-1
gSD	Geometric Standard Deviation
HbA1c	Haemoglobin A1C
HBS	Human Biological Sample(s)
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
CCI	
HIV	Human Immunodeficiency Virus
CCI	
hsCRP	High-sensitivity C-reactive protein
CCI	
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation

Abbreviation or special term	Explanation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalised Ratio
IQ	International Consortium for Innovation and Quality in Pharmaceutical Development (also known as IQ Consortium)
IRB	Institutional Review Board
IRT	Interactive Response Technology
CCI	
MAD	Multiple Ascending Dose
MASH	Metabolic Dysfunction-associated Steatohepatitis
MASLD	Metabolic Dysfunction-associated Steatotic Liver Disease
MetALD	Metabolic and Alcohol-related Liver Disease
MMRM	Mixed model of repeated measures
MRI	Magnetic Resonance Imaging
CCI	
N/A	Not Applicable
NASH	Nonalcoholic Steatohepatitis
NHP	Nonhuman Primate
NIMP	Non-investigational Medicinal Product
NQ	Not Quantified
NTproBNP	N-terminal Prohormone of Brain Natriuretic Peptide
OAT3	Organic Anion Transporter 3
CCI	
PD	Pharmacodynamic(s)
PEth	Phosphatidylethanol
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
CCI	
QTcF	Fridericia-corrected QT interval
Rac AUC	AUC Accumulation Ratio
Rac Cmax	Cmax Accumulation Ratio
RR	Respiratory Rate

Abbreviation or special term	Explanation
RTSM	Randomisation and Trial Supply Management
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SLD	Steatotic Liver Disease
SMAD	Single and Multiple Ascending Doses
SoA	Schedule of Activities
SpO ₂	Oxygen Saturation
SRC	Safety Review Committee
CCI	
SVR	Sustained Virologic Response
t _{1/2λz}	Terminal Half-life
T2DM	Type 2 Diabetes Mellitus
T4	Thyroxine
TBL	Total Bilirubin
TCP	Temporal Change Parameter
TE	Target Engagement
CCI	
CCI	
CCI	
Tmax	Time to Maximum Concentration
TSH	Thyroid-stimulating Hormone
ULN	Upper Limit of Normal
CCI	
CCI	
CCI	
V _z /F	Apparent Volume of Distribution

1 **PROTOCOL SUMMARY**

1.1 **Synopsis**

Protocol Title:

A Phase 2a, Randomised, Single-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics and Explore the Pharmacodynamic Effects of AZD2389 in Participants with Liver Fibrosis and Compensated Cirrhosis (BORANA)

Brief Title:

A study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of AZD2389 in participants with liver fibrosis and compensated cirrhosis.

Regulatory Agency Identifier Number(s):

Registry	ID
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IND Number	165806
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Rationale:

The prevalence of CLD is increasing and currently accounts for approximately 1 million deaths per year globally. The chronic cycle of liver inflammation, destruction, and regeneration results in fibrosis and ultimately cirrhosis with deterioration of liver function. Currently, there are no approved therapies for the treatment of advanced hepatic fibrosis that is agnostic to aetiology, leaving a huge unmet need and residual risk, especially in those with cirrhosis. AZD2389 is a potent selective first-in-class small molecule oral inhibitor of FAP and is being developed for the treatment of CLDs with advanced hepatic fibrosis, including cirrhosis. FAP is a membrane-bound serine protease. Human tissue studies have demonstrated that FAP is overexpressed in hepatic fibrosis of different aetiologies including MASH/NASH, ALD, chronic viral hepatitis, and cholestatic liver diseases. FAP overexpression has been demonstrated to correlate with stage of disease, being most highly expressed in cirrhosis disease. Preclinical data has demonstrated AZD2389 has a CCI

CCI and studies CCI

The aim of this study is to obtain safety, PK, and PD data in the target population prior to initiating a larger, longer-term Phase 2b study.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the safety and tolerability of AZD2389 following oral administration in participants with CLD and hepatic fibrosis	- AEs - Vital signs (BP, pulse rate, SpO₂, body temperature, and RR) 12-lead safety ECG - Physical examination - Laboratory assessments (haematology, coagulation, clinical chemistry, CCI and urinalysis)
Secondary	
To characterise the PK of AZD2389 in participants with CLD and hepatic fibrosis	- Plasma and urine PK parameters of AZD2389 - C_{max}, T_{max}, AUC_{last}, AUC_{inf}, AUC_{tau}, t_{1/2λz}, V_z/F, CL/F, TCP, Rac C_{max}, Rac AUC, CLR, Ae, and Fe
To evaluate the effect of AZD2389 on plasma FAP activity following oral administration of AZD2389 in participants with CLD and hepatic fibrosis	Inhibition of FAP activity at Days 1, 7, 14, 28, and follow-up (calculated as change and percentage change in FAP activity against baseline) compared to placebo

For exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design Synopsis:

This is a Phase 2a, Randomised, Single-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics and Explore the Pharmacodynamic Effects of AZD2389 in Participants with Liver Fibrosis and Compensated Cirrhosis.

The study will be conducted in approximately 7 sites in 2 countries.

The dose of AZD2389 selected for this study has been assessed as CCI. The definition of CCI is that none of the CCI CCI

Brief Summary:

The purpose of this study is to measure the safety, tolerability, and the way the body absorbs, distributes, and metabolises AZD2389 as compared to placebo in participants with liver fibrosis and compensated cirrhosis. The study will also examine how the drug acts on the body.

Study details include:

The study duration will be up to 63 days (9 weeks).

- 1 or 2 screening visits (up to 28 days before treatment)
- 28 days of treatment including 5 clinic visits
 - Week 1: 24-hour in-clinic stay (Day 1)
 - Week 2: Outpatient clinic visit (Day 7)
 - Week 3: Outpatient clinic visit (Day 14)
 - Week 4: Telephone visit (Day 21)
 - Week 5: 24 to 48-hour in-clinic stay (Day 28)
- Week 6: Follow-up visit (Day 35)

Disclosure Statement: The study consists of two cohorts, each with a parallel-group design and two arms, with participants blinded to treatment allocation.

Number of Participants:

The study will randomise approximately 36 participants in total.

Cohort A: Approximately 75 participants with presumed MASH/NASH with fibrosis will be screened such that approximately 18 participants will be randomised. Twelve participants will be randomised to receive AZD2389 and 6 participants will receive placebo.

Cohort B: Approximately 75 participants with SLD with advanced fibrosis including compensated cirrhosis will be screened such that approximately 18 participants will be randomised. Twelve participants will be randomised to receive AZD2389 and 6 participants will receive placebo.

Note: ‘Screened’ means a participant’s or their legally authorised 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 randomised/assigned in the study, are considered ‘screen failures’, unless otherwise specified by the protocol.

Study Arms and Duration:

Cohort A will include 18 participants with presumed MASH/NASH with fibrosis. Twelve

participants will receive oral AZD2389 (CCI mg) CCI for 28 days while 6 participants will receive matched oral placebo CCI for 28 days.

Cohort B will include 18 participants with SLD with advanced fibrosis including compensated cirrhosis. Twelve participants will receive oral AZD2389 (CCI mg) CCI for 28 days while 6 participants will receive matched oral placebo CCI for 28 days.

The visit schedule is the same for each cohort.

The total duration of study participation for each participant in Cohorts A and B will be approximately 63 days (9 weeks) and will include an up to 28-day screening period, a 28-day treatment period, and a follow-up visit seven days following completion of treatment.

Data Monitoring / Other Committee: Yes

An ad hoc SRC may be appointed for this study. The SRC is composed of core study team individuals, including the Principal Investigator (Chair), AstraZeneca Study Clinical Lead(s), AstraZeneca Clinical Scientist, AstraZeneca Safety Physician, AstraZeneca Clinical Pharmacology Scientist, AstraZeneca Clinical Pharmacokinetic Scientist or designee and Fortrea Project Manager, may evaluate the available safety, tolerability, PK, and PD data as needed.

Statistical Methods

Analysis will be presented separately for each cohort.

Presentation and Analysis of Safety and Tolerability Data:

Safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarised using descriptive statistics by cohort, treatment, and overall as needed. Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment, cohort, and overall as appropriate. The analysis of the safety variables will be based on the safety analysis set.

Presentation and Analysis of Pharmacokinetic Data

The plasma and urine concentration of AZD2389 and the PK parameters will be listed and presented in tabular and graphical form as appropriate. Statistical inference will also be performed.

Presentation and Analysis of Plasma FAP Data

The plasma concentration of FAP parameters will be listed and presented in tabular and graphical form as appropriate. Statistical inference will also be performed.

Determination of Sample Size

This is a Phase 2a study to investigate the safety and tolerability of a novel compound in participants living with CLD and hepatic fibrosis. The sample size was chosen to obtain reasonable evidence of safety and tolerability without exposing undue numbers of study participants to the compound at this phase of clinical development.

1.2 Schema



1.3 Schedule of Activities

Table 1 Schedule of Activities – Screening

Visit	Screening Visit 1	Screening Visit 2 ^a	Details in protocol section or appendix
Day	Day -28 to -1	Day -7 to -1	
Written informed consent	x		Appendix A 3
Medical and surgical history, including smoking and alcohol history	x		Section 8.1.1
Demographics	x		Section 8.1.2
Full Physical examination	x		Section 8.3.1
Brief physical examination		x	Section 8.3.1
Weight ^b , height, and BMI calculation	x		Section 8.1.4
Safety ECG	x		Section 8.3.3
Vital signs ^c (BP, pulse rate, SpO ₂ , body temperature, RR)	x	x	Section 8.3.2
FibroScan ^d	x		Section 8.2.2
AUDIT questionnaire	x		Section 8.1.7
Assessment of SAEs	x	x	Section 8.4 Appendix B;
Concomitant medications	x	x	Section 8.1.3
Collect blood for:			
Clinical chemistry	x	x	Section 8.3.4
Haematology	x	x	Section 8.3.4
Coagulation parameters including calculated INR	x	x	Section 8.3.4
Fasting lipid profile	x		Section 8.3.4
HbA1c	x		Section 8.3.5
TSH, free T4	x		Section 8.3.5
Virology: hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody; HIV-1 and HIV-2 ^{e,f}	x		Sections 8.1.6, 8.3.5
HCV RNA ^f	x		Sections 8.1.5, 8.3.5
FSH (females only) ^g	x		Sections 8.1.5, 8.3.5
Serum pregnancy test (females only)	x	x	Section 8.3.5
Collect urine for:			
Urinalysis	x	x	Section 8.3.4
Urine drug and alcohol screen	x	x	Sections 8.1.7, 8.3.5

^a **Note:** Screening Visit 2 will only be needed if the screening assessments at Visit 1 are completed > 7 days prior to first dose.

^b Body weight should be measured in the morning, after the participant has toileted and removed bulky clothing, including shoes. Calibrated scales should be used.

- c Vital signs measurements should be measured after the participant has rested in the seated position for at least 10 minutes (rest period for ECG will suffice). Two consecutive BP readings should be taken at intervals of at least 1 minute, and the average recorded in the eCRF.
- d FibroScan should be performed CCI with the participants in a fasted state with CCI. The FibroScan assessments performed at CCI can be performed within a $\pm$ 2-day window. A single retest is permitted where screening values that are in close proximity to eligibility criteria lead to exclusion. This must be performed within the screening window.
- e CCI
- f
- g FSH levels will be used only to determine postmenopausal status (FSH > 40 IU/L) in females.

Table 2 Schedule of Activities – Treatment Period

Visit	3	4	5	6	7 / E/D	8 Follow-up	Details in protocol section or appendix
Day	Day 1	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 2 days)	Day 28 ^j (-1 day)	Day 35 (± 1 day)	
Verify inclusion and exclusion criteria prior to randomisation	x						Section 5
Randomisation	x						Section 6.3
Admission to clinic for 24-48 hours	x (24 h)				x (24-48 h)		
Outpatient visit		x	x			x	
Teleconference call				x			
Full physical examination	x				x	x	Section 8.3.1
Brief physical examination		x	x				Section 8.3.1
Body weight	x	x	x		x	x	Section 8.1.4
ECG ^a	x	x	x		x	x	Section 8.3.3
Vital signs (BP, pulse rate, SpO ₂ , body temperature, RR) ^b	x	x	x		x	x	Section 8.3.2
Assessments of AEs/SAEs	x	x	x	x	x	x	Section 8.4, Appendix B
Concomitant medications	x	x	x	x	x	x	Section 8.1.3
IMP dispensation for at-home administration	x	x	x				Section 6.3
IMP accountability		x	x		x		Section 6.2
IMP administration	x CCI						Sections 6.1, 6.2.2
Collect blood for:							
Clinical chemistry ^c	x	x	x		x	x	Sections 8.3.4, 8.3.5
Haematology ^c	x	x	x		x	x	Section 8.3.4
Coagulation parameters including calculated INR ^c	x	x	x		x	x	Section 8.3.4
CCI	CCI						Section 8.3.4
CCI	CCI						Section 8.3.4
Fasting lipid profile, glucose and insulin ^c	x				x	x	Section 8.3.4
Lipase	x				x	x	Section 8.3.5

Visit	3	4	5	6	7 / E/D	8 Follow-up	Details in protocol section or appendix
Day	Day 1	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 2 days)	Day 28 ⁱ (-1 day)	Day 35 (± 1 day)	
NTproBNP	x				x	x	Section 8.3.5
hsCRP	x				x	x	Section 8.3.5
PEth	x		x		x		Sections 8.1.7, 8.3.5
Plasma for AZD2389 pharmacokinetics ^d	x CCI	x	x		x CCI		Section 8.5
Serum markers CCI	CCI						CCI
Scores of CCI							CCI
Serum markers of CCI							CCI
Markers of CCI							CCI
CCI							
Plasma for FAP activity analyses ^e	x CCI	x	x		x CCI	x	Sections 8.2.1, 8.6.1, 8.8.1
CCI /plasma FAP protein ^c	CCI						CCI
Genomics Initiative optional, exploratory genomics and multi-omics samples	x						Section 8.7, Appendix D
Serum, EDTA plasma and citrate plasma samples for future use (optional) ^c	x				x		Section 8.8.2
Collect urine for:							
AZD2389 pharmacokinetics ⁱ	CCI						CCI
Urinalysis for safety evaluation	x	x	x		x	x	Section 8.3.4
Pregnancy test (females only)	x						Sections 8.1.5, 8.3.4
Imaging							
FibroScan CCI ^f	CCI						CCI
FibroScan CCI							CCI

^a ECG schedule: Recordings should be collected pre-dose, 1 h, 4 h post-dose on Day 1 and Day 28. All other visits should be collected pre-dose. The ECG recording should be taken prior to the PK samples for AZD2389 or planned blood sampling at the same timepoint.

- b Vital signs schedule: Recordings should be collected pre-dose, 1 h, 4 h post-dose on Day 1 and Day 28. All other visits should be collected Pre-dose. Vital signs measurements should be measured after the participant has rested in the seated position for at least 10 minutes (rest period for ECG will suffice). Two consecutive BP readings should be taken at intervals of at least 1 minute, and the average recorded in the eCRF.
- c Blood collection to be drawn CCI. Participants should be in fasted for minimum of 8 hours if blood collection occurs for CCI visits.
- d AZD2389 plasma PK sampling schedule: For Day 1, samples taken CCI. For Day 7 and Day 14, samples should be taken CCI. For Day 28, samples taken CCI. At Day 28, the CCI PK samples may be taken as either an CCI visit (up to CCI) or as an CCI visit between CCI.
- e Plasma sampling schedule for FAP activity analyses: For Day 1, samples taken CCI. For Day 7 and Day 14, samples should be taken pre-dose. For Day 28, samples taken CCI. At Day 28, the CCI FAP activity samples may be taken as either an CCI visit (up to CCI) or as an CCI visit between CCI.
- f FibroScan should be performed CCI with the participants in a fasted state CCI. The timing of the FibroScan should be kept as consistent as possible at each study visit where these assessments are required.
- g FibroScan assessment conducted at CCI can be performed CCI. The FibroScan assessments performed CCI can be performed within a $\pm$ 2-day window.
- h FibroScan conducted at CCI do not need to be repeated at CCI.
- i Urine PK collection to occur at intervals of CCI following treatment CCI.
- j Maximum treatment duration with AZD2389 is limited to 28 days.

2 INTRODUCTION

AZD2389 is a potent selective first-in-class small molecule oral inhibitor of FAP. FAP is a membrane-bound serine protease and its levels are elevated during fibrogenesis in multiple diseases (Keane et al 2014; Lee et al 2004; Oatmen et al 2020, Yang et al 2023a), including MASLD, ALD, viral hepatitis, and cholestatic liver diseases. AZD2389 is being developed as an oral medication for CCI treatment of CLDs with fibrosis, including SLD aetiologies.

2.1 Study Rationale

The prevalence of CLD is increasing and currently accounts for approximately 1 million deaths per year globally (Younossi et al 2023). The chronic cycle of liver inflammation, destruction, and regeneration results in fibrosis and ultimately cirrhosis with deterioration of liver function (Huang et al 2023; Younossi et al 2023). In the more economically developed countries, the most common CLDs include ALD, chronic viral hepatitis (hepatitis B and C), MASLD, and hemochromatosis.

Currently, there are no approved therapies for the treatment of advanced hepatic fibrosis that is agnostic to aetiology, leaving a huge unmet need and residual risk, especially in those with cirrhosis (Devarbhavi et al 2023, Li et al 2024, Younossi et al 2023, Huang et al 2023). AstraZeneca is developing AZD2389 as a selective FAP inhibitor for the treatment of CLDs with advanced hepatic fibrosis, including cirrhosis.

AZD2389 is a small molecule inhibitor of FAP. A CCI and data are reviewed on CCI. A full review of the data will be conducted prior to the commencement of dosing in this Phase 2a study.

This Phase 2a safety study is the first study to evaluate AZD2389 in human participants with SLDs and hepatic fibrosis or cirrhosis, which will consist of 2 parts (Cohort A and Cohort B), detailed below. The AZD2389 dose will be selected based on CCI. The same dose will be used in Cohorts A and B and is expected to be in the CCI.

Cohort A will consist of CCI of AZD2389 for 28 days in participants with MASH/NASH with fibrosis, to assess the safety and tolerability of AZD2389, as well as to characterise PK and explore PD. It is expected that CCI CCI.

Cohort B will consist of CCI of AZD2389 for 28 days in participants with advanced fibrosis (F3 or cF4) in participants with underlying SLDs of varying aetiologies (eg, MetALD, ALD, and treated hepatitis C virus [HCV SVR12]) to assess the safety and tolerability of AZD2389, as well as characterizing PK and exploring PD.

2.2 Background

Fibroblast activation protein (also known as FAP α EC 3.4.21.B28), is a membrane bound protein and a member of the S9 family of proline-specific proteases that include DPP4, DPP7, DPP8, DPP9 and PREP, which possess dipeptidyl peptidase activity and cleaves after the second proline of N-terminus in various secreted proteins and peptide hormones (Bainbridge et al 2017, Xin et al 2021). Different from DPP4, FAP also exhibits endopeptidase activity, preferentially cleaving C-terminal to a Gly-Pro sequence (Zhang et al 2019). In addition to the membrane bound form, FAP also exists in circulation in a soluble form (sFAP) (Lee et al 2006).

Expression/activity of FAP in the healthy liver is nearly undetectable but is increased markedly at the site of tissue remodeling and fibrosis induced by steatosis, alcohol, and/or viral infection (Ryaboshapkina and Hammar 2017, Yang et al 2023a). The pro-fibrotic effects of FAP are not limited to liver, but are also observed in cancer, post myocardial infarction cardiac fibrosis (Sun et al 2023), inflammatory bowel disease, and idiopathic pulmonary fibrosis (Yang et al 2023b). In liver, FAP expression by activated hepatic stellate cells and its positive correlation with severity of liver fibrosis suggest a profibrotic role of FAP in liver diseases. Furthermore, pharmacological FAP inhibition has demonstrated anti-fibrotic benefit in a fast-progressing CCl₄-induced liver fibrosis mouse model (Yang et al 2023a). Both the differential pattern of expression in disease as well as the pharmacological intervention in disease model support the role of FAP as a potential disease biomarker and a useful therapeutic target for drug development to treat fibrosis, the risk factor driving adverse liver outcomes in CLDs.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of AZD2389 may be found in the IB.

2.3.1 Risk Assessment

2.3.1.1

CCI

[REDACTED]

CCI

[REDACTED]

CCI [REDACTED]

CCI [REDACTED]

2.3.1.2 CCI [REDACTED]
CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

2.3.1.3 CCI [REDACTED]

2.3.1.4 Potential Risks Based on Nonclinical Data

CCI [REDACTED]. More detailed

information about safety findings based on nonclinical data can be found in the IB.

2.3.2 Benefit Assessment

Participants are not expected to derive any health benefits from participation in this study.

However, benefits of study participation may include:

- Medical evaluations/assessments/monitoring associated with study procedures (eg, physical examination, ECG, laboratory tests, etc), including potential diagnosis of a more advance liver disease state
- Contributing to the process of developing new therapies in an area of unmet need.

2.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimise risk to participants in this study, the potential risks identified in association with AZD2389 are justified by the anticipated benefits that may be afforded to participants with CLDs/SLDs with hepatic fibrosis and cirrhosis.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of AZD2389 following oral administration in participants with CLD and hepatic fibrosis	- AEs - Vital signs (BP, pulse rate, SpO₂, body temperature, and RR) 12-lead safety ECG - Physical examination - Laboratory assessments (haematology, coagulation, clinical chemistry, CCI, and urinalysis)
Secondary	
To characterise the PK of AZD2389 in participants with CLD and hepatic fibrosis	- Plasma and urine PK parameters of AZD2389 - C_{max}, T_{max}, AUC_{last}, AUC_{inf}, AUC_{tau}, t_{1/2λz}, V_z/F, CL/F, TCP, Rac C_{max}, Rac AUC, CLR, Ae, and Fe.
To evaluate the effect of AZD2389 on plasma FAP activity following oral administration of AZD2389 in participants with CLD and hepatic fibrosis	Inhibition of FAP activity ^a at Days 1, 7, 14, 28, and follow-up (calculated as change and percentage change in FAP activity against baseline) compared to placebo ^a
Exploratory	
To evaluate effects of AZD2389 on CCI following oral administration of AZD2389 in participants with chronic advanced liver disease	Change and percentage change from CCI compared to placebo CCI
Optional as per site capability: To evaluate effects of AZD2389 on CCI following oral administration of AZD2389 in participants with compensated advanced liver disease	Change and percentage change from CCI compared to placebo CCI

To evaluate effects of AZD2389 on CCI [REDACTED]	Change and percentage change from CCI [REDACTED] compared to placebo in: CCI [REDACTED]
To evaluate the effects of AZD2389 on CCI [REDACTED]	Change and percentage change from CCI [REDACTED] compared to placebo in: CCI [REDACTED]
To evaluate effects of AZD2389 on CCI [REDACTED]	- Change and percentage change from CCI [REDACTED] compared to placebo in: CCI [REDACTED] - Not included in CSR CCI [REDACTED]
To evaluate effects of AZD2389 on CCI [REDACTED]	Change and percentage change from CCI [REDACTED] compared to placebo in: CCI [REDACTED]
To evaluate effect of AZD2389 on CCI [REDACTED]	Change and percentage change from CCI [REDACTED] compared to placebo in: CCI [REDACTED]

• <u>Optional</u>: To collect and store plasma and serum samples for future research. Note: This optional sample is taken from consented participants.	• Results will not be reported in the CSR.
• <u>Optional</u>: To explore how multi-omics variations, including genetics, may affect CCI [REDACTED] as detailed in Appendix D Optional Genomics Initiative. Note: The samples are taken from consented participants for DNA and blood derivatives isolation and storage. Results will not be reported in the CSR.	• Exploratory endpoints are related to the data generated from multi-omics analysis, including genetics CCI [REDACTED].
a CCI [REDACTED] to be performed at PPD as third-party vendor b CCI [REDACTED] to be performed at CCI [REDACTED] as third-party vendor c CCI [REDACTED] to be performed in-house at AZ	

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2a, randomised, single-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics and explore the pharmacodynamic effects of AZD2389 in participants with liver fibrosis and compensated cirrhosis.

AZD2389 will be evaluated in two cohorts, each with a parallel-group design and two arms, with participants blinded to treatment allocation. Cohort A will consist of participants with presumed MASH/NASH with fibrosis. CCI

CCI Cohort B will include participants with underlying SLDs of varying aetiologies (eg, MetALD, ALD, and treated hepatitis C virus [HCV SVR12]) and have advanced fibrosis including compensated cirrhosis (F3-cF4).

The total duration of study participation for each participant in Cohorts A and B will be approximately 63 days (9 weeks) and will include an up to 28-day screening period, a 28-day treatment period, and a follow-up visit seven days following completion of treatment. Assessments will be conducted as described in the SoA (Section 1.3).

CCI
CCI at a dose range that covers the planned dose in the current study. CCI

4.2 Scientific Rationale for Study Design

Preclinical data has demonstrated AZD2389 has a CCI

, and studies CCI

CCI. Human tissue studies have demonstrated that FAP is overexpressed in hepatic fibrosis of different aetiologies including MASH/NASH, ALD, chronic viral hepatitis, and cholestatic liver diseases. FAP overexpression has been demonstrated to correlate with stage of disease, being most highly expressed in cirrhosis (F4) disease. In view of this, the clinical program may include MASH/NASH with fibrosis, and other aetiologies of SLD with more severe fibrotic disease. The aim of this study is to obtain safety, PK, and PD data in the future target population prior to initiating a larger, longer-term Phase 2b study.

4.3 Justification for Dose

AZD2389 dose of CCI mg in this study was selected based on the review of CCI

CCI were completed and concluded to be CCI

CCI [REDACTED]. At the time of authoring this clinical study protocol, the first cohort of participants in the MAD part receiving CCI [REDACTED] dose of [REDACTED] mg AZD2389 for CCI [REDACTED] was completed CCI [REDACTED]. The planned doses in MAD Cohorts 2 and 3 are [REDACTED] mg and [REDACTED] mg CCI [REDACTED] for CCI [REDACTED]. The dosing of [REDACTED] mg AZD2389 in this study will start provided that the doses in Cohorts 2 and 3 in MAD are well tolerated and no clinically significant safety issues are reported. AZD2389 displayed dose-proportional and time-independent PK with no accumulation in plasma C_{max} or AUC following repeated dosing up to a steady state. Inhibition of plasma FAP activity was > 90% at peak plasma concentration starting at a single dose of [REDACTED] mg with the level and duration of inhibition increasing with increasing doses. Inhibition of plasma FAP activity at trough CCI [REDACTED] CCI [REDACTED] ranged between CCI [REDACTED] at a single dose of [REDACTED] mg to CCI [REDACTED] CCI [REDACTED] at a single dose of [REDACTED] mg in the SAD part of the study. Following repeated dosing in the MAD part, the maximum and trough inhibition of plasma FAP activity were CCI [REDACTED] CCI [REDACTED], respectively, on Day 1 and CCI [REDACTED] respectively, after the last dose on Day 10.

CCI [REDACTED] A PK study in participants with hepatic impairment is planned prior to the start of phase 2b and a renal impairment study is planned later in the development program. Exposure and safety data from CCI [REDACTED] of up to [REDACTED] mg and CCI [REDACTED] of up to [REDACTED] mg generated in healthy volunteers in the combined SAD/MAD study provides reasonable margins for the AZD2389 [REDACTED] mg CCI [REDACTED] used in this study.

In a preclinical study in NHP MASH/NASH model, following CCI [REDACTED] AZD2389 dose of [REDACTED] mg/kg for CCI [REDACTED], liver histology-based assessments showed efficacy in terms of improvement in liver steatosis, ballooning, and fibrosis. CCI [REDACTED] CCI [REDACTED].

Currently, there is no knowledge about the relationship between the level of inhibition of FAP activity in plasma and clinical efficacy on liver histology-based MASH/NASH endpoints. In a planned Phase 2b study, doses corresponding to approximately CCI [REDACTED] plasma FAP inhibition at trough will be investigated for the selection of the dose in Phase 3.

The dose in this study was selected to test the safety and tolerability of a dose within the anticipated therapeutic range in the target population prior to testing a wider dose range in a larger, longer-term Phase 2b study.

4.4 End-of-study Definition

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

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

Food and Drug Administration requirements defines 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 scheduled procedure shown in the SoA.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

Age

- 1 Males and females aged ≥ 18 years based on the date of the screening visit

2 Type of Participant and Disease Characteristics

Cohort A Only:

- (a) Participants with liver histology consistent with a diagnosis of MASH/NASH with at least mild fibrosis as diagnosed by liver biopsy within 12 months of provision of written informed consent, in the absence of a competing aetiology. Participants must have histological evidence of liver fibrosis consistent with stages F1-F4, CCI

CCI

CCI

- (b) Diagnosis of presumed MASH/NASH with fibrosis as defined below, in the absence of a competing aetiology:

- (i) There is at least one coexisting metabolic comorbidity such as obesity/overweight defined by BMI ≥ 27 kg/m², T2DM, dyslipidaemia, or hypertension

AND

- (ii) CCI [REDACTED] as determined by CCI [REDACTED] with CCI [REDACTED]
CCI [REDACTED] as determined by CCI [REDACTED]

AND

- (iii) In those with CCI [REDACTED] at baseline or if available, a historical CCI [REDACTED] within the last 3 months.

Cohort B Only:

A diagnosis of ALD or MetALD as defined by EASL/AASLD consensus (Rinella et al 2023), HCV with SVR > 12 weeks from documented completion viral eradication therapy and hepatic steatosis as defined by CCI [REDACTED] at baseline or if available, a historical CCI [REDACTED] within the last 3 months

AND

The presence of at least advanced fibrosis including compensated cirrhosis, evidenced by

- (c) Severe fibrosis or cirrhosis (eg, F3-F4 or Ishak 4-6) on historical biopsy in the prior 12 months,

OR

- (d) a CCI [REDACTED] as determined by CCI [REDACTED]

Weight

- 3 No significant change in weight (> 5%) over the last 6 months.

Sex and Contraceptive/Barrier Requirements

- 4 Male and female

Contraceptive use by males or females should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- (a) Male participants:

Use of a condom plus an additional contraceptive method until the end of relevant systemic exposure (95 days [> 5 terminal half-lives plus 90 days following the last dose]).

- (b) Female participants:

Only females of non-childbearing potential may participate in the study.

- Females not of childbearing potential are defined as females who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral

salpingectomy), or who are postmenopausal.

- Females would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment, with FSH levels in the postmenopausal range (> 40 IU/L), with a negative serum pregnancy test result at screening, and a negative urine pregnancy test at Visit 3 prior to treatment.

Informed Consent

- 5 Capable of giving signed informed consent as described in [Appendix A](#) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
- 6 Provision of signed and dated written Optional Genomics Initiative Research Information and Consent Form prior to collection of samples for optional genomics initiative research that supports the Genomic Initiative (see [Appendix D 2](#))

Other Inclusion Criteria

- 7 Participant judged by the investigator to be suitable for participation in this study

5.2 Exclusion Criteria

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

Medical Conditions

- 1 History of, or any existing condition that, in the opinion of the investigator, would interfere with evaluation of the study intervention, put the participant at risk, influence the participant's ability to participate or affect the interpretation of the results of the study.
- 2 Any positive results for HIV infection or positive results for hepatitis B surface antigen or hepatitis B core antibody. Additionally:

CCI

CCI

3 Liver Disease

Cohort A: Liver disease of other aetiologies (eg, ALD or alcoholic hepatitis; drug-induced, viral, or autoimmune hepatitis; primary biliary cholangitis; primary sclerosing cholangitis; haemochromatosis; alpha-1 antitrypsin deficiency; Wilson's disease).

Cohort B: Any liver diseases which are not ALD, MetALD, or HCV (post SVR12).

- 4 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.
- 5 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.
- 6 Severe congestive heart failure (New York Heart Association Class IV).
- 7 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.
- 8 Prolonged QT interval (Fridericia-corrected QT interval, QTcF > 470 ms) on ECG at screening (Visit 1) or at randomisation (Visit 3), known congenital long QT syndrome, or family history of cardiac sudden death at age < 40 years.
- 9 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.
- 10 History of hypersensitivity to DPP4 inhibitors, as judged by the investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to DPP4 inhibitors. See [Appendix F](#) for a list of DPP4 inhibitors with chemical structure similar to AZD2389.
- 11 History of hypersensitivity such as anaphylaxis requiring carriage of adrenaline/epinephrine, or angioedema
- 12 Changes in new medications in the 4 weeks prior to randomisation that are deemed relevant/ hold potential to impact results analysis by the Investigator
- 13 Participants should be on stable dose of GLP-1 medication for > 6 months and exhibit no symptoms related to delayed gastric emptying (ie, bloating, nausea, etc) that the investigator believes could affect drug absorption or study interpretation
- 14 History of decompensated liver disease including but not limited to jaundice, ascites, hepatic encephalopathy, variceal bleeding
- 15 History of acute pancreatitis within the last 3 years

- 16 Signs or symptoms of portal hypertension such as palpable splenomegaly, caput medusae, hepatic foetor, known oesophageal/gastric/rectal varices
- 17 CCI as measured by CCI /FibroScan
- 18 For Gilbert's disease, TBL $< 3 \times$ ULN is permitted provided that direct (or conjugated) bilirubin $< \text{ULN}$
- 19 Prior or planned liver transplantation
- 20 Hepatocellular carcinoma or cholangiocarcinoma or other liver tumour
- 21 Active consumption alcohol > 21 units male, > 14 units female/week
- 22 Positive screen for drugs of abuse at screening. Note: participants who test positive for drugs (ie, opioids) that are prescribed for appropriate medical use are eligible to participate in the study (see Section 8.1.7).
- 23 Cohort A Only: Evidence of alcohol dependence as assessed by the AUDIT questionnaire at screening
- 24 Abnormal laboratory values including any of the following:
 - (a) AST or ALT $> 4 \times \text{ULN}$.
 - (b) ALP $> 1.5 \times \text{ULN}$, unless not of hepatic origin.
 - (c) TBL $> 1.5 \times \text{ULN}$
 - (d) INR > 1.5
 - (e) MELD score > 12
 - (f) Platelets $< 140 \times 10^9/\text{L}$
 - (g) Impaired renal function defined as estimated glomerular filtration rate $< 60 \text{ mL/min/1.73m}^2$ at screening (estimated according to chronic kidney disease epidemiology collaboration).
 - (h) Any other clinically significant abnormalities in clinical chemistry, haematology, or urinalysis results as judged by the investigator, eg, significant hypercalcaemia, hyperlipidaemia or thyroid dysfunction
- 25 History of coagulation or bleeding disorders, or blood dyscrasias with increased risk of bleeding including idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic

- purpura, or symptoms of increased risk of bleeding (frequent bleeding gums or nosebleeds)
- 26 History of major bleeding or high-risk of bleeding diathesis
 - 27 Ongoing wound healing/post-surgery in prior 3 months
 - 28 History of dermatological disorders such as bullous pemphigoid, Steven's Johnson syndrome, or clinically significant new or healing wounds in areas of the body not always covered by clothing eg, face, forearms, lower leg, as judged by the investigator
 - 29 Severe stage 2 hypertension with systolic BP ≥ 170 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 randomisation
 - 30 Uncontrolled or newly diagnosed (< 3 months since diagnosis) T2DM:
 - (a) Participants must have HbA1c level $\leq 9.5\%$ (or 80 mmol/mol) at screening.
 - (b) Participants must have been on a stable antidiabetic regimen for 3 months prior screening.
 - 31 Vulnerable participants, eg, kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

Prior/Concomitant Therapy

- 32 Cohort A: To be included in the study, participants on GLP-1 medications must be on a stable dose for > 6 months, and should have no symptoms related to delayed gastric emptying (ie, bloating, nausea) that the investigator believes could affect drug absorption or study interpretation
- 33 Use of moderate to strong inhibitors of CYP3A4 and P-gp/BCRP/OAT3 within 2 weeks or 5 half-lives, whichever is longer (see [Appendix F](#) for detailed list)
- 34 Use of moderate to strong inducers of CYP3A4 within 3 weeks or 5 half-lives, whichever is longer (see [Appendix F](#) for detailed list)
- 35 Use of warfarin, direct and indirect thrombin inhibitors, factor Xa inhibitors or any antiplatelet therapy other than low-dose aspirin (≤ 81 mg/day) within one week of screening visit and during the study
- 36 Begin use of vitamin E > 800 IU/day within one week of screening visit and during the study. Participants taking a stable dose of vitamin E for ≥ 3 months is acceptable.

Prior/Concurrent Clinical Study Experience

- 37 Participation in another clinical study with an IMP administered in the last 3 months or 5 half-lives of the therapy (whichever is longer) at the time of screening
- 38 Participants with a known hypersensitivity to AZD2389 or any of the excipients of the product
- 39 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

Other Exclusions

- 40 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.

5.3 Lifestyle Considerations

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. For CCI and CCI, participants should fast overnight for at least 8 hours, ie, no food or beverage except water, until 2 hours post-dose. Prior to FibroScan assessments, CCI is required.

Participants must refrain from consumption of grapefruit juice from the start of study intervention until the final dose.

5.3.2 Caffeine, Alcohol, and Tobacco

As described in exclusion criterion #21 (see Section 5.2), active consumption of alcohol > 21 units male, > 14 units female/week is exclusionary for this study.

Participants must abstain from using caffeine products and tobacco products 2 hours before assessment of vital signs. In general, participants should **abstain** from ingesting caffeine or xanthine-containing products (eg, coffee, tea, Red Bull, chocolate) 24 hours prior to site visits. In addition, participants should **abstain** from the use of tobacco/nicotine-containing products, including cigarettes, vapes, and nicotine patches products, during visit days at the study site.

5.3.3 Activity

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

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention/entered in 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. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 Criteria for Temporarily Delaying Enrolment/Randomisation/Administration of Study Intervention

Not applicable.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, IMPs and NIMPs, medical devices, and other interventions (eg, surgical and behavioural) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

Table 4 Study Intervention

Arm name	Treatment (Cohorts A and B)	Placebo (Cohorts A and B)
Intervention name	AZD2389	Placebo
Type	Small molecule	N/A
Dose formulation	CCI [REDACTED]	CCI [REDACTED]
Unit dose strength(s)	CCI mg and CCI mg CCI	N/A
Dosage level(s)	The planned dose is CCI mg for both Cohorts A and B. CCI [REDACTED]	N/A
Route of administration	Oral	Oral
Regimen	CCI [REDACTED]	CCI [REDACTED]

Use	Experimental	Experimental placebo comparator
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca
Packaging and labelling	Study intervention will be provided in bottles. Each bottle will be labelled as required per country requirement	Study intervention will be provided in bottles. Each bottle will be labelled as required per country requirement
Current Name	AZD2389	AZD2389 – placebo

AZD2389 and placebo will be supplied as **CCI**.

6.2 Preparation, Handling, Storage, and Accountability

The investigator or designee (eg, unblinded pharmacist) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorisation is provided for on-site destruction or removal of the IMP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying AstraZeneca (or designated party); release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by AstraZeneca (or designated party).

Only participants enrolled in the study may receive study intervention, and only authorised site staff may supply, prepare, 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 labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator or authorised site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.2.1 Dose Preparation

The dose of AZD2389 and placebo for administration must be dispensed by the pharmacy staff members (or an appropriate designee), in compliance with local regulations and site requirements.

Refer to the Pharmacy Manual for detailed information on dose preparation and handling procedures for AZD2389 and placebo.

6.2.2 Dose Administration

Doses of **CCI** mg AZD2389 or placebo will be administered orally, **CCI**

6.3 Assignment to Study Intervention

All participants will be centrally assigned to randomised study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the login information and directions for the RTSM will be provided to each site.

Study intervention will be dispensed for at-home administration at the study visits summarised in the SoA ([Table 2](#)).

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

6.4 Blinding

The IRT/RTSM will provide to the investigator(s) or pharmacist(s) the kit identification number to be allocated to the participant at the dispensing visit.

Routines for this will be described in the IRT/RTSM user manual that will be provided to each centre.

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

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to regulatory authorities. Randomisation 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 participant's 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, AstraZeneca 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 the participant to the AstraZeneca staff.

6.5 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention(s) directly from the investigator or designee, under medical supervision. 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(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned **CCI**, etc, 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.

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

6.6 Dose Modification

No dose modification is planned in this study.

6.7 Continued Access to Study Intervention After the End of the Study

Not applicable.

6.8 Treatment of Overdose

For this study, any dose of AZD2389 that is greater than the planned dose according to the study protocol will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose. Symptoms of overdose should be treated as per clinical judgment.

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the Study Clinical Lead, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate. Refer to Section 8.4.12 for details of AE/SAE reporting related to overdose.

- Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Study Clinical Lead (determined on a case-by-case basis). The date/time of overdose and sampling should be noted by the investigator.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Prior and 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 enrolment 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

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

Prohibited medications are described in [Appendix F](#), and include drugs with structural similarity to AZD2389 ([Table 10](#)), and relevant CYP/P-gp/BCRP/OAT3 inhibitors and CYP inducers ([Table 11](#)). Refer to concomitant medications summary of product characteristics for further information and clarification.

During the follow-up period, if required, prohibited medications may be administered (at the discretion of the Principal Investigator) providing that the last study PK sample has been collected.

6.9.1 Rescue Medicine

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are handled as part of [Appendix A](#). Specifically, stopping rules can be found in [Appendix A 10](#).

7.1 Discontinuation of Study Intervention

Note that discontinuation from study intervention is *not* the same thing as a discontinuation or

withdrawal from the study (see Section 7.2).

If study intervention is permanently discontinued, the participant should, if possible, remain in the study. See the SoA (Table 2) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1 Platelet Count Stopping Criteria

Discontinuation of study intervention will occur if the participant's platelet count drops to $< 100 \times 10^9/L$ and is confirmed by taking a second measurement in 5 to 7 days.

7.1.2 Hepatic Decompensation Stopping Criteria

Discontinuation of study intervention will occur if the participant develops evidence of hepatic decompensation, such as ascites, variceal bleeding, or hepatic encephalopathy.

7.1.3 Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Appendix E and Section 8.3.5.1 in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, if the investigator believes that it is in best interest of the participant.

7.1.4 QTc Stopping Criteria

If a clinically significant finding is identified on or after enrolment, including, but not limited to absolute QTcF > 500 ms, or changes in QTcF > 60 ms from baseline, confirmed with repeated 12-lead ECGs recording within 5 minutes, the investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. For QTcF, the review of the ECG printed at the time of collection must be documented.

7.1.5 AE Stopping Criteria

Discontinuation of study intervention will occur if the participant develops evidence of

- a. Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher that is attributed to study intervention

OR

- b. CTCAE grade 4 or higher regardless of attribution to study intervention

7.1.6 Rechallenge

Not applicable.

7.2 Participant Discontinuation/Withdrawal From the Study

Discontinuation of the participant from the study by the investigator:

- A participant may be discontinued from the study at any time at the discretion of the investigator for behavioural, or compliance reasons.
- At the time of discontinuing from the study, if the participant has not been discontinued from the study intervention, see Section 7.1.

Voluntary withdrawal from the study by the participant:

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant who wishes to withdraw 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 discontinuing from the study, if possible, an E/D visit should be conducted, as shown in the SoA (Table 2). Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, AstraZeneca may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented to unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the investigator and the investigator must inform the Local and Global Study Team. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

7.2.1 Replacement of Participants

Participants who are withdrawn from the study due to AEs or changes in safety parameters will not be replaced unless a specific sample size is to be met for statistical purposes and if the Sponsor's responsible Study Clinical Lead and the Principal Investigator agree it is safe to do so. Participants who withdraw or are withdrawn from the study for other reasons may be replaced following discussion with the Medical Monitor and Sponsor.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant 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 study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counselled on the importance of maintaining the assigned visit schedule. At this time ascertain whether the participant should or wishes to or 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, telephone calls, texts, emails, 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, the participant will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the Section 1.3 SoAs. Protocol waivers or exemptions are not allowed.
- Urgent safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- 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.
- A single retest is permitted where screening values that are in close proximity to eligibility criteria lead to exclusion. This must be performed within the screening window.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- Instructions for the collection and handling of HBS will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on handling of HBS, see [Appendix C](#).

- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by AstraZeneca or the investigator, as per local health authority/ethics requirements.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be specified in the Laboratory Manual. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General/Baseline Procedures

8.1.1 Medical and Surgical History

The investigator will record details of each participant's medical and surgical history at Screening ([Table 1](#)). Details recorded for medical history will include diagnosis, date of onset, and status (end date or ongoing). Details of surgery will include name of procedure and date.

8.1.2 Demographics

Demographic data recorded at Screening ([Table 1](#)) will include age, sex, race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White), and ethnicity (Hispanic or Latino or Non-Hispanic or Latino) of participants.

8.1.3 Concomitant Medications

The investigator will record details of each participant's concomitant medications at the timepoints specified in the SoA (Section [1.3](#)). This includes name (generic), dose, route of administration, reason for use, and start and stop dates.

8.1.4 Height and Weight

Height (in cm) and weight will be measured (in kg) at the timepoints specified in the SoA (Section [1.3](#)).

8.1.5 Females of Non-childbearing Potential

Only females of non-childbearing potential will be included in this study.

- Females not of childbearing potential are defined as females who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal.
- Females would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment, with FSH

levels in the postmenopausal range (> 40 IU/L), with a negative serum pregnancy test result at screening, and a negative urine pregnancy test at Visit 3 prior to treatment.

8.1.6 Viral Serology

Viral serology for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody; HIV-1 and HIV-2 antibodies will be determined at screening, for eligibility.

8.1.7 Alcohol and Drugs of Abuse

Urine for drugs of abuse (Table 6) will be assessed at screening for eligibility.

Participants may be included should they test positive for anti-depressants, benzodiazepines, opiates, or cannabinoids where there is evidence of a legal prescription that is appropriately indicated, the participant has been on stable dose for at least 3 months prior to randomisation, and the Principal Investigator is satisfied that the participant is suitable for study inclusion.

Where these criteria do not apply, a urine drug screen should be conducted to confirm the result, and if positive, the participant should be excluded.

The Study Physician and Medical Monitor should be contacted for questions regarding retest for positive drug test result where there is ambiguity.

The AUDIT questionnaire will be utilised as a measure of alcohol dependence during screening.

The PEth will be evaluated at the timepoints specified in the SoA (Table 2) to determine alcohol use, but results are not required for randomisation.

8.2 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1 FAP Activity

Inhibition of FAP activity in plasma will be determined at Days 1, 7, 14, 28, and follow-up (calculated as change and percentage change in FAP activity against baseline) compared to placebo.

8.2.2 Imaging - FibroScan

A FibroScan CCI is a non-invasive ultrasound-based method used for the CCI CCI as well as CCI

The CCI. The CCI requires the use of the CCI

(Echosens, Paris, France), CCI .

The FibroScan CCI assessments should be performed CCI CCI with the participants in a fasted state with CCI . The timing of the FibroScan should be kept as consistent as possible at each study visit where these assessments are required. Sites are expected to follow standard procedures as required for FibroScan assessments and quality as provided by the training modules for FibroScan (eg, take 10 valid measurements with an interquartile range/median ratio that does not exceed 30%, appropriate-sized probe for body habitus, etc).

The FibroScan assessments performed at CCI (Table 1) and CCI can be performed within a ± 2 -day window. A single retest is permitted where screening values that are in close proximity to eligibility criteria lead to exclusion. This must be performed within the screening window.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the Section 1.3 SoA.

8.3.1 Physical Examinations

A full physical examination will be performed and 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.

Note: The full physical examination at screening will include an examination of the participants' feet to observe skin integrity, circulation (pedal pulses), and presence of any neuropathy (ankle reflex and sensation).

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Physical examination will be performed at timepoints as specified in the SoA (Section 1.3).

8.3.2 Vital Signs

Vital signs will be performed at timepoints as specified in the SoA (Section 1.3). Participants must abstain from using caffeine products and tobacco products 2 hours before assessment of vital signs (see Section 5.3.2).

Vital signs measurements should be measured after the participant has rested in the seated position for at least 10 minutes.

Days 1 and 28: Recordings should be collected pre-dose, 1 hour, 4 hours post-dose.

All other visits should be collected pre-dose.

8.3.3 Electrocardiograms

12-lead safety ECGs will be performed at timepoints as specified in the SoA (Section 1.3) and as clinically indicated by the investigator, and will allow the site investigator to review the ECG tracings at bedside to determine any potential abnormalities and risks.

Ten-second 12-lead safety ECGs will be obtained after the participant has been resting in the supine position for at least 10 minutes whenever it is required by the investigator. The ECGs will be performed in triplicate, with 1 minute between readings. All ECGs will be evaluated with respect to rhythm; heart rate; and PR, RR, QRS, QT, and QTcF intervals from the 12-lead safety ECG, and the investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether the abnormality is clinically significant or not, and the abnormality will be recorded. The investigator or delegate will evaluate the safety ECG in real time.

The date, time, and the physician interpretation (normal, abnormal - clinically not significant, or abnormal - clinically significant) for the safety ECGs will be recorded in the eCRF and stored as source documents.

Days 1 and 28: ECG recordings should be collected pre-dose, 1 hour, 4 hours post-dose.

All other visits should be collected pre-dose. The ECG recording should be taken prior to the pharmacokinetic samples for AZD2389 or planned blood sampling at the same timepoint.

8.3.4 Clinical Safety Laboratory Tests

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Section 1.3).

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology, and urinalysis will be performed at a central laboratory. Sample tubes and sample sizes will be described in the laboratory manual.

The following laboratory variables will be measured (see Table 5).

Additional analytes are listed in Appendix E 7.

Table 5 Laboratory Safety Variables

Haematology (whole blood)	Clinical Chemistry (serum)
B-haemoglobin	Creatinine (Cr)
B-haematocrit	eGFR (calculated based on Cr)
B-leucocyte count	Blood urea nitrogen
B-leucocyte differential count, neutrophils, lymphocytes, monocytes, eosinophils, basophils	Potassium
	Sodium
B-platelet count	ALT
B-erythrocytes	AST
B-mean corpuscular volume	TBL
B-mean corpuscular haemoglobin	ALP
B-mean corpuscular haemoglobin concentration	GGT
	Albumin
Coagulation	Calcium, total
Prothrombin time	Albumin-corrected calcium
Activated partial thromboplastin time	Phosphate
INR	Creatine kinase
CCI	Urinalysis (mid-stream sample)
CCI	U-haemoglobin/erythrocytes/blood
	U-leukocytes
	U-protein/albumin
	U-glucose
	U-bilirubin
	U-ketones
Metabolic Panel	U-nitrites
Glucose (fasting)	U-colour
Insulin (fasting)	U-clarity
Lipid profile (fasting)	U-pH
	U-specific gravity
Females Only	U-creatinine
Urine Pregnancy Test (Visit 3)	

Note: In case a participant shows an AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN please refer to [Appendix E](#), for further instructions.

8.3.5 Other Safety Assessments

Table 6 Additional Clinical Safety Laboratory Variables

Clinical Chemistry	Females Only (Visit 1)
TSH	FSH
Free T4	Serum Pregnancy Test
NTproBNP	
Lipase	Urine Drug and Alcohol Screen (Visit 1)
hsCRP	Alcohol
	Amphetamine
Whole blood	Antidepressants
HbA1c	Barbiturates
PEth	Benzodiazepines
	Cannabinoids
Viral Serology	Cocaine
HIV-1 and HIV-2 antibodies	
Hepatitis B surface antigen	Methadone
Hepatitis B core antibody	Opioids
Hepatitis C virus antibody	Phencyclidine
HCV RNA (Cohort B)	

8.3.5.1 Liver Enzyme Elevations

Participants with liver enzyme elevations, including possible DILI or Hy's Law, should be managed according to the instructions in [Table 7](#). These recommendations are based on FDA Guidance on DILI and IQ DILI consensus frameworks for detection, assessment, and management of suspected acute drug-induced liver injury during clinical trials in participants with CLDs ([Regev et al 2019](#), [Treem et al 2021](#)).

Note that the evaluation for other potential causes of liver chemistry elevations of participants with potential DILI will be the same as in [Appendix E](#) (Hy's Law).

Table 7 Recommended Monitoring and Discontinuation Criteria for Possible DILI ^a

Treatment-emergent ALT or ALP Elevations ^b	TBL or INR Values at Time of Treatment-emergent ALT Elevation	Presence of Liver Related Symptoms ^c	Action
Normal baseline: ALT $\geq 3\text{-}5 \times \text{ULN}$ Elevated baseline: ALT $\geq 2\text{-}3 \times \text{baseline}$ and < 300 U/L whichever comes first	TBL < $2 \times \text{ULN}$ ^d OR INR < 1.5 if normal baseline/ INR elevation of ≤ 0.3 above elevated baseline value	Absent	Repeat ALT, AST, ALP, GGT, and TBL in 1 week. Follow up for symptoms.
		Present	Repeat ALT, AST, ALP, GGT, and TBL in 2 to 3 days. Follow up for symptoms. Initiate evaluation for other aetiologies of abnormal liver tests.*
	TBL $\geq 2 \times \text{ULN}$ ^d OR INR > 1.5 if normal baseline/ INR elevation > 0.3 above elevated baseline value	Irrespective of symptoms	Discontinue study intervention. Initiate close monitoring and workup for other aetiologies.*
Normal baseline: ALT $\geq 5\text{-}8 \times \text{ULN}$ Elevated baseline: ALT $\geq 3\text{-}5 \times \text{baseline}$ and < 500 U/L whichever comes first	TBL < $2 \times \text{ULN}$ ^d OR INR < 1.5 if normal baseline/ INR elevation of ≤ 0.3 above elevated baseline value	Absent	Repeat ALT, AST, ALP, GGT, and TBL in 2 to 3 days. Follow up for symptoms. Initiate evaluation for other aetiologies of abnormal liver tests.* If elevations for more than 2 weeks without an alternate cause found, consider discontinuing study intervention.
		Present	Discontinue study intervention. Initiate close monitoring and workup for other aetiologies.*

	TBL $\geq 2 \times$ ULN ^d OR INR > 1.5 if normal baseline/ INR elevation > 0.3 above elevated baseline value	Irrespective of symptoms	Discontinue study intervention. Initiate close monitoring and workup for other aetiologies.*
Normal baseline: ALT $\geq 8 \times$ ULN Elevated baseline: ALT $\geq 5 \times$ baseline or ≥ 500 U/L whichever comes first	Irrespective of TBL or INR	Irrespective of symptoms	Discontinue study intervention. Initiate close monitoring and workup for other aetiologies.*
ALP > $2 \times$ ULN and GGT > $4 \times$ ULN	TBL < $2 \times$ ULN ^d OR INR < 1.5 if normal baseline/ INR elevation of ≤ 0.3 above elevated baseline value	Irrespective of symptoms	Repeat ALT, AST, ALP, GGT, and TBL in 2 to 3 days. Follow-up for symptoms. Initiate evaluation for other aetiologies of abnormal liver tests.* If elevations for more than 2 weeks without an alternate cause found, consider discontinuing study intervention.
	TBL $\geq 2 \times$ ULN ^d OR INR > 1.5 if normal baseline/ INR elevation > 0.3 above elevated baseline value	Irrespective of symptoms	Discontinue study intervention. Initiate close monitoring and workup for other aetiologies.*
^a Adapted from (Regev et al 2019) ^b Elevated baseline is defined as ALT $\geq 1.5 \times$ ULN. ^c Liver-related symptoms include: severe fatigue, nausea, vomiting, right upper quadrant pain. ^d For Gilbert's syndrome, replace TBL 2-fold threshold with direct (conjugated) bilirubin 1.5-fold threshold. * Workup as per Appendix E.			

8.4 AEs, SAEs, and Other Safety Reporting

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

The definitions of an AE or SAE can be found in [Appendix B](#).

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorised representative) will notify the investigator or designees of symptoms. These must then be assessed by the investigator and if considered an AE it will be reported by the investigator.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

AE variables

The following variables will be collected for each AE:

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

SAEs variables

The following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE description
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

The AEs will be collected from the first treatment throughout the treatment period and

including the follow-up period.

The SAEs will be recorded from the time of signing of the ICF.

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

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate 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.

8.4.3 Causality Collection

The investigator should assess causal relationship between IMP 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 IMP?'

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

A guide to the interpretation of the causality question is found in [Appendix B](#).

8.4.4 AEs Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should only be reported as AEs if they meet any of the following:

- fulfil any of the SAE criteria
- are the reason for discontinuation of the IMP
- are the reason for other management change (ie, addition of a medication to treat the AE)
- are clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required or other action was taken with the IMP, 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, anaemia vs low haemoglobin 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 DUS.

The results from the protocol-mandated laboratory tests and vital signs will be summarised in the CSR.

8.4.5 AEs Based on Signs and Symptoms

All signs or symptoms spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: “Have you had any health problems since the previous visit/you were last asked?” 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.

8.4.6 Hy’s Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of $AST \text{ or } ALT \geq 3 \times ULN$ together with $TBL \geq 2 \times ULN$ may need to be reported as SAEs. Please refer to [Appendix E](#) for further instruction on cases of increases in liver biochemistry and evaluation of Hy’s Law.

8.4.7 Disease Progression

Disease progression can be considered as a worsening of a participant’s condition attributable to the disease for which the IMP is being studied. It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease. The development of liver-decompensating events, such as ascites, hepatic encephalopathy, variceal bleeding, etc, should be considered as disease progression and not an AE so long as there is not definitive evidence of a drug-induced event.

8.4.8 Disease Under Study

Symptoms of DUS are those which might be expected to occur as a direct result of liver fibrosis. Events that are unequivocally due to DUS should not be reported as AEs during the study unless they meet SAE criteria or lead to discontinuation of the IMP.

8.4.9 Reporting of SAEs

All SAEs must be reported whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within one 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 one 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 one 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 the SAE via a secure method to the appropriate AstraZeneca representative.

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

For further guidance on the definition of an SAE, see [Appendix B](#).

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

8.4.10 Pregnancy

Pregnancy is not considered an SAE, however, 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

8.4.10.1 Maternal Exposure

Females of childbearing potential are excluded from this study. Should a pregnancy still occur, the study intervention should be discontinued immediately, and the pregnancy reported to AstraZeneca.

8.4.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 95 days (5 terminal half-lives plus 90 days following the last dose). Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly), occurring from the date of the first dose should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the pregnant partner must be obtained before the Pregnancy Report Form is completed.

8.4.11 Medication Error, Drug Abuse, and Drug Misuse

8.4.11.1 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 (see Section [8.4.9](#)) and **within 30 days** for all other events.

8.4.11.2 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 a medication error can be found in Appendix [B 4](#).

8.4.11.3 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 [B 4](#).

8.4.11.4 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 authorised product information, or for unauthorised 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 B 4.

8.4.12 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

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

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.4.9) and **within 30 days** for all other overdoses.

8.5 Pharmacokinetics

- Blood and urine samples will be collected for measurement of plasma and urine concentrations of AZD2389 as specified in Section 1.3 SoA.
- Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and AstraZeneca, eg, for urgent safety reasons, and this may be reflected as a protocol deviation.
- The timing of sampling may be altered during the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Plasma and urine samples may be used to analyse the PK of AZD2389 metabolites. Samples collected for analyses of AZD2389 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.
- For storage, re-use, and destruction of samples for PK, see Appendix C.

- Pharmacokinetics samples will be disposed of after the Bioanalytical Report finalisation 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 anonymised, pooled, or individual 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 Collection of Samples for Pharmacokinetics

Blood samples will be collected for measurement of AZD2389 as specified in the SoA ([Table 2](#)).

Urine samples will be collected for measurement of AZD2389 as specified in the SoA ([Table 2](#)).

8.5.2 Determination of Drug Concentration

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

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel 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 be reported in a separate Bioanalytical Report.

8.6 Pharmacodynamics

8.6.1 Collection of Samples for Pharmacodynamics

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

Blood samples will be collected for measurement of plasma FAP activity as specified in the SoA ([Table 2](#)).

For storage, re-use, and destruction of samples for PD, see [Appendix C](#).

8.7 Optional Genomics Initiative

Collection of optional samples for Genomics Initiative research is also a part of this study as specified in the SoA and is subject to participant agreement in the optional Genomics Initiative research information ICF.

A blood sample for DNA and blood derivatives isolation will be collected from participants who have consented to participate in the genomic and multi-omics analysis component of the study. Participation is optional. Participants who do not wish to participate in genomic and multi-omics research may still participate in the study.

See [Appendix D](#) for information regarding the Genomics Initiative genomic and multi-omics samples. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices of this protocol or in the Laboratory Manual.

8.8 Biomarkers

8.8.1 Mandatory Biomarker Sample Collection

By consenting to participate in the study the participant consents to the mandatory research components of the study. Samples for biomarker research are required and will be collected from all participants in this study as specified in [Section 1.3 SoA](#).

To evaluate their association with the observed clinical responses to AZD2389, samples will be tested for the following biomarkers:



8.8.2 Optional Biomarker Sample Collection

Collection of optional samples for biomarker research is also part of this study as specified in the SoA and is subject to agreement to optional consent.

8.8.3 Other Study-related Biomarker Research

Already collected samples may be analysed on different biomarkers thought to play a role in CLD including, but not limited to, serum analytes, to evaluate their association with observed clinical responses to AZD2389.

For storage, re-use, and destruction of biomarker samples see [Appendix C](#).

8.9 Immunogenicity Assessments

Not applicable.

8.10 Health Economics OR Medical Resource Utilisation and Health Economics

Health economics/Medical resource utilisation parameters are not evaluated in this study.

8.11 Study Participant Feedback Questionnaire

The study participant feedback questionnaire is not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

The SAP will be finalised prior to clinical data lock and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

The primary objective of the study is to assess the safety and tolerability of AZD2389 following oral administration in participants with CLD and hepatic fibrosis.

No statistical hypotheses are planned to be tested in this study.

9.2 Sample Size Determination

This is a Phase 2a study to investigate the safety and tolerability of a novel compound in participants living with CLD and hepatic fibrosis. The sample size was chosen to obtain reasonable evidence of safety and tolerability without exposing undue numbers of study participants to the compound at this phase of clinical development.

The study will randomise approximately 36 participants in total.

Cohort A: Approximately 75 participants with presumed MASH/NASH with fibrosis will be screened such that approximately 18 participants will be randomised. Twelve participants will be randomised to receive AZD2389 and 6 participants will receive placebo.

Cohort B: Approximately 75 participants with SLD with advanced fibrosis including compensated cirrhosis will be screened such that approximately 18 participants will be randomised. Twelve participants will be randomised to receive AZD2389 and 6 participants will receive placebo.

Note: ‘Screened’ means a participant’s or their legally authorised 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 randomised/assigned in the study, are considered ‘screen failures’, unless

otherwise specified by the protocol.

9.3 Populations for Analyses

The following populations are defined:

Table 8 Populations for Analysis

Population/analysis set	Description
Enrolled	All participants who sign the ICF
Full Analysis Set	The Full Analysis Set consists of all participants who are randomised and receive at least one dose of study intervention. Participants will be evaluated according to the treatment assigned at randomisation. The Full Analysis Set will be used for all analyses of demographic and baseline characteristics, and efficacy data.
Safety Analysis Set	The Safety Analysis Set consists of all participants who are randomised and receive at least one dose of study intervention. Erroneously treated participants (eg, those randomised to AZD2389 but actually given placebo) are accounted for in the treatment group of the treatment they actually receive. The Safety Analysis Set will be used as the primary population for reporting safety data and exploratory endpoints.
PK	The PK analysis set will include all participants who received at least one dose of AZD2389 and have at least one evaluable (including concentrations reported as < lower limit of quantification after the first dose) PK concentration. The exclusion of any participants or timepoints from the calculation of the PK parameters will be documented by the Clinical PK Scientist including the reason(s) for exclusion.

9.4 Statistical Analyses

9.4.1 General Considerations

Safety and tolerability will be evaluated in terms of AEs/SAEs, physical examination, BP, pulse rate, SpO₂, body temperature, RR, haematology, coagulation, clinical chemistry, CCI, urinalysis, and 12-lead safety ECG. Safety data will be summarised descriptively and will not be formally tested. Continuous variables will be summarised using descriptive statistics by cohort, treatment, and overall as needed. Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment, cohort, and overall as appropriate. The analysis of the safety variables will be based on the Safety Analysis Set. Safety data (scheduled and unscheduled) will be presented in the data listings.

9.4.2 Efficacy

See Section 9.4.5 for a description of the planned analysis of efficacy assessments.

9.4.3 Safety

Safety analyses will be performed using the Safety Analysis Set. Safety data will be presented using descriptive statistics unless otherwise specified.

Baseline

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of IMP. Details are described in the SAP.

9.4.3.1 Adverse Events

The AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities that will have been released for execution at AstraZeneca or designee.

The AEs will be presented for each cohort and 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.

The SAEs occurring prior to start of IMP and treatment-emergent AEs will be presented separately.

An overview of AEs will be presented for each cohort and treatment group with the number and percentage of participants with any AEs, SAEs, SAEs with outcome of death, AEs leading to discontinuation of IMP, and possibly related SAEs.

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

Key subject information will be presented for participants with AEs with outcome of death, SAEs, and AEs leading to discontinuation of IMP.

An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

9.4.3.2 Vital Signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, minimum, median, and maximum.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will

be presented for observed values and change from baseline.

A frequency table will present the number of participants with their vital sign status (eg, low, normal, high) for each scheduled visit. A frequency table will present the number of participants reporting at least one on-treatment abnormality/clinically significant abnormality.

A shift table will present the vital sign status including abnormality (eg, low, normal, high) from baseline to maximum and minimum on-treatment/post-baseline value.

Supportive vital sign listings will cover observed values and changes from baseline as well as abnormalities.

Details of vital sign analyses will be provided in the SAP.

9.4.3.3 Laboratory

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

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

A frequency table will present the number of participants with their laboratory status (eg, low, normal, high) for each scheduled sampling occasion.

A shift table will present the laboratory status including abnormality (eg, low, normal, high) from baseline to maximum and minimum on-treatment/post-baseline value.

A frequency table will present the number of participants reporting at least one treatment-emergent changes in laboratory parameters.

Elevation in liver parameters for assessment of Hy's Law will be done and reported appropriately if potential cases have been identified during the course of the study.

Key subject information will be presented for participants with treatment-emergent changes in laboratory parameters outside of predefined criteria.

A frequency table for urinalysis presents number of participants reporting at least one treatment emergent increase in baseline category. Treatment-emergent increase in urinalysis defined as change from negative/trace at baseline to ++, +++, or ++++ at any visit after baseline or an increase of at least ++. A shift table for urinalysis presents the baseline assessment against the maximum on treatment category.

Supportive laboratory listings will cover observed values and changes from baseline for each individual participant as well as abnormalities.

Details of laboratory analyses will be provided in the SAP.

9.4.3.4 Electrocardiogram

Electrocardiogram parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, minimum, median, and maximum. Frequency tables and shift tables will cover number and percentage of participants in the respective category. The (uncorrected) QT interval will be corrected according to the Fridericia's formula.

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

A frequency table will present the number of participants with ECG parameters exceeding ICH reference values at any time during the treatment. A frequency table will present the number of participants with ECG parameters fulfilling the potentially clinically significant criteria at any time. For QTcF, a frequency table will present the number of participants with values exceeding thresholds of 450 ms, 480 ms and 500 ms at any time during the treatment, number of participants with changes from baseline in QTcF exceeding 30 ms, 60 ms and 90 ms at any time during the treatment, as well as combination of these criteria (exceeding thresholds and changes as specified).

A table will present the interpretation of the ECG reading (eg, normal, abnormal - clinically not significant, abnormal - clinically significant) at baseline and last assessment on treatment, including shifts in interpretation as compared to baseline.

Supportive ECG listings will cover observed values for each individual participant.

Details of ECG analyses will be provided in the SAP.

9.4.4 Pharmacokinetics

9.4.4.1 Plasma Concentration Data

AZD2389 plasma concentrations for each scheduled timepoint will be summarised by cohort and day using appropriate descriptive statistics, based on the PK analysis set. A listing of all concentration time data, ie, PK scheduled times, actual sample collection times, sample actual relative times, as well as derived sampling time deviations will be presented based on the safety analysis set.

9.4.4.2 Urine Concentration Data

Urine concentration and volume/weight data will be listed by collection interval and

cumulatively and not summarised. The listing will include protocol-scheduled sampling interval, and sample collection start and stop times and will be presented for all participants in the safety analysis set.

9.4.4.3 Pharmacokinetic Parameter Listings

All reportable PK parameters, including individual diagnostic and λ_z related parameters, will be listed for each participant by cohort and day.

9.4.4.4 Pharmacokinetic Parameter Descriptive Statistics

All PK parameters including diagnostic PK parameters will be summarised for AZD2389 by cohort and day using appropriate descriptive statistics, based on the PK analysis set.

9.4.4.5 Graphical Presentation

Individual concentration time data will be graphically presented on linear and semi-logarithmic scales in the individual values of plasma concentrations versus time figure, based on the PK analysis set. For repeat dose groups, the plots will overlay the single and multiple dose concentration-time profiles.

Combined individual plasma concentration versus actual times after starting dose will be plotted on both the linear and semi-logarithmic scale for all participants in the individual plasma concentrations versus time figure, based on the PK safety analysis set. Within every figure, plots will be grouped by cohort.

Figures for the geometric mean ($\pm$ gSD) concentration versus scheduled time data will be plotted for all cohorts on both a linear and semi logarithmic scale (no gSD presented), for all participants in the geometric mean (gSD) plasma trough concentration versus study daytime figure, based on the PK analysis set. Individual trough concentrations will be plotted versus PK Day and dose group (linear scale only).

Cumulative amount/fraction of AZD2389 excreted in urine will be listed by cohort, participant, and protocol-scheduled times and appropriate descriptive statistics. Geometric mean of cumulative amount/fraction of dose of AZD2389 excreted in urine ($\pm$ gSD) versus nominal sampling time will be plotted on linear scale with both cohorts overlaid on the same figure.

For geometric mean plots, below the limit of quantification values will be handled as described for the summary tabulations; for individual plots plasma concentrations which are NQ prior to the first quantifiable concentration will be set to a value of zero (linear plots only). After the first quantifiable concentration, any NQ plasma concentrations will be regarded as missing. All plots will be based on the PK analysis set.

9.4.5 Other Analyses

9.4.5.1 Change in FAP Activity

An MMRM will be used to fit change at Days 1, 7, 14, 28, and follow-up in FAP activity for each cohort separately, as well as for the combined cohorts. Of the multiple measurements of FAP activity on Days 1 and 28, the trough level CCI measurements will be used in the MMRM. The analysis models will be adjusted for the treatment, baseline, and other covariates as appropriate, and comparisons will be provided versus placebo. Descriptive summaries showing the mean change and percentage change from baseline over time may also be produced. Further detail will be provided in the SAP.

9.4.5.2 Change in CCI

The analysis of covariance models will be used to fit change at CCI in CCI for each cohort separately, as well as for the combined cohorts. The analysis models will be adjusted for the treatment, baseline, and other covariates as appropriate, and comparisons will be provided versus placebo. Descriptive summaries showing the mean change and percentage change from baseline over time may also be produced. Further detail will be provided in the SAP.

9.4.5.3 Change in CCI

The analysis of covariance models will be used to fit change at CCI in CCI for each cohort separately, as well as for the combined cohorts. The analysis models will be adjusted for the treatment, baseline, and other covariates as appropriate, and comparisons will be provided versus placebo. Descriptive summaries showing the mean change and percentage change from baseline over time may also be produced. Further detail will be provided in the SAP.

9.4.5.4 Change in CCI

The analysis of covariance models will be used to fit change at CCI in CCI, CCI for each cohort separately, as well as for the combined cohorts. The analysis models will be adjusted for the treatment, baseline, and other covariates as appropriate, and comparisons will be provided versus placebo. Descriptive summaries showing the mean change and percentage change from baseline over time may also be produced. Further detail will be provided in the SAP.

9.4.5.5 Change in CCI

An MMRM will be used to fit change at CCI and CCI in CCI for each cohort separately, as well as for the combined cohorts. The analysis models will be adjusted for the treatment, baseline, and other covariates as appropriate, and comparisons will be provided versus placebo. Descriptive summaries showing the mean change and percentage change from baseline over time may also be

produced. Further detail will be provided in the SAP.

9.4.5.6 Change in CCI

The analysis of covariance models will be used to fit change at CCI in CCI CCI for each cohort separately, as well as for the combined cohorts. The analysis models will be adjusted for the treatment, baseline, and other covariates as appropriate, and comparisons will be provided versus placebo. Descriptive summaries showing the mean change and percentage change from baseline over time may also be produced. Further detail will be provided in the SAP.

9.4.5.7 Change in CCI

The analysis of covariance models will be used to fit change at CCI in CCI, CCI for each cohort separately, as well as for the combined cohorts. The analysis models will be adjusted for the treatment, baseline, and other covariates as appropriate, and comparisons will be provided versus placebo. Descriptive summaries showing the mean change and percentage change from baseline over time may also be produced. Further detail will be provided in the SAP.

9.5 Interim Analyses

Not applicable.

9.6 Data Monitoring Committee

No Data Monitoring Committee is planned for this study. An ad hoc SRC will assess the available safety, tolerability, PK, and PD data as needed. A detailed description of the SRC can be found in [Appendix A 5](#).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences International Ethical Guidelines
 - Applicable ICH GCP Guidelines
 - Applicable laws and regulations
- The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised 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 authorisations to conduct the study from the concerned regulatory authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, 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 SAEs

- Prompt notification by the investigator to AstraZeneca of an 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.
- AstraZeneca 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. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- Adherence to 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 an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal obligations and ethical obligations are met.

- A “serious breach” means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.

AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators.

- Where the EU Clinical Trials Regulation 536/2014 applies, AstraZeneca has in place processes to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

The investigator should have a process in place to ensure that:

- The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca 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 study and for one year after completion of the study.

A 3 Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally authorised 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 authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study centre.
- 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 authorised person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be 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 authorised representative.
- Participants who are rescreened are required to sign a new ICF.

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation (GDPR) defines pseudonymisation as the

processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A ‘personal data breach’ means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller¹ for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The investigator should have a process in place to ensure that:

- site staff or service providers delegated by the investigator/institution are allowed to identify the occurrence of a (potential) personal data breaches.
- any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining

¹ The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).

- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal data breach to participants:

- notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches that occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involves an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data participants, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.

- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees Structure

An ad hoc SRC may be appointed for this study. The SRC is composed of core study team individuals, including the Principal Investigator (Chair), AstraZeneca Study Clinical Lead(s), AstraZeneca Clinical Scientist, AstraZeneca Safety Physician, AstraZeneca Clinical Pharmacology Scientist, AstraZeneca Clinical Pharmacokinetic Scientist or designee and Fortrea Project Manager, may evaluate the available safety, tolerability, PK, and PD data as needed.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca 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 included 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.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorised 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 a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 7.1 Quality Tolerance Limits

No quality tolerance limits will be defined for this study.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorised 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.

A 9 Study and Site Start and Closure

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

The first act of recruitment is the first participant signing first informed consent in line with first participant's first visit and will be the study start date.

Study/Site Termination

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. 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 AstraZeneca or the 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, AstraZeneca'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, AstraZeneca shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any CRO(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.

A 10 Study Stopping Criteria

An ad hoc SRC will be convened based on emerging safety data if any of the following occur:

- a. Three or more participants develop the same Grade 3 CTCAE or laboratory abnormality (confirmed by repeat testing) attributed to AZD2389

OR

- b. Two subjects develop any Grade 4 CTCAE or laboratory abnormality (confirmed by repeat testing) attributed to AZD2389

OR

- c. One participant develops a Grade 5 CTCAE or laboratory abnormality (confirmed by repeat testing) attributed to AZD2389.

The SRC will assess the causality and clinical relevance of the AEs or laboratory abnormalities and recommend to either halt study dosing for all subjects, pause enrolment, or take no action.

A 11 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 AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

B 1 Definition of AEs

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable 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 it's considered related to the medicinal product.

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

B 2 Definition of SAEs

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

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

The AEs for **malignant tumours** 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 judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, 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 medicinal 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).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). 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 judgement 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, hospitalisation, disability or incapacity but may jeopardise 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 judgement must be used.

Intensity Rating Scale:

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

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

B 3 A Guide to Interpreting the Causality Question

When assessing causality, consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the medicinal product.

- Time Course. Exposure to suspect drug. Has the participant 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 aetiology such as the underlying disease, other drugs, other host, or environmental factors.
- 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 recognised feature of an 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 DUS has deteriorated due to lack of effect should be classified as ‘no reasonable possibility’.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca 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 recognised 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, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, CCI in water when it should be taken as a CCI
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM - including those which led 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 DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study).
- The drug in the form of a CCI is CCI 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 authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

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

Examples of drug misuse include but are not limited to:

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

All appropriately consented samples will be retained for maximum 15 years from last participant's last visit.

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, 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 the participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.

- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

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

C 3 International Air Transport Association Guidance Document 62nd Edition

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

The 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 and 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 are substances that do not contain infectious substances, or substances that 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/contentassets/b08040a138dc4442a4f066e6fb99fe2a/dgr-62-en-pi650.pdf>).

- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.

Appendix D Optional Genomics Initiative Research

D 1 Use/Analysis of DNA and blood derivatives

- AstraZeneca intends to collect and store DNA and blood derivatives (such as plasma and serum) for genomic and comprehensive omics characterisation research (such as protein, nucleotides and other entities in circulation), which may include metabolomic, proteomic and lipidomic analysis, to explore how genomic and timepoint omics variations may affect clinical parameters, risk and prognosis of diseases, and the response to medicinal product.
- This genomic and multi-omics 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 IRB/IEC allow, a blood sample will be collected for DNA and multi-omics analysis from consenting participants.
- This optional genomic and multi-omics research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of these genetic and multi-omics analyses may be reported in a separate study summary.
- AstraZeneca will store the DNA and blood derivative samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Multi-omics Research Plan and Procedures

Selection of Multi-omics Research Population

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

Inclusion Criteria

For inclusion in this genomic and multi-omics research, participants must fulfil all of the inclusion criteria described in the main body of the protocol and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

Exclusion from this genomic and multi-omics 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

- Healthy volunteers and paediatric participant samples will not be collected for the Genomics Initiative.

Withdrawal of Consent for Multi-omics Research

- Participants may withdraw from this genomic and multi-omics 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 protocol.

Collection of Samples for Multi-omics Research

- The blood sample for this genomic and multi-omics research will be obtained from the participants at Visit 3 after randomisation. 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 3, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics and multi-omics research during the study.

Coding and Storage of DNA and Multi-omics Samples

The processes adopted for the coding and storage of samples for genomic and multi-omics analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years from the date of last participant's last visit, after which they will be destroyed. The DNA and blood derivatives are a finite resource that will be 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 samples either before or at the time of sample processing, 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 analysis laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA or blood derivatives).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant samples for analysis, facilitate correlation of genotypic, or multi-omics 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 genomics and multi-omics research component, are outlined in [Appendix A](#).

Informed Consent

- The genomic and multi-omics component of this study is optional and the participant may participate in other components of the main study without participating in this multi-omics component. To participate in the genomic and multi-omics component of the study the participant must sign and date both the consent form for the main study and the Optional Genomics Initiative Research Information and Consent Form. Copies of both signed and dated consent forms must be given to the participant and the originals filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdraw from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual sequencing, genotype, or multi-omics results to participants, any insurance company, any employer, their family members, or general physician unless required to do so by law. Extra precautions are taken to preserve confidentiality and prevent genomic and multi-omics 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 genomic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genomic files would remain physically separate.

Data management

- Any genomic or multi-omics data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genomics and multi-omics research with other researchers, such as hospitals, academic organisations, or drug- or health-related 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 multi-omics data in a suitable secure environment separate from the clinical database.

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

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law cases and Hy's Law cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential Hy's Law criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law 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, potential Hy's Law criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law 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 potential Hy's Law/Hy's Law cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law

Aspartate aminotransferase or ALT $\geq 3 \times \text{ULN}$ **together with** TBL $\geq 2 \times \text{ULN}$ at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law

Aspartate aminotransferase or ALT $\geq 3 \times \text{ULN}$ **together with** TBL $\geq 2 \times \text{ULN}$, 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 potential Hy's Law and Hy's Law, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe

within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law, 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:

- $ALT \geq 3 \times ULN$
- $AST \geq 3 \times ULN$
- $TBL \geq 2 \times ULN$

Central Laboratories Being Used:

When a participant meets any of the potential Hy's Law 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 remain vigilant for any laboratory reports where the potential Hy's Law 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 potential Hy's Law criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

Local Laboratories Being Used:

The investigator will without delay review each new laboratory report and, if the identification criteria are met, will:

- Notify the AstraZeneca representative and Fortrea medical monitor.
- Determine whether the participant meets potential Hy's Law criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet potential Hy's Law criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet potential Hy's Law criteria the investigator will:

- Determine whether potential Hy's Law criteria were met at any study visit prior to starting study intervention.
- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within one day of potential Hy's Law criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'important medical event' and causality assessment 'yes/related' according to the protocol process for SAE reporting.
- For participants who met potential Hy's Law criteria prior to starting IMP, the investigator is not required to submit a potential Hy's Law SAE unless there is a significant change[#] in the participant's condition.
- The Study Clinical Lead will contact the investigator, to provide guidance, discuss, and agree an approach for the study participant's 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 aetiology of the event and perform diagnostic investigations as discussed with the Study Clinical Lead. This includes deciding which the tests available in the Hy's Law laboratory 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 Clinical Lead if there is any uncertainty.

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

The instructions in this appendix should be followed for all cases where potential Hy's Law criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the Study Clinical Lead will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date potential Hy's Law 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 an 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 Potential Hy's Law 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 Hy's Law 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 the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and

seriousness criteria is medically important, according to protocol 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 Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following protocol process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

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

- Not applicable.

E 7 Laboratory Tests

Table 9 Hy's Law Laboratory 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 IgG anti-HSV and HSV 1/2 IgM testing or HSV 1/2 PCR testing ^c IgM & IgG anti-EBV
Alcoholic hepatitis	CD-transferrin ^d
Autoimmune hepatitis	ANA Anti-LKM ASMA
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin ^c Transferrin saturation

Abbreviations: ANA = antinuclear antibody; anti-LKM = anti-liver/kidney microsomal antibody; ASMA = anti-smooth muscle antibody; CD-transferrin = carbohydrate-deficient transferrin; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; GGT = gamma-glutamyl transferase; HAV = hepatitis A virus; HBc = hepatitis B core antigen; HBV hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalised ratio; LDH = lactate dehydrogenase; PCR = polymerase chain reaction; RNA = ribonucleic acid.

^a HBV DNA is only recommended when IgG anti-HBc is positive.

^b HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

^c HSV 1/2 IgM testing or HSV 1/2 PCR testing depending on region.

^d CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly.

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Appendix F Prohibited Medications

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