Clinical Study Protocol

Study Intervention	Zibotentan and Dapagliflozin
Study Code	D4326C00004
Version	3.0 EU
Date	09 September 2024

EU CT Number 2023-506893-11

A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase IIb Study to Evaluate the Safety of Zibotentan/Dapagliflozin in Combination Compared to Zibotentan Monotherapy as well as Zibotentan/Dapagliflozin and Zibotentan Monotherapy Compared to Placebo in Participants with Cirrhosis

Sponsor Name: AstraZeneca AB

Legal Registered Address:

AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number:

EU CT Number 2023-506893-11

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: Regional - EU

Protocol Number: D4326C00004

Study Intervention: Zibotentan and Dapagliflozin

Brief Title: A Phase IIb Study to Evaluate the Safety of Zibotentan/Dapagliflozin in Participants with Cirrhosis-ZEAL-UNLOCK

Study Phase: Phase IIb

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

Coordinating Investigator: PPD, Hull University Teaching Hospitals, Hull, United Kingdom.

SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
CSP version 3.0 / CSP version 3.0 EU	09-September-2024
CSP version 3.0	09-September-2024
CSP version 2.0 / CSP version 2.0 EU	16-May-2024
CSP version 2.0	16-May-2024
CSP version 1.0 / CSP version 1.0 EU	06-March-2024
CSP version 1.0	11-October-2023

CSP Version 3.0 EU (EEA regional modification) 09-September-2024

This modification to CSP version 2.0 EU is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU and in the EU Clinical Trial Regulation Article 2, 2 (13) because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Modification:

The purpose of this amendment is to permit the use of paper PROs when the provisioned handheld electronic devices cannot be used to record the PRO responses and to include additional laboratory tests to be conducted by the central laboratories when a participant meets any of the PHL identification criteria.

Summary of Changes:

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Summary of Changes Table	Section updated to reflect the changes made to CSP v2.0 EU to produce v3.0 EU.	To give details of changes made to the previous version of the CSP.
Section 3 Objectives, Endpoints, and Estimands	Endpoints relating to the exploratory objective, 'To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on fatigue, abdominal symptoms, physical functioning and health-related quality of life' have been split into 2 bullet points, and 'at baseline and Week 6' was added to the PGIS – Liver Disease questionnaire	• To separate the PGIS – Liver Disease questionnaire from the other questionnaires for clarity because it will not be evaluated as a change from baseline to Week 6 • To clarify that the PGIS – Liver Disease questionnaire will be evaluated at baseline and Week 6

Section Number and Name	Description of Change	Brief Rationale
Section 6.1.2 Medical Devices Including Combination Products with a Device Constituent	Digital devices sub-bullets amended to bullets of equal hierarchy	Correction of hierarchy
Section 8.2.2.4 Patient-reported Outcomes	Text amended to indicate that the preferred method of recording PRO data is via the provisioned handheld electronic device but that paper questionnaires may be used if a provisioned handheld electronic device is not available, or the participant is unable to use one.	To permit the use of paper questionnaires when needed.
Appendix A4	• Amended 'Regultaion' to 'Regulation' • Amended as follows: '… representative will provide ~~will provide~~ AstraZeneca with…'	Correction of minor spelling errors and typographical errors
Appendix B1	Deletion of repeated 'related to the medicinal product'	Correction of typographical error
Appendix E7 Laboratory Tests	IgG anti-HSV, and HSV 1/2 IgM testing or HSV 1/2 PCR testing (depending on the region) were added to the list of laboratory tests to be conducted at the central laboratory when a participant meets PHL criteria	Updated to reflect updated tests supporting acute HSV infection diagnosis in some regions
Appendix F	Appendix updated with the list of edits that were made to produce the previous modification (v2.0 EU) from v1.0 EU.	To capture the history of modifications to the EU CSP

CSP = clinical study protocol; EU = European Union; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; PCR = polymerase chain reaction; PGIS = Patient Global Impression of Severity; PHL = potential Hy's Law; PRO = patient-reported outcome

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
ABV	Alcohol by volume
ACE	Angiotensin-converting enzyme
AE	Adverse Event
AESI	Adverse events of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Transaminase
AST	Aspartate Aminotransferase/Transaminase
AUDIT	Alcohol Use Disorders Identification Test
AxMP	Auxiliary Medicinal Product
BIS	Bioimpedance spectroscopy
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CKD	Chronic kidney disease
CLDQ	Chronic liver disease questionnaire
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organisation
CRPC	Castration resistant Prostate Cancer
CSP	Clinical Study Protocol
CSPH	Clinically significant portal hypertension
CSR	Clinical Study Report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CTproET1	C-Terminal-Pro-Endothelin-1
DES	Data Entry Site
DILI	Drug Induced Liver Injury
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
DUS	Disease Under Study

Abbreviation or special term	Explanation
E/D	Early Study Intervention Discontinuation
ECHO	Echocardiography
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
ERA	Endothelin receptor antagonist
ET	Endothelin
EU	European Union
EU CT	EU Clinical Trial
EudraCT	EU Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FIB-4	Fibrosis-4
FOCBP	Female(s) of childbearing potential
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
Hb	Haemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HF	Heart Failure
HR	Heart rate
HVPG	Hepatic venous pressure gradient
IATA	The International Air Transport Association
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International normalised ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LFTs	Liver Function Tests
CCI	

Abbreviation or special term	Explanation
MELD	Model for end-stage-liver disease
MMRM	Mixed model repeated measures
N/A	Not applicable
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NIMP	Non-investigational Medicinal Product
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
PD	Pharmacodynamic(s)
PGIS	Patient Global Impression of Severity
PHL	Potential Hy's Law
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PRO	Patient-reported outcome
RTSM	Randomisation and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Screened analysis set
SD	Standard deviation
SGLT2	Sodium glucose cotransporter 2
SoA	Schedule of Activities
SPFQ	Study Participant Feedback Questionnaire
SU	Sulfonylurea
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TBL	Total Bilirubin
TIPS	Transjugular intrahepatic portosystemic shunt
ULN	Upper Limit of Normal
CCI [redacted]	

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase IIb Study to Evaluate the Safety of Zibotentan/Dapagliflozin in Combination Compared to Zibotentan Monotherapy as well as Zibotentan/Dapagliflozin and Zibotentan Monotherapy Compared to Placebo in Participants with Cirrhosis

Brief Title: A Phase IIb Study to Evaluate the Safety of Zibotentan/Dapagliflozin in Participants with Cirrhosis-ZEAL-UNLOCK

Regulatory Agency Identifier Numbers:

IND number 156901
EU CT Number 2023-506893-11

Rationale:

Cirrhosis is the end-stage result of chronic liver injury/disease and is characterised by advanced fibrosis and, ultimately, hepatic failure. Cirrhosis may be compensated in which no clinical complications that affect outcome (ie, variceal haemorrhage, ascites, hepatic encephalopathy, hepatocellular cancer) have occurred, or decompensated, in which patients have had at least one of these clinical complications. The aetiology of cirrhosis varies with viral hepatitis (hepatitis B and C), alcoholic liver disease, and non-alcoholic steatohepatitis (NASH) being the leading causes of cirrhosis globally, with less common causes including autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, haemochromatosis, and Wilson's disease. Cirrhosis is a serious condition which leads to significant morbidity, resource intensive complications, hepatocellular carcinoma, and, in the absence of liver transplantation, death. In 2017, over 1.32 million cirrhosis related deaths were reported globally, which was approximately 2.4% of all deaths worldwide. In 2019, cirrhosis caused 1.48 million deaths, an increase of 8.1% compared to 2017, and its disability-adjusted life-years ranked 16th among all diseases. The global burden of cirrhosis due to hepatitis B virus and hepatitis C virus infection is decreasing, while the burden of cirrhosis due to alcohol and non-alcoholic fatty liver disease is increasing rapidly.

Portal hypertension is the major cause of complications in liver cirrhosis. The primary cause of portal hypertension in cirrhosis is a combination of structural changes in the liver associated with fibrosis and increased vascular tone in the hepatic microcirculation both leading to an increase in intrahepatic vascular resistance. As portal hypertension develops, splanchnic vasodilation progresses, which results in increased blood flow to the portal circulation that further increases portal pressure. Consequently, a hyperdynamic circulation develops, collateral vessels are formed and there is an increased risk for decompensation events.

The mechanisms of action of zibotentan and dapagliflozin on liver cirrhosis and associated

complications are different and the outcome of combined treatment is expected to be complementary. The main biological effects of zibotentan are expected from blocking endothelin-1 driven increase in intrahepatic vascular resistance (including elements of portal vein and sinusoidal vasoconstriction). Furthermore, zibotentan is expected to decrease vascular stiffness, improve endothelial function, reduce hepatic inflammation and, in the longterm, potentially reduce fibrosis.

Separately, dapagliflozin is expected to have beneficial effects on metabolic dysfunction, reduce hepatocyte injury and sodium and water overload whilst avoiding hyponatraemia and hyperkalaemia. A reduced need for diuretics may also reduce the risk for potential acute kidney injury or other complications such as encephalopathy. In a pilot study, 3 cases of cirrhosis with ascites and type 2 diabetes mellitus (T2DM) were treated with a sodium-glucose cotransporter 2 (SGLT2) inhibitor. In these patients, SGLT2 inhibition resulted in weight loss and reduced ascites or peripheral oedema.

A particularly important limitation of endothelin receptor antagonists, which includes zibotentan, is the increased risk for fluid retention. Approximately 40% of patients treated with zibotentan (doses ranging from 5 to 22.5 mg, with the majority of patients receiving the 10 mg once daily dose) from the Phase I-III oncology studies reported peripheral oedema. Also, in patients with portopulmonary hypertension with or without liver cirrhosis endothelin receptor antagonists have been shown to increase risk for fluid retention. Adverse events of fluid retention were reported in 26% of patients with portopulmonary hypertension with or without cirrhosis receiving macitentan and 39% of patients with portopulmonary hypertension with cirrhosis receiving ambrisentan. Dapagliflozin's effect in correcting sodium and water overload is expected to mitigate this fluid retention safety concern in the liver cirrhosis population with or without a history of decompensation. A post-hoc analysis of the SONAR trial, in patients with type 2 diabetes and chronic kidney disease, has demonstrated a reduced body weight gain when atrasentan was combined with an SGLT2 inhibitor as compared to a control group treated with atrasentan, without an SGLT2 inhibitor (-0.7 kg, 95% CI -1.6 to 0.3 kg vs 0.6 kg, 95% CI 0.0 to 1.1 kg), for a between-group difference of 1.2 kg (95% CI, 0.1 to 2.3 kg, $p = 0.028$).

The study is designed to evaluate the safety of zibotentan/dapagliflozin in combination as compared to zibotentan monotherapy as well as zibotentan/dapagliflozin in combination and zibotentan monotherapy as compared to placebo in patients with cirrhosis with or without a history of decompensation.

Objectives and Endpoints:

Objectives	Endpoints
Key Objectives	
To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on a composite endpoint of fluid retention.	Occurrence of any of the following components of this composite endpoint from baseline to Week 6: • > 2 kg increase in body weight (office-based) • > 2 L increase in total body water • Increase in 2 or more loop-diuretic equivalents [a] • Fluid retention adverse event (AE)
To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on a composite endpoint of fluid retention.	Occurrence of any of the following components of this composite endpoint from baseline to Week 6: • > 2 kg increase in body weight • > 2 L increase in total body water • Increase in 2 or more loop-diuretic equivalents [a] • Fluid retention AEs
To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on body weight, body water volumes and body fat mass.	• Change in body weight (kg) over time course of study (home-based monitoring). • Change from baseline in body weight, total body water, extracellular and intracellular water volumes, and body fat mass at Week 6 (office-based monitoring).
To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on body weight, body water volumes and body fat mass.	
To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on total loop-diuretic equivalents use [a].	Change in total dosage of loop-diuretic equivalents use from baseline to Week 6 [a].
To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on total loop-diuretic equivalents use [a].	
To evaluate the effects of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on the composite of total body water and total dosage of loop-diuretic equivalents [a]	Occurrence of either of the two components of this composite: 1 > 3 L increase in total body water volume from baseline to Week 6. 2 Increase in 3 or more loop-diuretic equivalents use from baseline to Week 6 [a].
To evaluate the effects of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on the composite of total body water and total dosage of loop-diuretic equivalents [a]	
To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on office-based systolic and diastolic blood pressure.	Absolute change in systolic and diastolic blood pressure from baseline to Week 6.
To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on office-based systolic and diastolic blood pressure.	

Objectives	Endpoints
Safety Objectives	
To assess the safety and tolerability of zibotentan/dapagliflozin and zibotentan versus placebo.	• AEs, SAEs, and DAEs • AESIs CCI) • Vital signs • Safety laboratory tests • ECG assessments

[a] One loop-diuretic equivalent = 40 mg furosemide = 1 mg bumetanide = 20 mg torsemide = 50 mg ethacrynic acid. In Japan, one loop-diuretic equivalent = 40 mg furosemide = 8 mg torsemide = 60 mg azosemide.

AE = adverse event; AESI = adverse event of special interest; CCI ; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN= Blood urea nitrogen; DAE = discontinuation due to adverse event; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA1c = haemoglobin A1c; MELD = model for end stage liver disease; PD = pharmacodynamic; PGIS= Patient Global Impression of Severity; PK = pharmacokinetic; SAE = serious adverse event; CCI CCI

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

Overall Design Synopsis:

This is a Phase IIb multicentre, randomised, double-blind, parallel-group, placebo-controlled study to evaluate the safety of zibotentan/dapagliflozin in combination as compared to zibotentan monotherapy as well as zibotentan/dapagliflozin and zibotentan monotherapy as compared to placebo in participants with cirrhosis. Eligible participants could have a history of decompensation events or have compensated cirrhosis. If compensated cirrhosis, the eligible participants must have features of portal hypertension defined as signs and measures that would indicate that the participant has clinically significant portal hypertension (CSPH) and include, but not limited to, presence of gastro-oesophageal varices at endoscopy or collaterals at imaging (either one within 12 months prior to screening), and/or CCI CCI kPa, or of CCI kPa and CCI (at time of screening). All participants should have a MELD score < 15 and be classified as Child-Pugh A or B.

Brief Summary:

This study will consist of the following periods:

Screening Period of up to 3 weeks: The Screening Visit (Visit 1) will take place between 7 to 21 days before the Randomisation Visit (Visit 2) to confirm participant eligibility and collect baseline data. There must be at least 7 days between Visit 1 and Visit 2 to allow sufficient time for laboratory results to be examined. At the Randomisation Visit (Visit 2), eligibility criteria will be reassessed, safety laboratory data reverified, and participants will be provided digital devices to measure their body weight starting the first day after the Randomisation Visit and every day at home.

Treatment Period of 6 weeks: During the Treatment Period, participants will visit the study centre 5 times. At Visit 2, participants will be randomised and will receive the first dose of the study intervention. At each study visit during the treatment period (from Visit 3 till Visit 6) participants will receive the once daily dose at the study centre and will provide a pre-dose blood sample for PK analysis and other lab samples before the intake of study intervention. When not visiting the study centre the patients will take the once daily dose of study intervention at home.

Follow-up Period of 2 weeks: Participants will return to the study centre for follow-up assessments approximately 2 weeks after their planned last dose of study intervention (planned last dose is at Visit 6).

Disclosure Statement: This is a parallel-group, placebo-controlled study to evaluate the safety of zibotentan and zibotentan/dapagliflozin; the study is blinded to the participants, investigators, and Sponsor.

Number of Participants:

Approximately 22 eligible participants are planned to be randomised to each of the 3 treatment groups, for a total of up to 66 participants.

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

Study Arms and Duration:

Participants who meet the eligibility criteria and agree to participate will be randomised to one of the following treatment groups (22 participants per group). All participants will receive 1 capsule (zibotentan or matching placebo) and 1 tablet (dapagliflozin or matching placebo) at every dosing.

- Treatment Group 1: placebo matching zibotentan capsule + placebo matching dapagliflozin tablet.
- Treatment Group 2: zibotentan capsule [redacted] mg + placebo matching dapagliflozin tablet.
- Treatment Group 3: zibotentan capsule [redacted] mg + dapagliflozin tablet 10 mg.

Data Monitoring/Other Committee:

A Data Monitoring Committee (DMC) will monitor ongoing safety/tolerability data and may recommend stopping further recruitment and/or treatment of participants in a treatment group at any time. The DMC will conduct pre-specified meetings and ad hoc meetings as needed.

The role and responsibilities of the DMC, and stopping criteria for the study, will be described in the DMC charter.

Statistical Methods:

For fluid retention composite endpoints defined as:

- occurrence of any of the following events: (1) > 2 kg increase in body weight, (2) > 2 L increase in total body water, (3) increase in 2 or more loop-diuretic equivalents or (4) fluid retention AEs, from baseline to Week 6
- occurrence of either (1) > 3 L increase in total body water volume from baseline to Week 6; or (2) increase in 3 or more loop-diuretic equivalents use from baseline to Week 6

Exact 90% (two-sided) CIs for proportions of patients with the composite of fluid retention in treatment groups will be calculated using the Clopper-Pearson method. The exact unconditional 90% (two-sided) CIs for difference in proportions between 2 treatment groups will be computed based on score statistic (Chan and Zhang 1999).

The change in body weight, total dosage of loop-diuretic equivalents, body water volumes, body fat mass and blood pressure from baseline to Week 6 will be analysed using mixed model repeated measures (MMRM) methodology for pairwise comparisons between treatment groups. The analytic model will include the CCI of CCI , CCI , and CCI , and CCI of the CCI CCI An CCI will be used for the CCI CCI

Sample Size Calculation:

Approximately 22 participants are planned to be randomised to each of the 3 treatment groups. The sample size is not determined based on a formal statistical hypothesis testing for this Phase IIb study. With CCI evaluable participants per group, an observed difference of CCI % (CCI %) in proportion of patients with the composite of fluid retention between a zibotentan/dapagliflozin group and an observed CCI % composite of fluid retention in the corresponding zibotentan group, the lower limit of a two-sided 90% CI for the difference will be CCI %.

1.2 Schema

Figure 1 CCI

EOT = end of trial; F/U = follow-up; R = randomisation.

1.3 Schedule of Activities

Table 1 Schedule of Activities

	Screening period	Treatment period					Follow-up	Section in the CSP
		Randomisation	Visits					
Visit number	**1**	**2**	**3**	**4**	**5**	**6 [a]**	**7**	
Week	**-3**	**0**	**1**	**2**	**3**	**6**	**8**	
Study day	**-21 to -7 [a]**	**1**	**8**	**15**	**22**	**43**	**57**	
Visit window (days)			**± 3**	**± 3**	**± 3**	**± 5**	**± 3**	
Informed consent	X							Appendix A 3
Inclusion/exclusion criteria	X	X						Section 5.1 and Section 5.2
Alcohol breath test	X	X				X		Section 5.2
Screen for drugs of abuse	X							Section 8.3.5
AUDIT questionnaire	X							Section 8.3.6.2
Enrolment in IRT/RTSM	X							Section 6.3
Randomisation in IRT/RTSM		X						Section 6.3
Routine clinical procedures								
Demography and baseline characteristics (including smoking history and alcohol consumption)	X							Section 5.3.2

Table 1 Schedule of Activities

	Screening period	Treatment period					Follow-up	Section in the CSP
		Randomisation	Visits					
Visit number	**1**	**2**	**3**	**4**	**5**	**6 [a]**	**7**	
Week	**-3**	**0**	**1**	**2**	**3**	**6**	**8**	
Study day	**-21 to -7 [a]**	**1**	**8**	**15**	**22**	**43**	**57**	
Visit window (days)			**± 3**	**± 3**	**± 3**	**± 5**	**± 3**	
Medical/surgical history	X							
Concomitant medication	X	X	X	X	X	X	X	Section 6.9
Body weight	X	X	X	X	X	X	X	Section 8.2.1.2
Height, BMI calculation	X							Section 8.3.1
ECHO	X[c]							Section 8.3.4
HIV serology	X							Section 8.3.5
FSH (females only)	X[d]							Section 8.3.5
Pregnancy tests (females only; serum)	X							Section 8.3.5
Study intervention								
Study intervention dispensed		X			X			Section 6
Study intervention accountability (counting remaining tablets and capsules)			X	X	X	X		Section 6.2

Table 1 Schedule of Activities

	Screening period	Treatment period					Follow-up	Section in the CSP
		Randomisation	Visits					
Visit number	**1**	**2**	**3**	**4**	**5**	**6 [n]**	**7**	
Week	**-3**	**0**	**1**	**2**	**3**	**6**	**8**	
Study day	**-21 to -7 [a]**	**1**	**8**	**15**	**22**	**43**	**57**	
Visit window (days)			**± 3**	**± 3**	**± 3**	**± 5**	**± 3**	
Study intervention intake [o]		X	X	X	X	X		Section 6
Key assessments								
Daily digital body weight measurement		Daily home measurement using a digital device should begin at Visit 2 (randomisation) to end of follow-up [q].						Section 8.2.1.2
Bioimpedance spectroscopy [r]	X	X	X	X	X	X	X	Section 8.2.1.3
Safety assessments								
AE review [h]	X SAEs only	X	X	X	X	X	X	Section 8.4.2
Physical examination	X	X	X [b]	X [b]	X [b]	X [b]	X	Section 8.3.1
ECG central monitoring [p]	X	X (pre-dose) X (2 hours post-dose)	X	X	X	X	X	Section 8.3.3
Vital signs (supine and standing blood pressure and pulse)	X	X (pre-dose) X (60, 120, 180 minutes)	X	X	X	X	X	Section 8.3.2
Body temperature	X	X	X	X	X	X	X	Section 8.3.2

Table 1 Schedule of Activities

	Screening period	Treatment period					Follow-up	Section in the CSP
		Randomisation	Visits					
Visit number	**1**	**2**	**3**	**4**	**5**	**6** [a]	**7**	
Week	**-3**	**0**	**1**	**2**	**3**	**6**	**8**	
Study day	**-21 to -7** [a]	**1**	**8**	**15**	**22**	**43**	**57**	
Visit window (days)			**± 3**	**± 3**	**± 3**	**± 5**	**± 3**	
Clinical safety laboratory tests (haematology, clinical chemistry, coagulation, electrolytes, serum osmolality, and NT-pro BNP	X	X [i]	X [i]	X [i]	X [i]	X [i]	X	Section 8.3.5
PK assessments								
Pre-dose PK plasma sample (all participants) [j]			X [i]	X [i]	X [i]			Section 8.5
PK profile (Japanese)					X [k,l]			Section 8.5
Post-dose sample (Non-Japanese)					X [m]			Section 8.5

Table 1 Schedule of Activities

	Screening period	Treatment period					Follow-up	Section in the CSP
		Randomisation	Visits					
Visit number	**1**	**2**	**3**	**4**	**5**	**6** [n]	**7**	
Week	**-3**	**0**	**1**	**2**	**3**	**6**	**8**	
Study day	**-21 to -7** [a]	**1**	**8**	**15**	**22**	**43**	**57**	
Visit window (days)			± 3	± 3	± 3	± 5	± 3	
Exploratory assessments								
CCI [redacted]	X [g]					X[f,g]		Section 8.2.2.1
eGFR calculation [s]	X	X	X	X	X	X	X	Section 8.2.2.2
MELD score calculation	X	X	X	X	X	X	X	Section 8.2.2.3
Child-Pugh score	X	X	X	X	X	X	X	
Non-fasting plasma/serum biomarkers		X [i]			X [i]	X [i]		
HbA1c	X [i]	X [i]			X [i]	X [i]		
PROs: CLDQ, PGIS - Liver Disease, and SF-36v2 acute		X [o]				X		Section 8.2.2.4
Collect and store serum and plasma samples for exploratory assessment of biomarkers		X [i]				X [i]		Section 8.8.1

Table 1 Schedule of Activities

	Screening period	Treatment period					Follow-up	Section in the CSP
		Randomisation	Visits					
Visit number	1	2	3	4	5	6 [a]	7	
Week	-3	0	1	2	3	6	8	
Study day	-21 to -7 [a]	1	8	15	22	43	57	
Visit window (days)			± 3	± 3	± 3	± 5	± 3	
Collect and store urine samples for exploratory assessment of biomarkers		X [i]				X [i]		Section 8.8.1
Optional Genomics Initiative, exploratory genomics, and multi-omics samples		X						Section 8.7 and Appendix D

a. Screening visit can take place from 21 days up to 7 days before randomisation visit (Visit 2). It must be at least 7 days between Visit 1 and Visit 2 to allow time for laboratory results to be examined.
b. Brief physical examination.
c. Only in those participants with history of Heart Failure and if historical data from ECHO or cardiac MRI in the prior 12 months is not available.
d. Results need to be available before the randomisation visit (Visit 2).
e. Study intervention intake will take place at the study centre and at home when not visiting the study centre.
f. CCI [redacted] to be assessed ≥ 3 hours after study intervention administration at Visit 6. A CCI [redacted] assessment of CCI [redacted] s and/or CCI [redacted] should only be done if CCI [redacted] to complete an accurate CCI [redacted] and/or CCI [redacted] measurement. CCI [redacted] should only be done if CCI [redacted] is available.
g. CCI [redacted] must not take place earlier than at least 3 hours after a light meal, such as breakfast. If the participant is on a non-selective beta-blocker, the morning dose should not be taken, but taken directly after the CCI [redacted].
h. If a SAE occurs within 48 hours after the last dose, a PK sample will be taken if possible. The exact time of last dosing and of blood sampling will be recorded.
i. Pre-dose sample in all participants (both Japanese and non-Japanese).
j. Pre-dose sample and dosing at the study centre at every visit. Pharmacokinetics sample to be done at early termination visit as well. If no dosing takes place, sample at any time during the study centre visit and document exact date and time.

k. Pharmacokinetics profile only for Japanese patients. Samples for PK profile collected over 5 hours at the study centre. Sampling times: pre-dose, 0.5 to 1.0, 1.5 to 2.0, 2.5 to 3.0, 3.5 to 4.0, 4.5 to 5.5 hours post-dose; exact clock times need to be documented. See Section 5.3.1 for further details on meal restrictions.
l. Pharmacokinetics profile can be done at Visit 4 if not possible at Visit 5. At the day selected for the PK profile, the study intervention must be administered at the study centre so that PK sampling according to schedule is possible.
m. A post-dose sample is taken as late as possible after dosing on the dose day (at least 1h after dosing); the exact actual sampling time needs to be recorded.
n. Visit 6 is planned End of Treatment (EoT) visit. If participant terminates early from the study (ie Withdraw consent), please perform examinations as Visit 6.
o. Baseline PRO Questionnaires to be completed before treatment initiation.
p. Digital ECGs will be centrally read. The predose ECG read out from Visit 2 is to be reviewed by the investigator before randomisation as central report will not be available on the day. All ECGs will be recorded in triplicate after a 10-minute supine rest period with no more than about 2 minutes between individual ECGs, completing all 3 ECGs within a maximum of about 5 minutes. ECGs should be collected prior to vital signs, PK sample collection, or other assessments as these may alter autonomic tone. Unscheduled ECGs may be added if clinically indicated.
q. Participants should also perform first weight measurement at the study site on mobile application at Visit 2 (which is when it will be distributed to the participant).
r. Participants are recommended to not engage in eating a large meal before measurement collection. Collection of fasting time prior to measurement is required.
s. eGFR1 is at every visit and eGFR2 is at Visits 2, 5, and 6.

Abbreviations: AE = Adverse event; AUDIT = Alcohol Use Disorders Identification Test; BMI = body mass index; CLDQ = Chronic Liver Disease Questionnaire; CSP = Clinical study protocol; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; ECHO=echocardiography; EoT = End of Treatment; ET = Early Termination visit; FSH = follicle-stimulating hormone; h = hour; HbA1c = haemoglobin A1c; HIV = Human immunodeficiency virus; IRT = Interactive Response Technology; MELD = Model for End-stage Liver Disease; NT-pro BNP = N-terminal prohormone of brain natriuretic peptide; PGIS= Patient Global Impression of Severity; PK = pharmacokinetics; PRO = patient-reported outcome; RTSM = Randomisation and Trial Supply Management; SAE = serious adverse event; SF-36v2 = Short form 36 healthy survey questionnaire, version 2; CCI .

2 INTRODUCTION

Zibotentan is a selective endothelin (ET_A) receptor antagonist, originally investigated for cardiovascular and oncology indications. Zibotentan is currently being investigated as a treatment for CKD in combination with dapagliflozin. Zibotentan is available for oral administration and requires once daily dosing.

Dapagliflozin is a highly potent, selective, and reversible inhibitor of SGLT2 that improves glycaemic control in patients with diabetes mellitus and provides cardiorenal benefits in patients with and without T2DM. Dapagliflozin is available for oral administration and requires once daily dosing.

2.1 Study Rationale

The mechanisms of action of zibotentan and dapagliflozin on liver cirrhosis and associated complications are different, and the outcome of combined treatment is expected to be complementary. The main biological effects of zibotentan are expected from blocking endothelin-1 driven increase in intrahepatic resistance (including elements of portal vein and sinusoidal vasoconstriction). Furthermore, zibotentan is expected to decrease vascular stiffness, improve endothelial function, reduce hepatic inflammation, and, in the long-term, potentially reduce fibrosis (Zibotentan Investigator's Brochure).

Separately, dapagliflozin is expected to have beneficial effects on metabolic dysfunction, reduce hepatocyte injury, and sodium and water overload whilst avoiding hyponatraemia and hyperkalaemia (Dapagliflozin Investigator's Brochure). A reduced need for diuretics may also reduce the risk for potential AKI or other complications such as encephalopathy. In a pilot study, 3 cases of NASH cirrhosis with T2DM and ascites were treated with an SGLT2 inhibitor. In these patients, SGLT2 inhibition resulted in weight loss and reduced ascites or peripheral oedema (Montalvo-Gordon et al 2020).

A particularly important limitation of endothelin receptor antagonists, which includes zibotentan, is the increased risk for fluid retention. Approximately 40% of patients treated with zibotentan (doses ranging from 5 to 22.5 mg, with the majority of patients receiving a dose of 10 mg once daily) from Phase I to III oncology studies reported peripheral oedema. Also, in patients with portopulmonary hypertension with or without liver cirrhosis, endothelin receptor antagonists have been shown to increase risk for fluid retention. Adverse events of fluid retention were reported in 26% of patients with portopulmonary hypertension with or without cirrhosis receiving macitentan (Sitbon et al 2019) and 39% of patients with portopulmonary hypertension with cirrhosis receiving ambrisentan (Preston et al 2020). Dapagliflozin's effect in reducing sodium and water overload is expected to mitigate this fluid retention safety concern in the population of patient with liver cirrhosis with features of portal hypertension. A post-hoc analysis of the SONAR trial, in patients with T2DM and CKD, has

demonstrated a reduced body weight gain when atrasentan was combined with an SGLT2 inhibitor as compared to a control group treated with atrasentan, without an SGLT2 inhibitor (-0.7 kg, 95% CI -1.6 to 0.3 kg vs 0.6 kg, 95% CI 0.0 to 1.1 kg) (Heerspink et al 2020).

The study is designed to evaluate the safety of zibotentan/dapagliflozin in combination as compared to zibotentan monotherapy as well as zibotentan/dapagliflozin in combination and zibotentan monotherapy as compared to placebo in patients with cirrhosis with or without a history of decompensation.

2.2 Disease Background

Patients with compensated cirrhosis with signs of clinically significant portal hypertension and patients with decompensated cirrhosis have limited pharmacological treatment options and significant risk of decompensation and death.

2.2.1 Cirrhosis with Features of Portal Hypertension

Cirrhosis is the end-stage result of chronic liver injury/disease and is characterised by advanced fibrosis and, ultimately, hepatic failure. Cirrhosis may be compensated, in which case no clinical complications that affect outcome have occurred (ie, variceal haemorrhage, ascites, hepatic encephalopathy, hepatocellular cancer), or decompensated, in which case patients have had at least one of these clinical complications (Tsochatzis et al 2014). The aetiology of cirrhosis varies, with viral hepatitis (hepatitis B and C), alcoholic liver disease, and NASH being the leading causes of cirrhosis globally, and less common causes including autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, haemochromatosis, and Wilson's disease (Romanelli and Stasi 2016). Cirrhosis is a serious condition which leads to significant morbidity, resource intensive complications, hepatocellular carcinoma, and, in the absence of liver transplantation, death. The Global Burden of Disease study in 2017 reported over 1.32 million cirrhosis related deaths globally, which was approximately 2.4% of all deaths worldwide (GBD 2017). In 2019, cirrhosis caused 1.48 million deaths, an increase of 8.1% compared to 2017, and its disability-adjusted life-years ranked 16th among all diseases. The global burden of cirrhosis due to hepatitis B virus and hepatitis C virus infection is decreasing, while the burden of cirrhosis due to alcohol and non-alcoholic fatty liver disease is increasing rapidly (Liu et al 2022).

Portal hypertension is the major cause of complications in liver cirrhosis. The primary cause of portal hypertension in cirrhosis is a combination of structural changes associated with fibrosis and increased vascular tone in the hepatic microcirculation both leading to an increase in intrahepatic vascular resistance. As portal hypertension develops, splanchnic vasodilation progresses, which results in increased blood flow to the portal circulation that further increases portal pressure (Iwakiri 2014). Consequently, a hyperdynamic circulation develops, collateral vessels are formed and there is an increased risk for decompensation events (Poordad 2015).

2.2.2 Current Treatment Options for Patients with Cirrhosis with Features of Portal Hypertension

Standard treatment for patients with chronic liver disease centres upon treatment of the underlying cause of liver disease, eg, abstinence from alcohol, anti-viral agents for viral hepatitis, and treatment of underlying metabolic disease in NASH. Although HCV can now be eradicated, given the continued emergence of fatty liver diseases, disease modifying therapies are in general expected to have marginal impact on the outcome in patients with decompensated cirrhosis or compensated cirrhosis with signs of clinically significant portal hypertension. Accordingly, there is a significant clinical unmet need for new treatments in patients with cirrhosis. Current guidelines support the use of non-selective beta blockers, diuretics and vasoactive drugs (Gunarathne et al 2020). In patients developing variceal haemorrhage, intervention with TIPS may be used to reduce portal hypertension (García-Pagán et al 2020).

2.3 Benefit/Risk Assessment

2.3.1 Zibotentan

Zibotentan, ZD4054, is an ET_A antagonist with the highest level of selectivity over ET_B currently known (ET_A IC_{50} = 13 nM, no effect at the ET_B up to 50 mM) (Morris et al 2005). Zibotentan 10 and 15 mg was initially developed for treatment of patients with castration-resistant prostate cancer. It did not achieve its efficacy endpoint in Phase III (survival rate), however, it was demonstrated to have an acceptable safety profile in this population (Nelson et al 2012). Zibotentan is considered safe to use in clinical testing (non-clinical safety package completed) with a known safety profile from oncology studies (Zibotentan Investigator's Brochure). Currently, there are studies ongoing with zibotentan and dapagliflozin in combination in patients with cirrhosis with portal hypertension (ZEAL study, D4326C00003and chronic kidney disease (ZENITH-CKD, D4325C00001), as well as an investigator-sponsored study with zibotentan in microvascular angina (PRIZE, NCT04097314) ([redacted] mg, 8 weeks; n = 356). Furthermore, a Phase II study in patients with systemic scleroderma (CKD-ZEBRA, NCT02047708) ([redacted] mg; 52 weeks; n = 23) has been completed.

A detailed description of the chemistry, pharmacology, efficacy, and safety of zibotentan is provided in the Zibotentan Investigator's Brochure

2.3.2 Dapagliflozin

Dapagliflozin is a selective SGLT2 inhibitor (IC_{50} = 3.75 nM). It was originally developed and approved as an adjunct glucose lowering therapy in T2DM. Subsequently, it has been approved to treat heart failure with reduced ejection fraction in both T2DM and non-diabetic patients and in CKD in patients with and without T2DM. Dapagliflozin has also been demonstrated to reduce risk in patients with heart failure with preserved ejection fraction and

has been investigated in hospitalised patients with COVID-19 (Kosiborod et al 2021).

A detailed description of the chemistry, pharmacology, efficacy, and safety of dapagliflozin is provided in the Dapagliflozin Investigator's Brochure

2.3.3 Risk Assessment

Dapagliflozin administration is well tolerated with a well-established safety profile. The potential and identified risks of dapagliflozin treatment have been well characterised through the dapagliflozin clinical development program and from post-marketing data. In clinical studies, commonly reported AEs include UTIs, genital infections, polyuria, and hypoglycaemia when combined with insulin or a sulfonylurea. In addition, DKA was commonly seen in clinical trials in patients with T1DM treated with dapagliflozin but was rare in clinical trials in patients with T2DM. See Table 2 for further details.

The adverse clinical effects of zibotentan observed in healthy volunteers and oncology populations were largely due to its pharmacologically-mediated effects on ET_A receptor antagonism resulting in vasodilation, which are headache, hypotension, nasal congestion, peripheral oedema, conjunctival reddening, dizziness, flushing, minor decreases in systemic vascular resistance, minor increases in cardiac output, and effects due to haemodilution which lead to a reduction in Hb concentration, haematocrit and anaemia. Reduction in Hb tends to develop within a month of commencing the drug and is mild in most patients (CTC Grade 1/2), nonprogressive and tends to reverse on stopping the drug. However, some patients in oncology studies have developed clinical anaemia. The adverse clinical effect of heart failure has been observed, being more commonly reported in CRPC patients receiving zibotentan than in those receiving placebo. The frequency of reports in patients receiving zibotentan has been less than 10% and most cases have responded to standard heart failure treatment. See Table 2 for further details.

More detailed information about the known and potential benefits and risks of zibotentan and dapagliflozin may be found in respective Investigator's Brochures (Zibotentan Investigator's Brochure including the FDC development, and Dapagliflozin Investigator's Brochure).

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Dapagliflozin		
Diabetic ketoacidosis including events with atypical presentation	Diabetic ketoacidosis (DKA) has been identified as an important identified risk for dapagliflozin in patients with diabetes. Diabetic ketoacidosis was only observed in patients with diabetes mellitus: Type 2 diabetes mellitus: In the cardiovascular outcome study DECLARE TIMI-58 in patients with T2DM, 8574 patients received dapagliflozin 10 mg and 8569 patients received placebo, for a median exposure time of 48 months. Events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a T2DM population. In clinical trials in patients with heart failure (DAPA-HF) or CKD (DAPA-CKD) with and without T2DM, events of ketoacidosis were only observed in patients with T2DM. In the DAPA-HF study, events of DKA were reported in 3 patients with T2DM in the dapagliflozin group and none in the placebo group. In the DAPA-CKD study, events of DKA were not reported in any patient in the dapagliflozin group and in 2 patients with T2DM in the placebo group. In addition, there have been postmarketing reports of ketoacidosis, including DKA, in patients with T1DM and T2DM taking dapagliflozin or other SGLT2 inhibitors.	Participants with T1DM are excluded from the study (see exclusion criteria). DKA including euglycemic DKA have been reported with use of dapagliflozin. If DKA is suspected, temporary interruption of study treatment should be considered and the participant should be promptly evaluated. If DKA is confirmed, study intervention should be discontinued permanently. If DKA is not confirmed, re-start of study intervention should be considered (see Section 7.1).

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Zibotentan (in context of dapagliflozin combination treatment)		
Fluid retention	Fluid retention is a class effect of endothelin receptor antagonists. Peripheral oedema has been very commonly reported in oncology patients receiving zibotentan and tended to develop within a month of commencing the drug. Most cases are mild (CTC Grade 1/2) and tend to resolve with continued dosing.	The potential fluid retention risk from zibotentan is expected to be mitigated by the diuretic and natriuretic effects of dapagliflozin. CCI for CCI CCI of CCI is CCI CCI will be CCI (see Section CCI). CCI ther than CCI CCI (see below) that are CCI from the CCI (see criteria in CCI Monitoring of CCI, and CCI CCI according to the SoA will be performed.
Heart failure	Endothelin receptor antagonists have the potential to increase fluid retention and promote fluid overload which may lead to heart failure in susceptible patients, especially those with a known history of cardiac dysfunction. The clinical AEs of non-adjudicated cardiac failure have been observed, being more commonly reported in CRPC patients receiving zibotentan than in those receiving placebo. The frequency of reports in patients receiving zibotentan has been less than 10% and most cases have responded to standard heart failure treatment.	Participants with moderate to severe HF (NYHA class III or IV) will be excluded from the study. The potential risk of HF from zibotentan is expected to be mitigated by the diuretic and natriuretic effects of dapagliflozin. CCI (see Section CCI CCI (see criteria in Section CCI. Monitoring of CCI, and CCI will be performed.
Hypotension	The adverse clinical effect of hypotension is largely due to zibotentan's pharmacologically mediated effects of ETA receptor antagonism resulting in vasodilation. Small reductions in systolic and diastolic blood pressure of approximately 5 mmHg has been reported with zibotentan but this has usually been asymptomatic. Dapagliflozin causes osmotic diuresis, which may lead to a small reduction in blood pressure.	CCI according to the SoA. Participants with orthostatic hypotension or hypotension are excluded from the study (Section 5.2). CCI (see criteria in Section CCI. CCI will be reported as an CCI (see Section CCI).

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Teratogenicity	Exposure during gestation to ERAs, including zibotentan, is associated with major embryo-foetal harm. ERAs have been demonstrated to induce teratogenic effects in animals when dosed during organogenesis, early in pregnancy. When administered to pregnant rabbits during the period of major embryonic organogenesis, zibotentan caused foetal craniofacial and cardiac malformations at dose levels of CCI and above, consistent with ERAs (zibotentan IB). Due to the established teratogenic effect, pregnant women must not receive zibotentan. WoCBP are not eligible for participation in this study. There is an extremely high risk of embryo-foetal harm, if pregnancy occurs while being exposed to zibotentan in any amount, even for short periods of time. Potentially, any foetus exposed during pregnancy can be affected. Per the prescribing information, dapagliflozin must not be used in the second and third trimesters of pregnancy due to the increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. When pregnancy is detected, dapagliflozin should be discontinued. However, since zibotentan is teratogenic early in pregnancy, the more restrictive guidance for zibotentan must be followed.	WOCBP must not be included in the study (see inclusion criterion in Section 5.1). For reproductive restrictions for male participants, see inclusion criterion in Sections 5.1 and details in Section 5.3.4. Participants must not donate or bank blood (both male and females) or sperm, see Section 5.3.5 and Section 5.3.7. Negative pregnancy test will be collected as per the SoA. If a female participant or the female partner of a male participant becomes pregnant during the course of the study, study intervention must be discontinued immediately, see discontinuation criterion in Section 7.1. The investigator is required to inform participants fully and transparently of the teratogenic risk. As part of the ICF, information will be provided on restrictions for male participants.

AE = adverse event; AESI = adverse event of special interest; CKD = chronic kidney disease; CRPC = castration-resistant prostate cancer; CTC=Common Terminology Criteria; DKA = diabetic ketoacidosis; ECG = electrocardiogram; ERA = Endothelin receptor antagonist; HF = heart failure; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter 2; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; WOCBP= women of child-bearing potential.

2.3.4 Benefit Assessment

2.3.4.1 Evidence for the Role of Endothelin Antagonists in Cirrhosis with Features of Portal Hypertension

Endothelin-1 production has been found to be increased in patients with liver injury and in cirrhosis and is implicated in hepatic vasoconstriction driving increased portal venous pressure. Additionally, preclinical studies have indicated that the endothelin pathway is involved in the development of liver fibrosis (Okamoto et al 2016; Rockey and Chung 1996). Clinically, plasma endothelin levels are increased in patients with cirrhosis and correlate with the severity of liver disease and portal hypertension. In a study using the selective ET_A receptor antagonist BQ123 in patients with cirrhosis, local hepatic artery infusion of BQ123 resulted in a decrease in HVPG with no effect on systemic haemodynamic parameters (Zipprich et al 2021). The same report demonstrated that the effect of a single oral dose of

ambrisentan resulted in a significant decrease in HVPG. In this study, 40% of participants had a > 10% decrease in HVPG or a decrease below 12 mmHg.

2.3.4.2 Evidence for the Role of SGLT2 inhibitors in Cirrhosis and Features of Portal Hypertension

Several studies have evaluated the impact of SGLT2 inhibitors on liver biomarkers in patients with T2DM, NASH, and NAFLD. A review of results from 7 studies and 11 cohort studies demonstrated consistent decreases in liver aminotransferase levels, liver fat, and FIB-4 index after treatment with an SGLT2 inhibitor (Hsiang et al 2020). A pilot study indicated that 72 weeks of treatment with an SGLT2 inhibitor reduced liver fibrosis in patients with NAFLD and diabetes (Takahashi et al 2021). No studies in more advanced cirrhosis patients have been reported to date. A small pilot study evaluated the effect of SGLT2 inhibitors on body weight in patients with cirrhosis, T2DM and ascites (Montalvo-Gordon et al 2020). All 3 patients showed a decrease in body weight ranging from 4.9 kg (7.8%) to 11.2 kg (13.8%) across 6 months associated with decreased ascites and fluid overload, whilst hyponatraemia was corrected or sodium levels were unchanged, and no hyperkalaemia was observed. SGLT2 inhibitors have also been shown to improve endothelial function and decrease vascular stiffness which may bring additional benefit to patients with cirrhosis and portal hypertension.

2.3.4.3 Possible Complementary Actions of Zibotentan and Dapagliflozin

The combination of zibotentan and dapagliflozin is expected to target 2 distinct features of cirrhotic disease, that is, portal hypertension and fluid retention. Given reduction in portal venous pressure is established to improve outcomes in this population, it is anticipated that the combination will reduce the risk of variceal haemorrhage, ascites, and perhaps death. Fluid retention is a class effect of endothelin receptor antagonists which may limit their potential use as monotherapy in cirrhosis. The reduction in portal hypertension afforded by zibotentan has the potential to mitigate renin-angiotensin-aldosterone system activation, potentially reducing ascites formation. In addition, it is anticipated that potential fluid retention risk from zibotentan will be mitigated by the osmotic diuretic effects of dapagliflozin.

2.3.5 Overall Benefit/Risk Conclusion

The overall clinical evidence suggests that the combination of zibotentan and dapagliflozin should have clinical benefit, and an acceptable safety profile in patients with cirrhosis, justifying further drug development with appropriate risk mitigation strategies for potential risks related to hypotension, fluid retention, and heart failure.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 3 Objectives and Endpoints

Objectives	Endpoints
Key Objectives	
To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on a composite endpoint of fluid retention.	Occurrence of any of the following components of this composite endpoint from baseline to Week 6: • > 2 kg increase in body weight (office-based) • > 2 L increase in total body water • Increase in 2 or more loop-diuretic equivalents [a] • Fluid retention AEs
To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on a composite endpoint of fluid retention.	Occurrence of any of the following components of this composite endpoint from baseline to Week 6: • > 2 kg increase in body weight • > 2 L increase in total body water • Increase in 2 or more loop-diuretic equivalents [a] • Fluid retention AEs
To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on body weight, body water volumes, and body fat mass.	• Change in body weight (kg) over time course of study (home-based monitoring). • Change from baseline in body weight, total body water, extracellular and intracellular water volumes, body fat mass at Week 6 (office-based monitoring).
To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on body weight, body water volumes, and body fat mass.	
To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on total loop-diuretic equivalents use. [a]	Change in total dosage of loop-diuretic equivalents use from baseline to Week 6 [a].
To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on total loop-diuretic equivalents use. [a]	
To evaluate the effects of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on the composite of total body water and total dosage of loop-diuretic equivalents. [a]	Occurrence of either of the two components of this composite: 1 > 3 L increase in total body water volume from baseline to Week 6. 2 Increase in 3 or more loop-diuretics equivalents use from baseline to Week 6 [a].
To evaluate the effects of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on the composite of total body water and total dosage of loop-diuretic equivalents. [a]	
To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on office-based systolic and diastolic blood pressure.	Absolute change in systolic and diastolic blood pressure from baseline to Week 6.

Table 3 Objectives and Endpoints

Objectives	Endpoints
To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on office-based systolic and diastolic blood pressure.	
Exploratory Objectives	
To characterise the plasma exposure to zibotentan and dapagliflozin.	Plasma concentrations of zibotentan and dapagliflozin per treatment, visit, and timepoint.
To evaluate the effect of zibotentan/dapagliflozin in combination and zibotentan monotherapy versus placebo on CCI and/or CCI as measured with CCI .[b]	Percentage and absolute change in CCI and/or CCI from baseline to Week 6.
To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on liver health and portal hypertension biomarkers.	• Percentage and absolute change in AST and ALT from baseline to Week 6. • Absolute change in MELD score from baseline to Week 6.
To assess the effect of zibotentan/dapagliflozin in combination and zibotentan monotherapy versus placebo on plasma/serum levels of CCI and CCI .	Evaluation of changes in blood biomarkers across time from baseline to Week 6.
To evaluate the effect of zibotentan/dapagliflozin versus zibotentan monotherapy and placebo on eGFR.	Change in eGFR from baseline to Week 6.
To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on fatigue, abdominal symptoms, physical functioning and health-related quality of life	• Change from baseline to Week 6 in CLDQ Fatigue and Abdominal Symptoms scores, SF-36v2 Physical Functioning score, Total CLDQ score, SF-36v2 Physical Component Summary score, SF-36v2 Mental Component Summary score • Patient Global Impression of Severity – Liver Disease at baseline and Week 6
To collect and store plasma, serum and urine samples for exploratory research aimed at exploring biomarkers involved in PK, PD, safety and tolerability related to zibotentan and dapagliflozin in combination versus placebo or CCI to CCI CCI	Evaluation of changes in blood and urine biomarkers Results of this future analysis are to be reported separately from the CSR.

Table 3 Objectives and Endpoints

Objectives	Endpoints
Safety Objectives	
To assess the safety and tolerability of zibotentan/dapagliflozin and zibotentan versus placebo.	• AEs, SAEs, and DAEs • AESIs CCI [redacted] • Vital signs • Safety laboratory tests • ECG assessments

a) One loop-diuretic equivalent = 40 mg furosemide = 1 mg bumetanide = 20 mg torsemide = 50 mg ethacrynic acid. In Japan, one loop-diuretic equivalent = 40 mg furosemide = 8 mg torsemide = 60 mg azosemide.

b) CCI [redacted] assessment of CCI [redacted] and/or CCI [redacted] should only be done if CCI [redacted] CCI [redacted] to complete an accurate CCI [redacted] and/or CCI [redacted] measurement. CCI [redacted] should only be done if CCI [redacted] is available.

AE = adverse event; AESI = adverse event of special interest; CCI [redacted]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CCI [redacted]; DAE = discontinuation due to adverse event; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA1c = haemoglobin A1c; MELD = model for end-stage liver disease; PGIS= Patient Global Impression of Severity; PK = pharmacokinetic; SAE = serious adverse event; CCI [redacted].

4 STUDY DESIGN

4.1 Overall Design

This is a Phase IIb multicentre, randomised, double-blind, parallel-group, placebo-controlled study to evaluate the safety of zibotentan/dapagliflozin in combination as compared to zibotentan monotherapy as well as zibotentan/dapagliflozin and zibotentan monotherapy as compared to placebo in patients with cirrhosis. Eligible participants should have a history of decompensation events or compensated cirrhosis with signs of CSPH. If compensated cirrhosis, the eligible participant must have signs and measures that would indicate that the participant has CSPH and includes, but not limited to, presence of gastro-oesophageal varices at endoscopy or collaterals at imaging (either one within 12 months prior to screening), and/or CCI kPa, or of CCI kPa with CCI (at time of screening). Participants should have a MELD score < 15 and should be classified as Child-Pugh A or B (Table 6).

It is planned that approximately 22 eligible participants will be randomised to each of the 3 treatment groups, for a total of up to 66 participants (see Figure 1). For details of the study assessments, please see SoA (Table 1).

This study will consist of the following periods:

Screening Period of up to 3 weeks: The Screening Visit (Visit 1) will take place between 7 to 21 days before the Randomisation Visit (Visit 2) to confirm participant eligibility and collect baseline data. There must be at least 7 days between Visit 1 and Visit 2 to allow sufficient time for laboratory results to be examined. At the Randomisation Visit (Visit 2), eligibility criteria will be reassessed, safety laboratory data reverified, and participants will be provided digital devices to measure their body weight starting the first day after the Randomisation Visit and every day at home.

Treatment Period of 6 weeks: During the Treatment Period, participants will visit the study centre 5 times. At Visit 2, participants will be randomised and will receive the first dose of the study intervention. At each study visit during the treatment period (from Visit 2 till Visit 6) participants will receive the once daily dose at the study centre and will provide a pre-dose blood sample for PK analysis and other lab samples before the intake of study intervention. When not visiting the study centre the patients will take the once daily dose of study intervention at home.

Follow-up Period of 2 weeks: Participants will return to the study centre for follow-up assessments approximately 2 weeks after their planned last dose of study intervention (planned last dose is at Visit 6).

4.2 Scientific Rationale for Study Design

The mechanisms of action of zibotentan and dapagliflozin are different and the outcome of combined treatment is expected to be complementary. Fluid retention is a class effect of endothelin receptor antagonists which may limit their potential use as monotherapy in cirrhosis. It is anticipated that potential fluid retention risk from zibotentan will be mitigated by the osmotic diuretic effects of dapagliflozin without increasing the risk for hypo- or hyperkalaemia, hyponatraemia, or hypovolaemia. By investigating the effects of zibotentan monotherapy as compared to the combination of zibotentan and dapagliflozin and placebo the importance of dapagliflozin to reduce the risk for fluid retention caused by zibotentan will be evaluated. A placebo arm is included to assess the effect of zibotentan monotherapy.

4.3 Justification for Dose

Participants who meet the eligibility criteria and agree to participate will be randomised to one of the following treatment groups (22 participants per treatment group). All participants will receive 1 capsule zibotentan or matching placebo) and 1 tablet (dapagliflozin or matching placebo) at every dosing.

- Treatment Group 1: placebo matching zibotentan capsule + placebo matching dapagliflozin tablet.
- Treatment Group 2: zibotentan capsule [redacted] mg + placebo matching dapagliflozin tablet.
- Treatment Group 3: zibotentan capsule [redacted] mg + dapagliflozin tablet 10 mg.

In the previous Phase III programme in oncology, zibotentan 10 mg was used and extensive safety data are available for this dose. This study will include participants with mild or moderate hepatic impairment (Child-Pugh A and B) and with normal renal function or mild renal impairment (MELD score < 15 and eGFR > 60 mL/min/1.73 m^2). Concurrent moderate hepatic and moderate renal impairment has been found to increase zibotentan exposure approximately two-fold (Study D4326C00001); this maximal exposure increase has been taken into account by the [redacted] in this study [redacted] mg) being [redacted] of the [redacted] mg).

Dapagliflozin 10 mg has been extensively studied as monotherapy. A higher exposure of dapagliflozin is expected in participants with renal and/or hepatic impairment compared to healthy participants but does not require dose adjustment given the safety and tolerability profile of dapagliflozin. Dapagliflozin 10 mg once daily did not lead to any unique safety or tolerability signals in participants with renal impairment in both chronic kidney disease ($\geq$ 25 mL/min/1.73 m^2; DAPA-CKD outcomes study) and heart failure populations (DAPA-HF outcomes study). Administration of dapagliflozin doses of up to 100 mg for 14 days to healthy volunteers have been shown to be tolerable. Dapagliflozin 10 mg once daily has therefore also been selected for the planned clinical programme in cirrhosis.

4.4 End-of-study Definition

A participant is considered to have completed the study if they have completed all phases of the study, including the follow-up visit as shown in the SoA (Table 1).

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

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

- EU requirements define study completion as the last visit of the last subject for any protocol-related activity.

The FDA requirements define 2 completion dates:

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. All study inclusion/exclusion criteria and participant requirements in this section apply to all participants, except where expressly noted.

5.1 Inclusion Criteria

Age

1 Participant must be aged ≥ 18 years and ≤ 80 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Participants who have the following:

a) Clinical and/or histological diagnosis of cirrhosis
Note: Either history of decompensation or compensated cirrhosis with signs of CSPH, including varices at endoscopy or collaterals at imaging (either one within 12 months prior to screening), and/or CCI [redacted] of CCI [redacted] kPa, or of CCI [redacted] kPa CCI [redacted] (at time of screening)

b) Model for end stage liver disease score (MELD) < 15.

c) Child-Pugh score < 10.

d) No ascites or ascites up to and including grade 2 without change in diuretic treatment within the last month prior to first dose of study intervention and no paracentesis within the last month.

e) No evidence of worsening of hepatic function (eg, no clinically significant change in signs, symptoms, or laboratory parameters of hepatic disease status) within the last month prior to dosing, as determined by the investigator or usual practitioner.

Medical Treatment

3 No current or prior (within 1 month of enrolment) medical treatment with an SGLT2 inhibitor or endothelin receptor antagonist.

4 On no or a stable dose of beta blockers, with no major dose changes within 1 month prior to the first dose of study intervention.

Sex and Contraceptive/Barrier Requirements

5 Males or females of non-childbearing potential.

– **Male participants** must be surgically sterile, abstinent, or must use in conjunction with their female partner a highly effective method of contraception from the time they sign the informed consent document and for 3 months after the last dose of study intervention to prevent pregnancy in a partner. In addition, the male participant should use a condom for the duration of the study and for 3 months after the last dose of study intervention. Male participants must not donate or bank sperm during the same period See sections 5.3.5 and 8.4.9.2.

Highly effective birth control methods are defined as those that can achieve a failure rate of less than 1% per year when used consistently and correctly. For details, refer to Section 5.3.4.

- **Female participants must be of non-childbearing potential** confirmed at screening by fulfilling one of the following criteria:
  - Post-menopausal: defined as amenorrhoea for at least 12 months or more following cessation of all exogenous hormonal treatments; and also FSH levels in the post-menopausal range by central laboratory (Note: The post-menopausal range must be checked against the specific FSH assay used). In the absence of 12 months of amenorrhoea, a single FSH measurement is insufficient to define post-menopausal criteria. In case of perimenopause or infrequent periods with variable levels of FSH, women should be considered of childbearing potential and, therefore, not eligible for participation in this study.
  - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation.
- Female participants must have a negative pregnancy test at screening and must not be lactating.

Informed Consent

6 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.

7 Provision of signed and dated, written ICF prior to any mandatory study-specific procedures, sampling, and analyses.

8 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 Genomic Initiative.

5.2 Exclusion Criteria

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

Medical Conditions

1 Any evidence of a clinically significant disease, which in the investigator's opinion makes it undesirable for the participant to participate in the study.

2 Alanine aminotransferase/transaminase or AST $\geq$ 150 U/L and/or total bilirubin $\geq 3 \times$ ULN.

3 International normalised ratio > 1.7.

4 Serum/plasma levels of albumin $\leq$ 28 g/L.

5 Platelet count $< 50 \times 10^9$L.

6 Acute kidney injury (AKI) within 3 months of screening.

7 History of encephalopathy of West Haven Grade 2 or higher.

8 History of variceal haemorrhage within 6 months prior to screening.

9 Any history of hepatocellular carcinoma.

10 Any history of portal venous thrombosis.

11 Liver transplant or expected liver transplantation within 6 months of screening.

12 History of TIPS or a planned TIPS within 6 months from enrolment into the study.

13 Positive alcohol breath test or screen for drugs of abuse (excluding drugs prescribed by the participants' usual physician) at screening.

14 Ongoing or history of significant use of alcohol expected to preclude correct adherence to study procedures (For details, refer to Section 5.3.2).

15 Active treatment for HCV within the last 1 year or HBV anti-viral therapy for less than 1 year.

16 Active urinary tract infection or genital infection.

17 Uncontrolled diabetes mellitus (HbA1c > 8.5% or > 69 mmol/mol within the last month).

18 Participants with T1DM.

19 Renal transplant or chronic renal replacement therapy or short-term dialysis within the previous 6 months.

20 eGFR < 60 mL/min/1.73m^2 (eGFRcr[AS]).

21 Acute coronary syndrome events within 3 months prior to screening.

22 Orthostatic hypotension or hypotension (systolic blood pressure < 95 mmHg or diastolic blood pressure < 60 mmHg).

23 New York Heart Association functional heart failure Class III or IV or patients with unstable heart failure requiring hospitalisation for optimisation of heart failure treatment and who are not yet stable on heart failure therapy within 6 months prior to screening.

24 Heart failure due to cardiomyopathies that would primarily require specific other treatment.

25 High output heart failure (eg, due to hyperthyroidism or Paget's disease).

26 Heart failure due to primary cardiac valvular disease/dysfunction, severe functional mitral or tricuspid valve insufficiency, or planned cardiac valve repair/replacement.

27 Participants treated with CCI [redacted] or CCI [redacted] within CCI [redacted] of study intervention administration; this CCI [redacted]

28 History or ongoing allergy/hypersensitivity, as judged by the investigator, to SGLT2 inhibitors (eg, dapagliflozin, canagliflozin, empagliflozin), zibotentan, drugs with a similar chemical structure to zibotentan, or any of the excipients of the products.

29 Any clinically significant chronic disease or disorder (eg, cardiovascular, gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, psychiatric, major physical impairment) which, as judged by the investigator, might put the participant at risk because of participation in the study, or probable alternative primary reason for participant's symptoms in judgment of investigator.

30 Acute liver injury caused by drug toxicity or by an infection.

Prior/Concurrent Clinical Study Experience

31 Participation in another clinical study with a study intervention administered in the last 3 months prior to randomisation.

Other Exclusions

32 Implanted cardiac electronic device such as pacemaker or implantable cardioverter defibrillator.

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

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

35 Male participant in a sexually active relation with pregnant or breastfeeding partner.

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

Exclusion Criteria for Participants Consenting to Optional Genetic Sampling

The following participants are not eligible to consent to the optional genetic sampling:

37 Previous allogeneic bone marrow transplant.

38 Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants will be advised to adhere to diet as per recommendations by their usual physician/medical team.

Study intervention should be taken between approximately 08:00 to 10:00 each morning. If study intervention is not taken before noon (12:00 pm), it is recommended to take the next dose in the morning the next day. On the day of randomisation, study intervention can be taken after noon, without affecting the next day's dose.

On the days of CCI assessments, measurements will be performed at the timepoints specified in the SoA (Table 1) after an over-night fast or at least 3 hours after a meal. Additionally, for Visit 6, CCI should be performed ≥ 3 hours after study intervention is given.

On the day of the PK profile (this applies to Japanese patients only), participants will be asked to avoid high-fat, high-caloric meals (maximum approximately 600 kcal) in the morning before and for 2 hours after study intervention administration.

Participants should refrain CCI and CCI during the course of the study.

5.3.2 Caffeine, Alcohol, and Tobacco

Participants will be required to limit their alcohol consumption to < 2 units per day. For reference, the following represent 1 unit of alcohol: 76 mL of 13% ABV wine; 25 mL of 40% ABV spirit (eg, whisky); 250 mL of 4% ABV beer/lager; 218 mL of 4.5% ABV cider, or 250 mL of 4% ABV alcopop.

5.3.3 Activity

Participants should try to maintain their normal activity, including medically prescribed level of exercise activities during the study.

5.3.4 Reproductive Restrictions

Female participants:

Women of childbearing potential are not eligible for participation in this study (for definition of WOCBP, see Section 5.1).

Male participants:

It is important that women of childbearing potential, who are the partners of male participants, do not become pregnant during the study and for a total period of 3 months after the male study participant has received his last dose of study intervention.

- All male participants should avoid fathering a child by either true abstinence (see definition below) or use together with their female partner a highly effective method of contraception, starting from the time they sign informed consent until 3 months after the last dose of study intervention. In addition, the male participant should use a condom for the duration of the study and for 3 months after the last dose of study intervention.

  Highly effective birth control methods are defined as those that can achieve a failure rate of less than 1% per year when used consistently and correctly, and include:

a) Permanent sterilisation: male vasectomy or female hysterectomy, bilateral oophorectomy, or bilateral tubal occlusion/salpingectomy.
b) Combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); intrauterine device; intrauterine hormone-releasing system.
c) Total sexual abstinence (true abstinence in line with the preferred and usual lifestyle choice of the participant).

True abstinence refers to: when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception.

If the participant or male participant's partner becomes pregnant during the course of the study, study intervention must be discontinued immediately, and an AstraZeneca representative notified.

5.3.5 Sperm Donation

Male participants should not donate or bank sperm for the duration of the study and for at least 3 months after the last dose of study intervention.

5.3.6 Pregnancy

Women of childbearing potential are not eligible for participation in this study.

Male participants will be instructed that if their partner becomes pregnant during the study, or within three months after last dose of the study intervention, this should be reported to the investigator, and the study intervention should be discontinued. In the event that a participant's partner is subsequently found to be pregnant after the study participant is included in the study, then consent will be sought from the partner and if granted the pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery.

A pregnancy notification form and follow-up will be completed.

5.3.7 Other Restrictions

Participants should not donate blood during the study and for 1 month following discontinuation of the study intervention because of the potential risk to the foetus of a pregnant transfusion recipient.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT 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 blood analysis criteria for participation in this study (screen failure) may have these parameters retested up to 2 times during the screening period. Participants may be rescreened once, at the discretion of the investigator, if they have reason to believe they may be eligible.

Rescreened participants should be assigned the same participant number as for the initial screening. Participants who are rescreened are required to sign a new ICF.

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

Not applicable.

6 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

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

6.1 Study Interventions Administered

6.1.1 Study Intervention

All participants will receive 1 capsule (zibotentan or matching placebo) and 1 tablet (dapagliflozin or matching placebo), once daily in the morning.

Table 4 Study Intervention

Arm name	Treatment group 1	Treatment group 2	Treatment group 3
Intervention name	Placebo	Zibotentan + placebo	Zibotentan + dapagliflozin
Type	Placebo	Drug/placebo	Drug
Dose formulation	Placebo capsule (matching zibotentan capsule) and placebo tablet (matching dapagliflozin tablet)	Zibotentan capsule and placebo tablet (matching dapagliflozin tablet)	Zibotentan capsule and dapagliflozin tablet

Table 4 Study Intervention

Arm name	Treatment group 1	Treatment group 2	Treatment group 3
Unit dose strength(s)	NA	[redacted] mg zibotentan	[redacted] mg zibotentan 10 mg dapagliflozin
Dosage level(s)	One matching tablet and capsule once daily	One capsule and one tablet once daily	One tablet and one capsule once daily
Route of administration	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	Zibotentan, dapagliflozin, and their respective matching placebo treatments will be supplied centrally by AstraZeneca.		
Packaging and labelling	For each strength, zibotentan and matching placebo will be supplied in HDPE bottles. Dapagliflozin and matching placebo will be supplied in HDPE bottles. All bottles will be labelled as per country requirement.		

AxMP= auxiliary medicinal product; HDPE = high-density polyethylene; IMP = investigational medicinal product; NA = not applicable; NIMP = Non-investigational medicinal product.

Note: Study intervention refers to both zibotentan and dapagliflozin. Name of the study drug is specified if it is zibotentan or dapagliflozin alone.

6.1.2 Medical Devices Including Combination Products with a Device Constituent

No AstraZeneca manufactured medical devices (or medical devices manufactured for AstraZeneca by a third-party) will be provided for use in this study.

Digital devices (not manufactured by or for AstraZeneca) provided for use in this study are:

- Home-based body weight digital scales and associated handheld device.
- CCI [redacted] (for participants with CCI [redacted] and/or CCI [redacted] CCI [redacted]
- Glucometer (participants with T2DM and treated with insulin or sulfonylurea only).

Instructions for digital device use will be provided to each participant. All devices provided for the study will be returned by the participant on or before the final safety follow-up visit.

All digital device deficiencies (including malfunction, use error, and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation and appropriately managed by the sponsor. In this study, any deficiency observed with a third-party digital device will be collected and reported to the manufacturer. A digital device

deficiency is an inadequacy of a digital device with respect to its identity, quality, durability, reliability, safety, or performance. Digital device deficiencies include malfunctions, use errors, and information supplied by the manufacturer. The manufacturer's digital device complaint report will be used to collect the deficiency.

6.2 Preparation, Handling, Storage, and Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomised in the study may receive study intervention and only authorised study centre 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 study centre staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3 Assignment to Study Intervention

All participants will be centrally assigned to randomised, blinded study intervention using an IRT/RTSM. Before the study is initiated, directions for log in will be provided to each study centre. The IRT/RTSM will provide to the investigators or pharmacists the kit identification number to be allocated to the participant at the dosing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each study centre.

A separate randomisation list will be provided for Japan sites.

In this study, eligible participants will be randomised to Treatment Groups 1 to 3 with equal allocation (1:1:1). Japan will have up to 5 participants per arm (out of 22).

Participants will be CCI to the CCI of CCI at the time of randomisation, to ensure an approximate balance between treatment groups within each sub-population. There will be no CCI for Japanese participants as it may lead to CCI for the study.

6.4 Blinding

The randomisation code should not be broken except in medical emergencies when the

appropriate management of the participant requires knowledge of the treatment assignment. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

The following personnel will be unblinded as to the exact content of study intervention treatments (ie, the randomisation code):

- Personnel carrying out the packaging and labelling of study intervention treatment.
- Personnel generating the randomisation list.
- Personnel analysing the PK samples.
- The DMC.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to 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 blindbreaking 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 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, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the participant to the AstraZeneca staff.

6.5 Study Intervention Compliance

At the visits specified in the SoA (Table 1), participants will receive study intervention at the study centre or will take the study intervention at home. When participants are dosed at the site, they will receive study interventions directly from the investigator or designee, under medical supervision. The date and time of the dose administered on the visit day, as well as the date and time of the dose taken the day before each visit to the study centre, 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 centre staff other than the person administering the study intervention.

A record of the number of study interventions (capsules and tablets) 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 will also be recorded in the eCRF.

6.6 Dose Modification

Dose modification of study intervention is not permitted. All participants will receive the assigned dosage of study intervention to be taken in the morning. If a participant forgets to take a study intervention dose in the morning and the time has past noon (12:00 PM), the next dose must be taken the next day. When taking the next dose after a missed dose, participants should not take a double dose to make up for the missed dose.

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

After the end of the study (follow-up visit), participants will no longer receive zibotentan and/or dapagliflozin. Participants should maintain their other prescribed treatments at the discretion of the investigator.

6.8 Treatment of Overdose

For this study, an overdose will be defined as the use of the study intervention in doses in excess of that specified in the protocol. For information regarding reporting of overdose, see Section 8.4.11.

If an overdose is suspected, monitoring of vital functions as well as treatment should be performed as appropriate.

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 and at least until the next scheduled follow-up. Refer to Section 8.4.11 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).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Prior and Concomitant Therapy

As ET-1 has a potential role in the maintenance of blood pressure, hypotension may be

encountered following ET receptor blockade. Although only minor reductions in blood pressure were seen studies with zibotentan in oncology patients, it is possible that more marked changes might occur in hypertensive patients, especially those taking hypotensive therapy such as ACE inhibitors, calcium antagonists, or alpha blockers. If symptomatic hypotension occurs, participants should remain supine until resolution of symptoms. Intravenous fluid support should be considered for cases considered severe by the investigator.

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

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

As zibotentan has been associated with an increased risk of headache in previous clinical studies, paracetamol/acetaminophen may be administered to the study participants as needed, provided it is prescribed in accordance with the label and taking into account the participant's degree of hepatic impairment; dosing and time of administration will be documented. Other concomitant medication may be considered on a case-by-case basis by the investigator, in consultation with the study physician, if required.

The preclinical and clinical data indicated no drug-drug interaction risk between zibotentan and paracetamol/acetaminophen (Zibotentan Investigator's Brochure).

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

6.9.1 Prohibited Medications

The medications and supplements listed below are prohibited from the time of informed consent and for the duration of the study.

- Other SGLT2 inhibitors.
- Other Endothelin receptor antagonists.

Dose changes of beta blockers should ideally be kept to a minimum during the treatment period but are permitted, if required for safety.

Other prohibited medications CCI and CCI of CCI , including CCI , within CCI CCI prior to dose of zibotentan (Table 5) and during the course of the study. Antacids are

prohibited from 2 hours before dosing until discharge on all days where dosing takes place and PK or PD measurements are taken (Days 8, 15, and 22).

Table 5 List of CCI

Medication	Rationale
CCI	

Note: This list is not intended CCI , and the CCI should CCI to CCI that are CCI CCI

6.9.2 Permitted Procedures and Medications

6.9.2.1 Paracentesis

Paracentesis is permitted during the study if required for safety.

6.9.2.2 Medications Inducing Hypoglycaemia

Participants using medications that can cause hypoglycaemia in T2DM participants, including insulin or sulfonylurea, may be required to reduce insulin by 10% to 20% (total daily dose) and sulfonylurea by 25% to 50%. In addition, participants on any of these drug classes will be provided with a home-based glucometer to monitor their blood glucose (if they do not already have a glucometer at home), since more frequent blood glucose monitoring should be considered in participants receiving insulin and/or sulfonylurea, especially with HbA1c $\leq$ 7% at randomisation. Also, ketones, eg, plasma levels of beta-hydroxybutyrate, should be considered to be monitored more frequently- if insulin dosing is reduced (see Section 7.1.1 for details about diabetic ketoacidosis and Section 8.3.6.1 for details about hypoglycaemia).

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.

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation)

study intervention.

An individual participant may be discontinued from study intervention in the following situations:

- CCI ; Section CCI.
- New diagnosis of CCI of the CCI.
- New or worsening of symptoms of CCI other than CCI that is not responsive to CCI doses of CCI.
- Overt encephalopathy (Grade 2 or higher), variceal haemorrhage, or hepatocellular cancer.
- Serious/severe CCI.
- Serious/severe CCI.
- Diabetic ketoacidosis including euglycaemic DKA have been reported with use of dapagliflozin. Consider temporary interruption of study intervention if DKA is suspected. The participant should be promptly evaluated. If DKA is confirmed, study intervention should be discontinued permanently (see Section 7.1.1 for details). If DKA is not confirmed, re-start of study intervention should be considered.
- When DILI is suspected and re-start of the study intervention is not permitted based on the algorithm outlined in Section 7.1.2.
- eGFR < 45 mL/min/1.73 m^2 confirmed upon repeat testing.
- Development of CCI or other causes of CCI
- Liver transplantation.
- Transjugular intrahepatic portosystemic shunt.
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- An AE that, in the opinion of the investigator or AstraZeneca, warrants discontinuation from further dosing.
- Severe non-compliance with the CSP.
- Pregnancy: if a female participant or the female partner of a male participant becomes pregnant during the course of the study, study intervention should be discontinued immediately, and an AstraZeneca representative notified.
- Safety reasons as judged by the investigator and/or sponsor where continued treatment may put participant at undue risk.

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

the study (Section 7.2).

Participants who prematurely discontinue study intervention should remain, in the study and attend all planned study visits including the Follow-up Visit as per SoA (Table 1).

7.1.1 Diabetic Ketoacidosis

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (eg, T1DM, history of pancreatitis or pancreatic surgery), insulin dose reduction, reduced caloric intake or increased insulin requirements due to infections, illness or surgery, and alcohol abuse. Dapagliflozin should be used with caution in these participants.

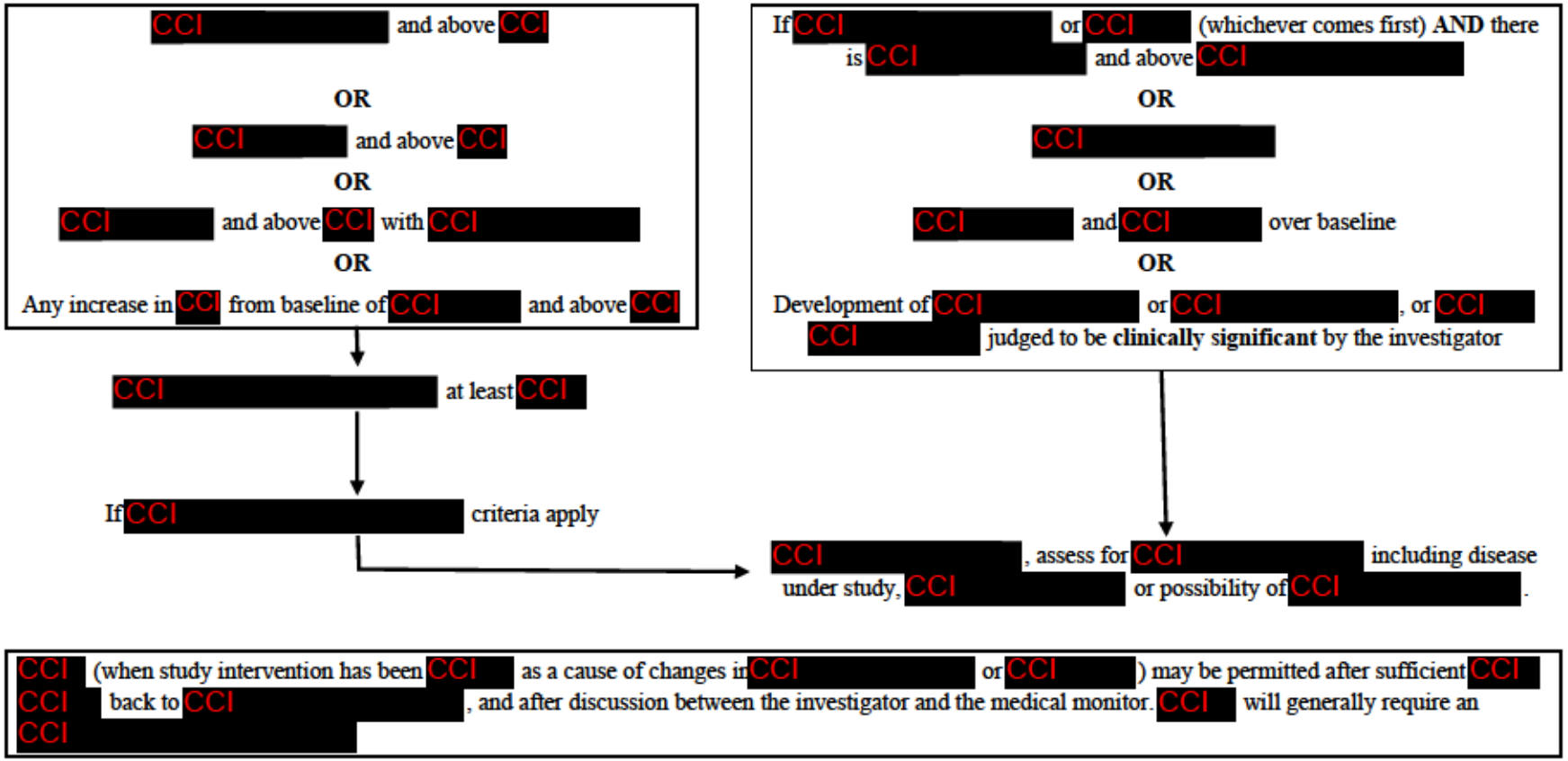
Participants on study intervention who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of study intervention should be considered, and the participant should be promptly evaluated.

7.1.2 Management of Treatment-emergent Abnormalities in Liver Function Tests (LFTs)

In order to identify cases of suspected DILI, the following algorithms must be followed (see Appendix E for actions required for evaluation of modified Hy's Law). The DILI algorithms account for CCI of the CCI value (defined as the CCI of the CCI during the CCI period CCI visit values) or a CCI value, whichever comes first, and not solely on CCI of the CCI. The algorithms also account for the status of the participant at CCI as CCI and take into consideration normal or abnormal baseline CCI for participants with CCI CCI It is important to perform a comprehensive review of laboratory data for any participant who meets any of the criteria.

*In this study, and for the purpose of the DILI algorithm, CCI is defined as CCI with presence at baseline of CCI or history of CCI CCI or history of CCI .

Management guidelines for participants with CCI at baseline, and normal baseline CCI at baseline)



Management guidelines for participants with CCI at baseline, with abnormal baseline CCI CCI at baseline)

CCI but CCI and CCI ,

AND

- CCI (if normal at CCI) or CCI (if abnormal at CCI), **AND**
- CCI , **AND**
- CCI (if normal at CCI or CCI (if CCI was CCI

CCI drug, CCI

CCI is CCI or CCI (whichever comes first)

AND AT LEAST CCI OF THE FOLLOWING

- CCI if normal at CCI (with CCI) **OR** CCI if CCI ,
- CCI over baseline,
- CCI) OR increased by CCI was CCI

OR

CCI (whichever comes first)

OR

CCI and CCI over baseline

OR

Development of CCI or CCI , or CCI CCI judged to be **clinically significant** by the investigator.

CCI study intervention, assess for CCI including disease under study, additional CCI or possibility of CCI .

CCI (when study intervention has been CCI as a cause of changes in CCI or CCI) may be permitted after sufficient CCI CCI back to CCI , and after discussion between the investigator and the medical monitor. CCI will generally require an CCI .

Management guidelines for participants with CCI at baseline, with either normal or abnormal baseline CCI

CCI (and CCI) or CCI, whichever comes first; or CCI × post-baseline on-treatmen CCI values

OR

CCI with CCI of the total, or any increase in CCI over baseline

OR

CCI × baseline

OR

CCI (if normal CCI at baseline) or any increase of CCI if baseline CCI

OR

CCI increased by CCI over baseline (if CCI at baseline) or by CCI over baseline (if CCI at baseline)

OR

Development of new CCI or CCI of CCI or CCI judged to be **clinically significant** by the investigator.

↓

CCI study intervention, assess for cause of CCI including disease under study, CCI or possibility of CCI.

Due to variability in CCI patients with CCI meeting requirement for hold of study drug based solely on CCI change, and not meeting any other criteria for drug hold, may have one CCI re-test with 1-2 days at the discretion of the investigator to determine whether the CCI change is sustained.

CCI (when study intervention has been CCI as a cause of changes in CCI or CCI) may be permitted after sufficient CCI CCI back to CCI × baseline, and after discussion between the investigator and the medical monitor. CCI will generally require an CCI

[a] CCI is defined as CCI with presence at baseline of CCI or CCI or CCI CCI

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.

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 considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Termination Visit should be conducted, that will comprise of the same assessments as for Visit 6, as per the SoA (Table 1).
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation the investigator must document the decision on use of existing samples in the study centre records and inform the Global Study Team.

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 centre.

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

- The study centre 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 wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with AstraZenenca 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 (Table 1), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures such as ECHO (to exclude valvular disease and/or significant cardiomyopathy as defined in Section 5.2), clinical chemistry, and haematology conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilised for screening purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 165 mL. Repeat or unscheduled samples may be collected for safety reasons or for technical issues with the samples and may be tested at the local laboratory.
- A mobile software application, and associated website system, will provide digital support to participants from randomisation through to, and including, Follow-up. AstraZeneca will provide a handheld device to access the mobile software application. The system will provide participants and site study staff with information and tools relevant to the conduct of the study in accordance with this protocol. This will comprise of study intervention reminders, clinical visit reminders, PRO questionnaires, and educational content relating to the disease and medication. AstraZeneca (or those acting on behalf of AstraZeneca) will set up clinical sites and invite site staff to use the digital

platform by provisioned email but will not have the ability to view any patient level system data during the trial. Any data collected will only be used for functionality of the digital health platform and is not considered to be clinical trial data. AstraZeneca will own any system data collected which may be used after the trial to make improvements to digital health platform and the associated data collected will be retained for a period of 10 years after trial closure. The use of the participant mobile software application is mandatory for the patient and captured in the ICF. The mobile software application is the primary input to capture the PROs and the daily home-based weight measurements in the protocol.

8.1 Administrative and General/Baseline Procedures

None.

8.2 Efficacy Assessments

There are no efficacy assessments in this study. Planned timepoints for key and exploratory assessments carried out in this study are provided in the SoA (Table 1).

8.2.1 Key Variables

8.2.1.1 Fluid Retention

The fluid retention composite variables are defined as:

- Occurrence of any of the following events from baseline to Week 6:
  (1) > 2 kg increase in body weight,
  (2) > 2 L increase in total body water,
  (3) increase in 2 or more loop-diuretic equivalents or
  (4) fluid retention AEs.
- Occurrence of either:
  (1) > 3 L increase in total body water volume from baseline to Week 6, or
  (2) increase in 3 or more loop-diuretic equivalents use from baseline to Week 6.

8.2.1.2 Electronic Scale Measurement of Body Weight

Body weight will be measured at the study centre at study visits. There will be safety monitoring of body weight from the home-based monitoring devices, or as an alternative, paper diaries can be used for capturing the information. A body weight change of CCI kg per CCI is regarded as a CCI weight change and needs to be followed up by the investigator.

The investigator will have direct access to the online data for their participants using digital

devices. If there is a significant weight gain, the investigator will contact the participant immediately and arrange a clinic visit to assess health status. Participants with paper diaries will be instructed to contact the study staff if there is a significant weight gain.

Participants will also be advised to self-monitor and contact the investigator with any concerns.

8.2.1.3 Bioimpedance Spectroscopy

Bioimpedance spectroscopy will be performed at the study centre at the timepoints specified in the SoA (Table 1) to monitor body fluid volumes. This non-invasive procedure uses skin electrodes to pass a low-level alternating current through the body and measures the impedance to the flow of this current. Tissues such as fat and bone act as insulators, whereas electrolyte body fluids conduct electrical current. As the fluid increases, impedance to current flow decreases (ie, changes in impedance are inversely proportional to the volume of the extracellular fluid in the body). At low frequencies, cell membranes are non-conductive and current passes only through the extracellular fluid, while at high frequencies, the current passes through cell membranes in addition to the extra-and intracellular fluids.

8.2.2 Exploratory Variables

8.2.2.1 CCI

CCI will be performed at the timepoints specified in the SoA (Table 1), at least 3 hours after a meal, as well as ≥ 3 hours after study intervention administration at Visit 6. If the participant is taking a non-selective beta-blocker, the dose should not be taken in the morning before CCI but right after the CCI assessment. CCI and/or CCI is assessed as an exploratory endpoint to investigate to what extent it may be used as a CCI for CCI . CCI will be measured only if CCI is available. The measurement should preferably be done by the same examiner on all occasions.

CCI assessment of CCI or CCI should only be done if CCI and its use is up to the CCI of the investigator at the study centre.

8.2.2.2 Serum Analysis of Creatinine and Cystatin C (eGFR)

The participant's eGFR will be calculated at the timepoints specified in the SoA (Table 1) according to the 2021 CKD-EPI equation, based on serum creatinine concentration alone (Inker et al 2021) for eligibility and safety, referred to below as eGFR1. This formula is used for safety monitoring as well as for exploratory assessment. Additionally, eGFR for exploratory assessment will be calculated based on both serum creatinine and serum cystatin C concentrations (Inker et al 2021), referred to below as eGFR2.

Estimated GFR using serum creatinine alone or together with serum cystatin C is calculated as follows:

$eGFR1 = 142 \times \min(S_{cr}/\kappa,1)^{-0.241\ (\text{if female})/\ -0.302\ (\text{if male})} \times \max(S_{cr}/\kappa,1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female]

$eGFR2 = 135 \times \min(S_{cr}/\kappa, 1)^{-0.219\ (\text{if female})/\ -0.144\ (\text{if male})} \times \max(S_{cr}/\kappa, 1)^{-0.544} \times \min(S_{cys}/0.8, 1)^{-0.323} \times \max(S_{cys}/0.8, 1)^{-0.778} \times 0.996^{Age} \times 0.963$ [if female]

Where:
S_{cr} = serum creatinine (mg/dL)
S_{cys} = serum cystatin C (mg/L)
κ = 0.7 for females; and 0.9 for males
min = minimum of S_{cr}/κ or 1
max = maximum of S_{cr}/κ or 1

Based on the SoA (Table 1), eGFR1 calculations will be at every visit, while eGFR2 calculations will be at Visits 2, 5 and 6.

8.2.2.3 Laboratory Assessments for Exploratory Analyses

Blood samples will be collected at the timepoints specified in the SoA (Table 1) to measure levels of the following biomarkers for analysis of exploratory variables:

- Plasma/serum AST, ALT are derived from safety variables (Table 7).
- Model for end stage liver disease score (MELD = 3.78 × ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57 × ln[serum creatinine (mg/dL)] + 6.43) calculated at every visit. If bilirubin, INR and/or creatinine values are less than 1.0, the value is set as 1.0.
- Plasma/serum CCI [redacted], and CCI [redacted] are the non-fasting plasma biomarkers in the SoA.

All blood samples for exploratory analyses will be handled by the central laboratory.
Child-Pugh score, calculated as per Table 6.

Table 6 Child-Pugh Score

Clinical and laboratory criteria	Points		
	1	2	3
Encephalopathy	None	Mild to moderate (West Haven grade 1 or 2)	Severe (West Haven grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2 - 3	> 3
Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
Prothrombin time			
Seconds prolonged	< 4	4 - 6	> 6
INR	< 1.7	1.7 – 2.3	> 2.3
Child-Turcotte-Pugh class obtained by adding score for each parameter (total points) Class A = 5 to 6 points (least severe liver disease) Class B = 7 to 9 points (moderately severe liver disease) Class C = 10 to 15 points (most severe liver disease)			

Abbreviations: INR = International Normalised Ratio.

8.2.2.4 Patient-reported Outcomes

Patient-reported outcomes (PROs) refer to all symptoms, impacts, and outcomes that are directly reported by the participant. PROs have become important endpoints for regulatory and reimbursement authorities when evaluating efficacy or safety of treatment in clinical trials.

The following PROs will be administered in this study at the timepoints specified in the SoA (Table 1):

- Chronic Liver Disease Questionnaire (CLDQ)
- SF-36v2 acute
- Patient Global Impression of Severity - Liver Disease (PGIS - Liver Disease)

Participants will be asked to complete the questionnaires on a provisioned handheld electronic device. Paper questionnaires may be used if a provisioned handheld electronic device is not available or the participant is unable to use one.

The handheld device has been programmed to allow flexibility for participants to complete PRO questionnaires prior to the Visit 6 in-clinic visit. In case the PRO questionnaires are not completed before the in-clinic Visit 6, the participant should complete PROs at the site prior to other Visit 6 study procedures.

The following best practice guidelines should be followed:

- PRO questionnaires should be completed before any other study procedures during Visit 6, to avoid bias when responding to questions.
- Site personnel must show participants how to use the electronic PRO device, in accordance with the instructions provided.
- Participants must not receive help from relatives, friends, or site staff to answer or to clarify PRO questions.
- If participants have any medical problems, they should discuss them with their doctor or research nurse separately from the PRO assessment.
- Site staff must remind participants there are no right or wrong answers, and that the value and relevance of PRO data are to hear directly from participants, without interpretation from anyone else, how they function and feel.

CLDQ:
The CLDQ is a disease-specific PRO instrument, assessing symptoms and health-related quality of life, relevant for patients with liver disease. The CLDQ includes 29 items with a recall period of the past 2 weeks. The CLDQ includes 6 domains: Abdominal symptoms (3 items), Fatigue (5 items), Systemic symptoms (5 items), Activity (3 items), Emotional function (8 items), Worry (5 items). Scoring of this instrument produces a global score, as well as scores for each of the domains.

SF-36v2:
The SF-36v2 is a validated generic PRO instrument for assessing health-related quality of life. The acute version of SF-36v2 asks about the past week and the participant's current experience. The SF-36v2 consists of 36 items combined into domains, and 2 aggregated summary scores: Mental Component Summary and Physical Component Summary. The 8 domains are: Physical Functioning, Role-Physical (role limitations caused by physical health problems), Bodily Pain, General Health, Vitality, Role-Emotional (role limitations caused by emotional problems), Social Functioning and Mental Health. Responses to 35 of the 36 items are used to compute an 8-domain profile of functional health and wellbeing scores. The remaining item, referred to as the "Health Transition" item, asks participants to rate how their current state of health compares to their state of health 1 year ago and is not used to calculate domain scores.

Patient Global Impression of Severity - Liver Disease (PGIS - Liver Disease):
The PGIS measures the participant's overall perceptions of their liver disease-related symptoms. The PGIS is a static, single-item measure of the severity of liver disease symptoms during the last 2 weeks. The PGIS has 4 response options: "no symptoms," "mild," "moderate," and "severe." PGIS is useful for determining the meaningful change values of

other PRO measures such as CLDQ.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

8.3.1 Physical Examinations

Physical examination, and measurement of weight and height will be conducted at the timepoints outlined in the SoA (Table 1).

- A full physical examination will include assessments of general appearance, respiratory (respiratory rate and breath sounds), cardiovascular (HR, jugular venous pressure, sounds), abdomen (liver and spleen to detect any increase as well as clinical ascites grade), skin (colour, turgor), head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems and an assessment of the presence and extent of peripheral (ankle/leg) oedema.
- A brief physical examination will include assessment of skin (colour, turgor), respiratory (respiratory rate and breath sounds), cardiovascular system (HR, jugular venous pressure, sounds), and abdomen (liver and spleen to detect any increase as well as clinical ascites grade) and an assessment of the presence and extent of peripheral (ankle/leg) oedema.

For information on how AEs based on physical examination findings should be recorded and reported, see Section 8.4.4.

In addition, body weight will be monitored at home using an electronic scale throughout the interventional period as part of the key measurements (Table 1); Section 8.2.1.2). For measurement, the participant should wear indoor, daytime clothing with no shoes and no coats/jackets and removal of heavy objects from pockets.

8.3.2 Vital Signs

Vital signs assessments will be performed at timepoint as specified in the SoA (Table 1).

Vital signs will include supine and standing blood pressure, pulse, and body temperature measurements.

Routine blood pressure, pulse, and body temperature will be assessed at the study centre, as outlined in the SoA (Table 1), prior to blood collection for laboratory tests with the participant resting in a supine position using a completely automated device. Manual techniques will be used only if an automated device is not available.

Participants who suffer from CCI and/or CCI of CCI during the course of the study, will be provided with CCI

(Sections 6.1.2 and 8.4.6).

Vital sign measurements in a supine position should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones) and will consist of one pulse, one body temperature, and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF. In addition, CCI CCI should be CCI in the CCI. These assessments should preferably be done in the morning. If CCI is confirmed during the test, it should be reported as an AESI including symptoms related to the measurement of CCI if present (Section 8.4.6).

For information on how AEs based on vital sign results should be recorded and reported, see Section 8.4.4.

Body weight will be measured at the study centre at study visits. There will be safety monitoring of body weight from the home-based monitoring devices, or as an alternative, paper diaries can be used for capturing the information. A body weight change of CCI kg per CCI is regarded as a CCI weight change and needs to be followed up by the investigator.

The investigator will have direct access to the online data for their participants using digital devices. If there is a significant weight gain, the investigator will contact the participant immediately and arrange a clinic visit to assess health status. Participants with paper diaries will be instructed to contact the study staff if there is a significant weight gain.

Participants will also be advised to self-monitor and contact the investigator with any concerns.

8.3.3 Electrocardiograms

ECGs will be recorded at the sites using 12-lead ECG recorders in the supine position after the participant has been resting for at least 10 minutes, at the timepoints specified in the SoA (Table 1). The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

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

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

scanned or paper ECGs is also established. Confirmed ECGs will be available on a study portal within the contracted turnaround time.

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

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

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

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

For information on how AEs based on ECG results should be recorded and reported, see Section 8.4.4.

8.3.4 Echocardiogram

In participants with a known history of HF from any aetiology, and no historical ECHO or cardiac MRI available within 12 months prior to Visit 1, a baseline ECHO should be obtained during the screening period and prior to randomisation.

8.3.5 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, electrolyte, coagulation, and haematology for safety analysis will be taken at the timepoints specified in the SoA (Table 1). Some of the laboratory variables are also collected for assessments for exploratory endpoints, as described in Section 8.2.2.3.

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 laboratory assessments for clinical chemistry and haematology will be performed at a central laboratory.

The following laboratory variables will be measured (Table 7).

Table 7 Laboratory Safety Variables

Haematology and differential panel	
White blood cell count	Lymphocytes absolute count
Red blood cell count	Monocytes absolute count
Haemoglobin	Eosinophils absolute count
Haematocrit	Basophils absolute count
Neutrophils absolute count	Platelet absolute count
Chemistry panel	
BUN	Alanine aminotransferase
Creatinine and calculated eGFR (CKD-EPI)	Aspartate aminotransferase
Total bilirubin and direct bilirubin	Alkaline phosphatase
Albumin	Creatine kinase
Calcium	Serum glucose
Phosphate	Gamma-glutamyl transferase
Other	
Serum Osmolality	NT-pro BNP
Coagulation groups (frozen samples)	
International normalised ratio	Prothrombin time
Partial thromboplastin time	
Electrolyte panel	
Bicarbonate (HCO_3-)	Sodium
Chloride (Cl-)	Potassium
Magnesium (Mg^+)	
Urine screen for drugs of abuse (Screening only)	
Amphetamine/MDMA	Opiates
Antidepressants	Methadone
Barbiturates	Phencyclidine
Benzodiazepines	Propoxyphene
Cannabinoids	Cocaine
HIV serology	
Human Immunodeficiency Virus load	
Reproductive screening	
FSH (females only)	Pregnancy test (females only; serum)

Note: Refer to Appendix E for actions required in cases of increases in liver biochemistry and

evaluation of modified Hy's Law.

Instructions for the collection and handling of the samples will be provided in the study-specific Laboratory Manual.

8.3.6 Other Safety Assessments

8.3.6.1 Self-Monitored Glucose and Hypoglycaemic Events

The participants with T2DM and on concomitant treatment with insulin or sulfonylurea will be asked to check their blood glucose regularly and, if they develop symptoms suggestive of hypoglycaemia, to record specific symptoms. Participants on insulin or sulfonylurea will be provided with a home-based glucometer to monitor their blood glucose if they do not already have a glucometer at home (Section 6.1.2). Participants will be instructed to record any hypoglycaemic event and to contact the investigator.

During the visits specified in the SoA (Table 1), the investigator is responsible for reviewing any blood glucose data collected from the participant and questioning the participant about all symptoms reported and for determining if they meet the clinical definition of hypoglycaemia. Only symptoms and/or blood glucose values that meet the following criteria should be reported on the dedicated hypoglycaemia eCRF pages:

- A glucose level of < 3.0 mmol/L (< 54 mg/dL).
- Severe hypoglycaemia, as defined by severe cognitive impairment requiring external assistance for recovery.

In all participants, hypoglycaemic events should be reported on the AE eCRF page if fulfilling the AE definition (see Appendix B).

8.3.6.2 Alcohol Use Disorders Identification Test Questionnaire

The AUDIT questionnaire to assess alcohol use habits will be completed at screening only (Table 1). The self-assessment version of the questionnaire will be completed by the participant. The results will be used for determining participant eligibility. A score of 8 or more is associated with harmful or hazardous drinking, a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.

Definition of a Standard Drink:

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

8.4 Adverse Events, 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.

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

Adverse Event Variables

The following variables will be collected for each AE:

- Adverse event (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality assessment against the study intervention (yes or no)
- Action taken with regard to study intervention
- Outcome

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Adverse event description
- Adverse event 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

Serious AEs will be recorded from the time of signing of the ICF.

All AEs will be collected after the participant has received the first dose of the study intervention throughout the treatment period and including the follow-up period.

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

8.4.2 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 study intervention and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study intervention?'.

For SAEs, causal relationship should also be assessed for other medications 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, vital signs, and ECGs 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 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, 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 AEs (Section 8.4).

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.

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 AEs spontaneously reported by the participant (or care provider) or reported in response to the open question from the study centre 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 Adverse Events of Special Interest

Additional monitoring and data collection will be performed during the study for the following safety events classified as AESI, based on the CCI identified for zibotentan in oncology clinical studies conducted previously, as CCI of both zibotentan and dapagliflozin (eg, CCI), and CCI associated with the use of dapagliflozin:

- New diagnosis of CCI or CCI of the existing CCI condition. Any CCI CCI suggestive of CCI should be properly assessed by the investigator, to ensure timely and proper management of the participant's condition.
- CCI or worsening of CCI (eg, CCI CCI of any CCI, etc).
- CCI defined as a CCI of CCI mmHg in CCI or a CCI of CCI mmHg in CCI within CCI. Participants will be educated about the symptoms of CCI and participants with CCI or CCI will be provided with a CCI and asked to contact the investigator if symptoms occur or if their CCI is CCI mmHg.

- CCI . In the event of symptoms of CCI , a CCI CCI should be performed.
- CCI .
- CCI , including the following: increase in CCI by CCI mg/dL (CCI µmol/L) within 48 hours; or increase in CCI to CCI which is known or presumed to have occurred within the prior 7 days (or using the last available value of outpatient CCI within 3 months as the baseline value); or CCI CCI mL/kg/h for 6 hours.

8.4.7 Hy's Law

Cases where a participant shows elevations in LFTs or relevant clinical manifestations as defined in Appendix E 2 and identified in Appendix E 3 may require further evaluation and 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 modified Hy's Law.

8.4.8 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 study centre 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 centre staff reports a SAE to the appropriate AstraZeneca representative by telephone, email or as per local approved process. 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.

The AstraZeneca representative will advise the investigator/study centre staff how to proceed.

In the EU, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

For further guidance on the definition of a SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the Dapagliflozin Investigator's Brochure and Zibotentan Investigator's Brochure.

8.4.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except if the pregnancy is discovered before the study participant has received any study intervention.

8.4.9.1 Maternal Exposure

Exposure during gestation to ERAs, including zibotentan, is associated with major embryo-foetal harm. ERAs have been demonstrated to induce teratogenic effects in animals when dosed during organogenesis, early in pregnancy. When administered to pregnant rabbits during the period of major embryonic organogenesis, zibotentan caused foetal craniofacial and cardiac malformations at CCI and above, consistent with ERAs (zibotentan IB). There is an extremely high risk of embryo-foetal harm if pregnancy occurs while being exposed to zibotentan in any amount, even for short periods of time. Potentially, any foetus exposed during pregnancy can be affected. Women of childbearing potential are not allowed to be included in this study (for definition see inclusion criteria, Section 5.1).

Dapagliflozin must not be used in the second and third trimesters of pregnancy (refer to Dapagliflozin Investigator's Brochure for details).

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

If any pregnancy occurs during the study, then the investigator or other study centre personnel

informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for SAEs (see Section 8.4.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.4.9.2 Paternal Exposure

To prevent potential exposure via semen, men receiving zibotentan who are sexually active with a woman of childbearing potential should employ the use of condoms together with other highly effective methods of contraception during the study and for a total period of 3 months after the male study participant has received his last dose of study intervention.

Highly effective birth control methods are defined as those that can achieve a failure rate of less than 1% per year when used consistently and correctly. For details refer to Section 5.3.4.

Male participants should not donate or bank sperm for the duration of the study and for at least 3 months after the last dose of study intervention.

Male participants will be instructed that if their partner becomes pregnant during the study, or within 3 months after last dose of the study intervention, this should be reported to the investigator, and the study intervention must be discontinued immediately. The investigator or other study centre personnel should inform the appropriate AstraZeneca representatives about the pregnancy within the timelines specified in section 8.4.9.1.

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/birth defect), occurring during the study or within 3 months after last dose of the study intervention should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.4.10 Medication Error, Drug Abuse, and Drug Misuse

8.4.10.1 Timelines

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

it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.4.8) and **within 30 days** for all other events.

8.4.10.2 Medication Error

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

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

8.4.10.3 Drug Abuse

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

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

8.4.10.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the 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.

8.4.11 Reporting of Overdose

Dapagliflozin has been well tolerated at doses up to 500 mg/day in single dose testing in healthy participants and up to 100 mg/day in repeat dose testing for 14 days in healthy participants and patients with T2DM.

If an overdose is suspected, monitoring of vital functions as well as treatment should be performed as appropriate.

The maximum well tolerated daily dose of zibotentan in oncology patients was considered to be CCI mg; however, presently there is limited information regarding overdose of zibotentan in combination with dapagliflozin in patients with liver cirrhosis.

For the purposes of this study, an overdose will be defined as the use of the study intervention in doses in excess of that specified in the protocol.

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

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other study centre 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 8.4.8) and **within 30 days** for all other overdoses.

8.4.12 Medical Device Deficiencies

No AstraZeneca manufactured medical devices (or medical devices manufactured for AstraZeneca by a third-party) will be provided for use in this study. For details on digital devices used in this study and not manufactured by or for AstraZeneca, refer to Section 6.1.2.

8.5 Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentrations of study intervention as specified in the SoA (Table 1).

Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons such as an SAE; these samples may be reported outside the CSR.

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 samples will be used to analyse the PK of study interventions. Samples collected for analyses of study intervention plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

- For storage, re-use, and destruction of samples for PK see Appendix C.
- PK samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier).

- 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

Plasma samples will be collected for measurement of concentrations of zibotentan and dapagliflozin at the timepoints specified in the SoA (Table 1).

8.5.2 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by bioanalytical test sites operated by LabCorp 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 would unblind the study will not be reported to investigative study centres or blinded personnel until the study has been unblinded. Only samples from participants on active treatment will be analysed, unless there is a need to confirm that correct treatment has been given to study participants.

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

8.6 Pharmacodynamics

During the study plasma/serum samples will be collected for the evaluation of the exploratory endpoints. Parameters will be assessed from the blood samples collected for safety analyses at a central core laboratory (see Section 8.3.5).

8.6.1 Collection of Samples for Pharmacodynamics

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

During the study blood samples will be collected as described in the SoA (Table 1) and analysed by a central laboratory.

For storage, re-use, and destruction of PD samples, see Appendix C.

8.7 Optional Genomics Initiative

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA (Table 1) and is subject to agreement in the optional Genomics Initiative research information ICF.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic and multi-omics analysis component of the study. Participants who do not wish to participate in the genetic 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 or in the Laboratory Manual.

The blood sample for exploratory genetic research will be obtained from the participants at Visit 2 or after randomisation.

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. Mandatory collection of samples for biomarker research is part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study at the timepoint specified in the SoA (Table 1):

- Plasma/serum and urine samples are collected for exploratory analyses to assess the effect of zibotentan and dapagliflozin on liver diseases and drug mechanism-related biomarkers at a central laboratory.

For storage, re-use, and destruction of biomarker samples see Appendix C.

8.9 Immunogenicity Assessments

Immunogenicity analysis will not be done in this study.

8.10 Medical Resource Utilisation and Health Economics

Medical resource utilisation and health economics are not evaluated in this study.

8.11 Study Participant Feedback Questionnaire

Not applicable.

9 STATISTICAL CONSIDERATIONS

The SAP will be finalised within 90 calendar days after First Participant In 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 or key endpoints.

9.1 Statistical Hypotheses

As this is an early-phase safety study, no formal statistical hypothesis tests or multiplicity adjustment will be performed.

9.2 Sample Size Determination

Approximately 22 participants are planned to be randomised to each of the 3 treatment groups. The sample size is not determined based on a formal statistical hypothesis testing for this Phase IIb study. With CCI evaluable participants per treatment group, an observed difference of CCI% CCI%) in proportion of participants with the composite of fluid retention between 2 treatment groups and an observed CCI% composite of fluid retention in the corresponding zibotentan group, the lower limit of a two-sided 90% CI for the difference will be CCI%.

9.3 Populations for Analyses

The following populations are defined:

Table 8 Populations for Analysis

Population/analysis set	Description
Screened analysis set	All participants who signed the ICF. Unless otherwise stated, the enrolled set will be used for the presentation of disposition data.
FAS	All participants who are randomised and receive any study intervention. Participants are evaluated according to the treatment assigned at randomisation. The FAS will be the analysis set for all endpoint analyses with the exception of the PK analyses.
PKS	All participants in the FAS who have at least one detectable zibotentan or dapagliflozin plasma concentration measurement post-treatment. Pharmacokinetic samples collected after Visit 5 may be excluded from the PKS and may be reported outside the CSR. The PKS will be used for all PK analyses.

Abbreviations: FAS: Full Analysis Set; ICF: Informed consent form; PKS: Pharmacokinetic Analysis Set; PK: Pharmacokinetics.

9.4 Statistical Analyses

9.4.1 General Considerations

All results will be presented by treatment group and overall, as appropriate, with descriptive statistics appropriate to the nature of the variables.

Demographic and baseline characteristics as well as prior and concomitant medication will be presented. For continuous variables, the number of non-missing observations, mean, SD,

median, minimum, and maximum will be presented. For categorical variables: counts (n) and percentages (%) (where specified) will be presented. These summaries will be provided by timepoint of assessment, as appropriate.

When change from baseline is described, the baseline value will be, in general, the last non-missing value prior to or on the same date as administration of the first dose. Further details will be described in the SAP.

In general, there will be no imputation of missing data for the safety analyses. Additional details will be provided in the SAP.

Deviations from the protocol will be assessed as "important" or "not-important". Important deviations from the protocol may lead to the exclusion of participants from any of the study analysis sets. Deviations will be defined before clinical data lock. Important deviations will include the following:

- Violation of inclusion and/or exclusion criteria
- Administration of prohibited concomitant medications that are expected to influence the measurement of the key endpoints.

All protocol deviations will be discussed at the data review meeting prior to clinical data lock in order to define the analysis sets for the study. All the important protocol deviations will be listed by participants. Further details will be described in the SAP.

9.4.2 Key Endpoints

The analysis of all key endpoints will be performed on the FAS. The non-terminal intercurrent events (eg, treatment discontinuations due to any reason, use of prohibited medication) will be handled by a treatment policy strategy. For terminal intercurrent events (ie, death), a while-alive strategy will be applied. The detailed estimand attributes will be provided in SAP.

For fluid retention, the composite endpoints are defined as:

- occurrence of any of the following events: (1) > 2 kg increase in body weight, (2) > 2 L increase in total body water, (3) increase in 2 or more loop-diuretic equivalents or (4) fluid retention AEs, from baseline to Week 6
- occurrence of either (1) > 3 L increase in total body water volume from baseline to Week 6; or (2) increase in 3 or more loop-diuretic equivalents use from baseline to Week 6

Exact 90% (two-sided) CIs for proportions of participants with the composite of fluid retention in treatment groups will be calculated using the Clopper-Pearson method. The exact

unconditional 90% (two-sided) CIs for difference in proportions between 2 treatment groups will be computed based on score statistic (Chan and Zhang 1999).

The change in body weight, body water volumes, total dosage of loop-diuretic equivalents, body fat mass, and blood pressure from baseline to Week 6 will be analysed using MMRM methodology for pairwise comparisons between treatment groups. The analytic model will include the CCI of CCI , and CCI CCI , and CCI of the CCI . An CCI CCI will be used for the CCI

Further details will be described in the SAP.

9.4.3 Safety

Safety analyses will be performed using the FAS. Safety data will be presented using descriptive statistics unless otherwise specified. In general, the baseline value for statistical analysis is the last nonmissing value prior to administration of the first dose of study intervention. Details will be described in the SAP.

9.4.3.1 Adverse Events

Adverse events will be coded using the most recent version of the MedDRA that will have been released for execution at AstraZeneca or designee.

Adverse events will be presented for each treatment group by system organ class and/or preferred term covering number and percentage of participants reporting at least one event.

Only AEs occurring with an onset date, or worsening, on or after first dose of study intervention, throughout the treatment period and including the follow-up period will be presented in summary tables. SAEs occurring prior to start of study intervention will be included in data listings.

An overview of AEs will be presented for each treatment group; the number and percentage of participants with any AE, AEs with outcome of death, SAEs, AEs leading to discontinuation of study intervention, AEs leading to study intervention dose interruptions, and AESIs.

Separate AE tables will be provided taking into consideration relationship as assessed by the investigator and maximum intensity, seriousness, death, and AEs leading to discontinuation of study intervention, as well as action taken with respect to the study intervention, and other significant AEs.

Key participant information will be presented for participants with AEs with outcome of death, SAEs, and AEs leading to discontinuation of study intervention. An AE listing for the FAS will cover details for each individual AE; an AE listing for participants who were not

exposed to study intervention is presented separately.

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

9.4.3.2 Vital Signs

Vital sign parameters (supine and standing blood pressure, pulse, and body temperature) will be presented for each treatment group.

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

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

Details of vital sign analyses including definition of abnormality criteria (eg, definition of low, normal, high) and project-specific predefined criteria for treatment-emergent changes in relevant vital sign parameters (eg, systolic and diastolic blood pressure) will be provided in the SAP.

9.4.3.3 Laboratory Assessments

Laboratory parameters will be presented for each treatment group.

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

Elevation in liver parameters for assessment of Hy's law (see Appendix E) will be done and reported appropriately if potential cases have been identified during the course of the study.

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

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

Details of laboratory analyses including definition of abnormality criteria (eg, definition of low, normal, high) and study-specific predefined criteria for treatment-emergent changes in relevant laboratory parameters will be provided in the SAP.

9.4.3.4 Electrocardiograms

Electrocardiogram findings will be listed for each participant and will include the ECG parameters (where applicable) and changes from baseline, assessment by the investigator (normal/abnormal not clinically significant/abnormal clinically significant) and details of any

abnormalities. ECG parameters will be summarised by time-point including changes from baseline. The baseline for the safety ECG parameters will be the results obtained pre-dose on Day 1.

ECG parameters to be tabulated will be provided in the SAP.

9.4.4 Exploratory endpoints

9.4.4.1 Exploratory Pharmacokinetic Endpoints

Plasma concentrations of zibotentan and dapagliflozin will be summarised by treatment group, visit, and time-point based on the PKS.

Additional PK analyses may be conducted as appropriate but will be reported outside the CSR.

Further details of this will be provided in the SAP.

9.4.4.2 Exploratory Pharmacodynamic and Biomarker Endpoints

The exploratory PD and biomarker endpoints described in Section 8.2.2.3 will be summarised by treatment group and time-point based on the FAS.

Further details on this will be provided in the SAP.

9.4.4.3 Exploratory PRO Endpoints

Results for patient-reported outcomes will be summarized by treatment group for FAS.

Further details on this will be provided in the SAP.

9.4.4.4 Other Exploratory Endpoints

Percentage and absolute change in CCI and/or CCI assessed using CCI at Week 6, change in eGFR at Week 1, Week 6, and evaluation of changes in blood biomarkers across time course of the study will be analysed according to treatment group. For details on exploratory objectives and endpoints, see Section 3.

Further details about analyses of exploratory endpoints will be provided in the SAP.

9.4.4.5 Exploratory Research and Optional Genetic Research

The following analyses will not be part of the CSR:

- Evaluation of changes in other blood and urine biomarkers, not outlined in this protocol, but relevant to liver diseases and drug-related mechanisms over the time course of the study.

- Optional exploratory research into genes/genetic variation that may influence response to treatment.

Analyses for these exploratory objectives will be described in a separate analysis plan and results will be presented separately from the main CSR.

9.5 Interim Analyses

Not applicable.

9.6 Data Monitoring Committee

A DMC will monitor ongoing safety/tolerability data (including monitoring of modified CCI [redacted] and CCI [redacted] including CCI [redacted]) and have the authority to unblind a participant's intervention assignment due to safety concerns if warranted. The DMC will be asked to meet at regular intervals and may also meet more often if they think it is needed from a safety perspective. The DMC may recommend stopping further recruitment and/or treatment of participants in a treatment group at any time after a comprehensive assessment of safety data. The recommendation will be evaluated by an unblinded senior manager who will provide a decision based on the DMC recommendation to the study team. Further details will be provided in a separate DMC charter.

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any 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.
- In the EU, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

- For all studies except those utilising medical devices, investigator safety reports must be prepared for SUSARs, according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches 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 and ethical obligations are met.

> A "serious breach" means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

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 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 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.

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

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

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that 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 Controller 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:

- They allow site staff or service providers delegated by the investigator/institution 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 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 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 involving 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 subjects, 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

A DMC will be set up for this study in accordance with the AstraZeneca charter for data review committees.

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the protocol and letters to investigators.

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 main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted. Describe sponsor -specific policy on provision of study results.

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 non-compliance 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 Medical Oversight 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 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in source data acknowledgment or monitoring guidelines.

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 screened and included in the study (ie, who signed consent) and will be the study start date.

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 CROs 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 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.

A 11 Study Participant Feedback Questionnaire

Not applicable.

A 12 Clinical Outcome Assessment/Patient-reported Outcome Questionnaires

Chronic Liver Disease Questionnaire (CLDQ)

Patient Reported Outcome Questionnaire: CLDQ was removed due to copyrights.

Patient Reported Outcome Questionnaire: CLDQ was removed due to copyrights.

Patient Reported Outcome Questionnaire: CLDQ was removed due to copyrights.

Patient Reported Outcome Questionnaire: CLDQ was removed due to copyrights.

Patient Reported Outcome Questionnaire: CLDQ was removed due to copyrights.

Patient Reported Outcome Questionnaire: CLDQ was removed due to copyrights.

Patient Reported Outcome Questionnaire was removed due to copyrights.

Patient Reported Outcome Questionnaire was removed due to copyrights.

Patient Reported Outcome Questionnaire was removed due to copyrights.

Patient Reported Outcome Questionnaire was removed due to copyrights.

Patient Reported Outcome Questionnaire was removed due to copyrights.

Patient Reported Outcome Questionnaire was removed due to copyrights.

Patient Global Impression of Severity - Liver Disease (PGIS - Liver Disease) Questionnaire

Patient Reported Outcome Questionnaire: PGIS was removed due to copyrights.

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 or not related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and 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 in-patient 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.

Adverse Events 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 a 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.

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

Intensity Rating Scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not 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.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a

causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the 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, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refridgerator 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 nontherapeutic effect.

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

Examples of drug abuse include but are not limited to:

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

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the 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 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.

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

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

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

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

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

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/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 Sample

D 1 Use/Analysis of DNA

- 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 time-point 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 analyses may be reported in a separate study summary.
- AstraZeneca will store the DNA 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

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 2 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 2, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics research during the study.

Coding and Storage of DNA Samples 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 subject last visit, after which they will be destroyed. 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 genetics 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 component of this study are optional and the participant may participate in other components of the main study without participating in this genetic 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 genetic research information ICF. 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

- Data will be reported separately from the CSR.
- 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 genetic 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 genetic data in a suitable secure environment separate from the clinical database.

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

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law cases as defined in this study involving patients with cirrhosis. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Given the participant population, and the likely prevalence of abnormal and fluctuating LFTs, the criteria used to determine whether a case meets PHL and HL reporting criteria are CCI to this CCI and defined below.

Specific guidance on managing liver anomalies can be found in Section 7.1.2 Management of Treatment-emergent abnormalities in LFTs.

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

All sources of laboratory data are appropriate for the determination of PHL and 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, PHL criteria could be met by an elevated ALT from a central laboratory AND/OR elevated TBL from a local laboratory.

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

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether 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 study intervention.

The investigator is responsible for recording data pertaining to PHL/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

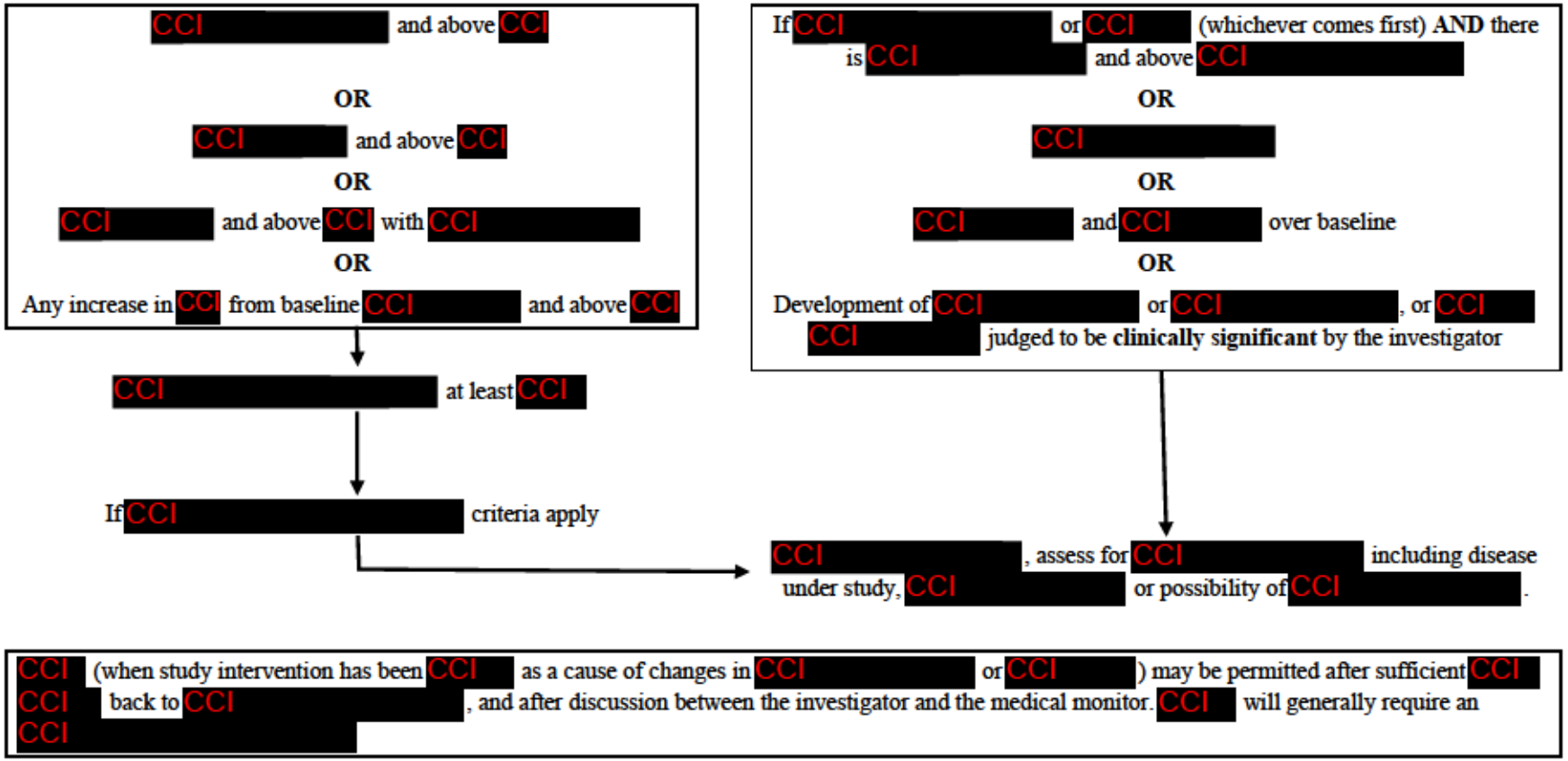
Potential Hy's Law
Elevation in LFTs or relevant clinical manifestations defined in Section E 3 flowcharts that lead to hold of the study intervention to assess the cause of these changes.

Hy's Law
Elevation in LFTs or relevant clinical manifestations defined in the flowcharts in Section E 3 that lead to hold of the study intervention and when there no other reason, other than the study intervention, can be found to explain the combination of such increases in LFTs.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following[redacted]:

Management guidelines for participants with CCI at baseline, and normal baseline CCI at baseline)



Management guidelines for participants with CCI at baseline, with abnormal baseline CCI CCI)

CCI but CCI and CCI ,

AND

- CCI (if normal at CCI or < CCI (if abnormal at CCI AND
- CCI over CCI AND
- CCI (if normal at CCI or CCI of CCI if CCI was CCI

CCI drug, CCI

CCI or CCI (whichever comes first)

AND AT LEAST CCI OF THE FOLLOWING

- CCI if normal at CCI) **OR** CCI if abnormal at CCI
- CCI over baseline,
- CCI (if CCI was CCI) OR increased by CCI (if CCI was CCI

OR

CCI is CCI or CCI (whichever comes first)

OR

CCI and CCI over baseline

OR

Development of CCI or CCI , or CCI CCI judged to be **clinically significant** by the investigator.

CCI study intervention, assess for CCI including disease under study, additional CCI or possibility of CCI .

CCI (when study intervention has been CCI as a cause of changes in CCI or CCI) may be permitted after sufficient CCI CCI back to CCI , and after discussion between the investigator and the medical monitor. CCI will generally require an CCI .

Management guidelines for participants with CCI at baseline, with either normal or abnormal baseline CCI

CCI and CCI) or CCI , whichever comes first; or CCI × post-baseline on-treatment CCI values

OR

CCI with CCI of the total, or any increase in CCI over baseline

OR

CCI × baseline

OR

CCI (if normal CCI at baseline) or any increase of CCI if baseline CCI

OR

CCI increased by CCI over baseline (if CCI at baseline) or by CCI over baseline (if CCI at baseline)

OR

Development of new CCI or CCI of CCI or CCI judged to be **clinically significant** by the investigator.

↓

CCI study intervention, assess for cause of CCI including disease under study, CCI or possibility of CCI.

Due to variability in CCI patients with CCI meeting requirement for hold of study drug based solely on CCI change, and not meeting any other criteria for drug hold, may have one CCI at the discretion of the investigator to determine whether the CCI change is sustained.

CCI (when study intervention has been CCI as a cause of changes in CCI or CCI) may be permitted after sufficient CCI CCI back to CCI × baseline, and after discussion between the investigator and the medical monitor. CCI will generally require an CCI

[a] CCI is defined as CCI with presence at baseline of CCI or CCI or CCI CCI

Central Laboratories Being Used:

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

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

- 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 laboratory test result.

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

- Determine whether the participant meets PHL criteria (see Section E 2 for definition and Section E 3) 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:

- Determine whether the participant meets PHL criteria (see Section E 2 for definition and Section E 3) 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 PHL criteria the investigator will:

- 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 PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central study team.

- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria "Important medical event" and causality assessment "yes/related" according to protocol process for SAE reporting.
- For participants that met PHL criteria prior to starting study intervention, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study physician.
  - Complete the three 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 in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change from before starting study intervention will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

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

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

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

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 LFT elevations or clinically relevant manifestation of significant changes in hepatic function, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the

criteria for a SAE:

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

If it is agreed that there is **no** explanation for the LFT elevations or clinically relevant manifestation of significant changes in hepatic function, other than the study intervention:

- 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 or not 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:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to study intervention 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 PHL 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 for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on study intervention visit, where assessment of the underlying cause of PHL was considered to be unlikely to relate to the study intervention (see Section E 5). Re-challenges (where a causal relationship of the study intervention could not be excluded) are not permitted.

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

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

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study?

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

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

If there is no significant change no action is required.

If there is a significant change[#] follow the process described in Section E 4.2 for reporting PHL as an SAE.

A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters 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, in consultation with the study physician.

E 7 Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA[a)] IgG anti-HCV HCV RNA[b)] IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgG anti-HSV, and HSV 1/2 IgM testing or HSV 1/2 PCR testing[c)] IgM and IgG anti-EBV
Alcoholic hepatitis	CD-transferrin
Autoimmune hepatitis	ANA Anti-LKM Ab ASMA Ab
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

ANA = antinuclear antibody; ASMA Ab = anti-smooth muscle; CD-transferrin = carbohydrate-deficient-transferrin; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; GGT = gamma-glutamyl transferase; HAV = hepatitis A virus; HBc = haemoglobin C; HBsAg = hepatitis B surface 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; LKM = liver/kidney microsomal; 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.

E 8 References

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, Hunt CM, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011; 89(6):806-15.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation.

Appendix F Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

CSP Version 2.0 EU (EEA regional modification) 16 May-2024

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

Overall Rationale for the Modification:

The CSP was modified for use in EU/EEA countries in response to the condition imposed as part of the approval of 2023-506893-11, received from the Reporting Member State, requesting removal of 'legally authorised representative' text from the informed consent process wording. In addition, minor corrections, additions, deletions, and clarifications (none of which significantly impact the safety or physical/mental integrity of participants nor the scientific value of the study) have been made to align with the global CSP version 2.0 that has been produced in parallel with this regional amendment.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Appendix A3 Informed Consent Process	Statement in bold regarding legally authorised representative removed from 3 places in this section: "..participant **or their legally authorised representative**.."	To address a regulatory agency request surrounding removal of 'legally authorised representative' text from the informed consent process wording

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Summary of Changes Table	Section updated to reflect the changes made to CSP v1.0 (EEA regional modification) to produce v2.0.	To give details of changes made to the previous version of the EEA regional modification.
1.1 Synopsis, 3 Objectives and Endpoints	In Objectives and Endpoints table, AESI of CCI ' edited to CCI [redacted] CCI [redacted] '.	To provide clarification
1.1 Synopsis, 3 Objectives and Endpoints	In Objectives and Endpoints table footnote, statement added about Japan one loop-diuretic equivalent.	To provide clarification for Japan
1.1 Synopsis	Objectives and Endpoints table footnote b removed.	Footnote not applicable to this table.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, 4.1 Overall Design, 5.1 Inclusion Criteria	Regarding the signs and measures of CSPH, the text was edited to "..presence of gastro-oesophageal varices at endoscopy or collaterals at imaging **(either one within 12 months prior to screening)**, and/or CCI CCI **of** CCI kPa, **or of** CCI kPa CCI CCI (at time of screening).". The new wording is slightly different in Section 5.1 but conveys the same meaning.	To provide clarification
1.1 Synopsis, 4.1 Overall Design	Unnecessary/confusing wording around not taking study intervention during the 2-week follow-up period was removed and the following additional wording in bold was added "..2 weeks after their **planned** last dose of study intervention **(planned last dose is at Visit 6)**".	To simplify and clarify text
1.1 Synopsis	Chan and Zhang 1999 reference added.	To provide a reference for the quoted statistical information.
1.3 Schedule of Activities, 8.2 Efficacy Assessments, 8.2.2.1 CCI , 8.3.4 Echocardiogram	Multiple minor updates made to Table 1: CSP section cross-references corrected in some instances (as well as in footnote k); cardiac MRI removed as an option - only ECHO will be used (affects Section 8.3.4 also); 'Efficacy assessments' changed to 'Key assessments' (affects Section 8.2 also); eGFR calculation and MELD score calculation rows switched around due to different CSP section cross references; additional cross added for HbA1c Visit 5; footnote g CCI timing modified to 'or at least 3 hours' from 'or 3 to 4 hours' (affects Section 8.2.2.1 also) and reference to an overnight fast removed; footnote o removed ('if urine test is positive, participant should undergo confirmatory serum test') and subsequent footnotes renumbered; new footnote p updated to specify 'digital' ECGs and 'predose' ECGs; new footnote q visit corrected from Visit 1	Multiple minor updates to correct incorrect information or to clarify.

Section Number and Name	Description of Change	Brief Rationale
	to Visit 2; footnotes r and s added (relating to not eating a large meal before measurement collection (r), and clarifying that eGFR1 is at every visit and eGFR2 at Visits 2, 5, and 6 (s).	
3 Objectives and Endpoints	Table 3: Endpoint of exploratory objective relating t CCI [redacted] etc, was edited; "Evaluation of changes in blood and urine biomarkers across time from baseline to Week 6" edited to remove reference to urine biomarkers.	Urine biomarkers will not be used for this objective
3 Objectives and Endpoints	Exploratory PRO endpoint "Patient Global Impression of Severity – Liver Disease severity level" added to PRO endpoints list.	Endpoint previously omitted from table in error.
5.2 Exclusion Criteria	Criterion 32 edited to add the words in bold: "Implanted **cardiac** electronic device such as pacemaker **or implantable cardioverter defibrillator**"	Additional details added for clarity
5.3.1 Meals and Dietary Restrictions	Revised text in bold was added: "Study intervention should be taken between approximately 08:00 to 10:00 each morning. If study intervention is not taken before noon (12:00 pm), it is recommended to take the next dose in the morning the next day. **On the day of randomisation, study intervention can be taken after noon, without affecting the next day's dose.** On the days of CCI [redacted] assessments, **measurements will be performed at the timepoints specified in the SoA (Table 1) after an over-night fast or at least 3 hours after a meal. Additionally, for Visit 6,** CCI [redacted] **should be performed ≥ 3 hours after study intervention is given.**"	For practical purposes, due to the number of activities on the day of randomisation (applies to dosing timing), and to provide clarification regarding CCI [redacted] assessment timing versus dosing and feeding.
6.9.1 Prohibited Medications	CCI [redacted] removed as a prohibited medication in Table 5.	CCI [redacted] is not absorbed so does not need to be prohibited
7.1 Discontinuation of Study Intervention	'Recurrent encephalopathy' was edited to 'Overt encephalopathy'	Correction of previous text

Section Number and Name	Description of Change	Brief Rationale
7.1.2 Management of Treatment-emergent Abnormalities in LFTs	Text in bold was added: "The DILI algorithms account for CCI of the CCI value (defined as the CCI of the CCI during the CCI period CCI CCI **visit values**)."	To provide clarification
7.2 Participant Discontinuation/Withdrawal from the Study	Second bullet removed: "At the time of discontinuing from the study, if the participant has not been discontinued from the study intervention, see Section 7.2"	Bullet considered unnecessary
7.3 Lost to Follow-up	Final bullet amended from "Should the participant continue to be unreachable, the participant will be considered **withdrawn from study**" to "Should the participant continue to be unreachable, the participant will be considered **lost to follow-up**"	Correction of previous text
8.2 Efficacy and Exploratory Assessments	"There are no efficacy assessments in this study" was added. The second sentence was updated to say '**key and exploratory** endpoints'.	To align with the objectives and clarify that there are no efficacy assessments
8.2.2.2 Serum Analysis of Creatinine and Cystatin C (eGFR)	Typographical errors corrected in eGFR1 and eGFR2 formulae, plus the following text was added at the end of this section "Based on the SoA, eGFR1 calculations will be at every visit, while eGFR2 calculations will be at Visits 2, 5 and 6" and removed from Section 8.2.2.3.	To correct typographical errors and to place text in more appropriate location
8.2.2.3 Laboratory Assessments for Exploratory Analyses	The following text was added to bullet 2: "If bilirubin, INR, and/or creatinine values are less than 1.0, the value is set as 1.0."	To add clarification
8.2.2.3 Laboratory Assessments for Exploratory Analyses	"Blood and urine samples" changed to "Blood samples" throughout this section	Urine samples will not be used
8.2.2.3 Laboratory Assessments for Exploratory Analyses	The following text was removed: "Note: Exploratory analyses laboratory results could be considered potentially unblinding and results for these exploratory assessments will not be made available to the study team until after the Last Subject Last Visit."	The statement was incorrect; only PK data would be unblinding
8.2.2.4 Patient-reported Outcomes	Entire subsection moved from 8.3.6.3 to become 8.2.2.4.	The subsection was incorrectly included under safety assessments

Section Number and Name	Description of Change	Brief Rationale
8.2.2.4 Patient-reported Outcomes	Text in bold added: "PRO questionnaires should be completed before any other study procedures **during Visit 6**, to avoid bias when responding to questions"	To provide clarification of timing
8.4 Adverse Events, SAEs, and Other Safety Reporting	Text in bold added: "Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative); **these must then be assessed by the investigator and if considered an AE it will be reported by the investigator**.	To provide additional detail of the reporting process
9.1 Statistical Hypotheses	The following text in bold was added: **"As this is an early-phase safety study**, no formal statistical hypothesis tests **or multiplicity adjustment** will be performed."	To clarify that no formal statistical hypothesis testing or multiplicity adjustment will be performed due to this being an early-phase safety study
9.1 Statistical Hypotheses	The following text was removed: "The analyses will be descriptive using an estimation approach.	The analyses are described in more detail in Section 9.4 and this brief sentence in 9.2 could have resulted in misunderstanding of the planned analyses.
9.4.2 Key Endpoints	Text edited from "All intercurrent events will be handled by a while-on-treatment strategy. Treatment discontinuations due to any reason (including terminal events, such as death) are regarded as intercurrent events. Post-intercurrent event measurements for the components of the composite endpoints will not be included in the efficacy analysis" to "The non-terminal intercurrent events (eg, treatment discontinuations due to any reason, use of prohibited medication) will be handled by a treatment policy strategy. For terminal intercurrent events (ie, death), a while-alive strategy will be applied.".	To better align with safety endpoint analysis
9.4.3.1 Adverse Events	Text edited as AEs leading to withdrawal from study will not be included in the overview of AEs and separate AE tables for timing of events will not be provided	AEs leading to withdrawal from study are no longer provided as company standard, and regarding separate AE tables for timing of events, this was a correction

Section Number and Name	Description of Change	Brief Rationale
9.4.3.2 Vital Signs	Text edited as details of the definition of clinically significant vital signs will not be provided in the SAP	Correction of previous text
9.4.3.3 Laboratory Assessments	Text edited as details of the definition of clinically significant laboratory assessments will not be provided in the SAP	Correction of previous text
9.4.4.3 Exploratory PRO Endpoints	New 'Exploratory PRO Endpoints' subsection added	Subsection was missing previously
9.4.4.4 Other Exploratory Endpoints	This section used to be 9.4.4.1 and entitled 'Exploratory Efficacy Endpoints', but was moved to become 9.4.4.4 so that the title could be changed to 'Other Exploratory Endpoints'	There are no efficacy endpoints in this study
9.4.4.4 Other Exploratory Endpoints	Bold text added (and incorrect text regarding urine biomarkers removed): "Percentage and absolute change in CCI and/or CCI **assessed using** CCI at Week 6, change in eGFR at Week 1, Week 6, and evaluation of changes in blood biomarkers across time course of the study will be analysed **according to treatment group"**	To provide clarification, including the fact that urine biomarkers will not be used
9.4.4.4 Exploratory CCI [section deleted]	Section deleted	CCI details are now added to Section 9.4.4.1.
Appendix A1	Text edits to comply with recent CSP template changes, including details of SUSAR reporting requirements and reporting in the case of a serious breach	To comply with new CSP template and reporting requirements.
A4 Data Protection	Personal data breaches text added	To comply with new CSP template and data-protection requirements.
A6 Dissemination of Clinical Study Data	Websites on which the clinical study description will be available was edited	Due to an update to the CSP template
D2 Multi-omics Research Plan and Procedures	Title and section content edited from 'genomics' to multi-omics' throughout	Due to an update to the CSP template
Appendix F	Appendix added to keep a record of the edits that were made to produce the previous EEA regional modification (v1.0) from the global CSP v1.0.	To capture the history of EEA regional modifications to the global CSP

Section Number and Name	Description of Change	Brief Rationale
11 References	Chan and Zhang 1999 added and all references ordered alphabetically	Reference originally missing and reference list not in alphabetical order

CSP version 1.0 EU (EEA regional modification) 06-March-2024

This modification to the global CSP version 1.0 was considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU and in the EU Clinical Trial Regulation Article 2, 2 (13) because it neither significantly impacted the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

This amendment to the global CSP version 1.0 focused on updates and clarifications in response to EU CTR comments. The key updates consisted of clarifying that statistical analyses applied to comparing all treatment groups, including the placebo group, and expanding the exclusion criterion about ongoing allergy/hypersensitivity to include the excipients of the listed products. Additionally, information on SUSAR reporting was added to the section on the reporting of SAEs.

Summary of Changes:

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated text to reflect changes made in the body of the CSP	To be consistent with the body of the CSP
5.2 Exclusion Criteria (#28)	Added "or any of the excipients of the products" to the exclusion criterion on history or ongoing allergy/hypersensitivity	To clarify that any excipients of the products are included in the exclusion criterion in response to EU CTR comments
8.4.8 Reporting of SAEs	Added statement regarding the Sponsor complying with European Clinical Trials Regulation (EU) No 536/2014 for reporting all SUSARs	To add information in response to EU CTR comments
9.1 Statistical Hypotheses	Clarified that formal statistical hypothesis testing or multiplicity adjustment will not be performed due to this being an early phase safety study	To add justification for not performing multiplicity adjustment in response to EU CTR comments

Section Number and Name	Description of Change	Brief Rationale
9.4.2 Key Endpoints	Deleted "zibotentan/dapagliflozin combination and corresponding zibotentan monotherapy" from the text discussing the calculation of 90% CIs using the Clopper-Pearson method Added "for pairwise comparisons between treatment groups" to text describing the analysis using MMRM methodology	To clarify that analysis methods apply to comparing all treatment groups, including the placebo group

11 REFERENCES

Chan and Zhang 1999
Chan I, Zhang Z. Test-based confidence intervals for the difference of two binomial proportions. Biometrics. 1999;55:1202-9.

Dapagliflozin Investigator's Brochure
Dapagliflozin Investigator's Brochure, Edition 18.

García-Pagán et al 2020
García-Pagán JC, Saffo S, Mandorfer M, Garcia-Tsao G. Where does TIPS fit in the management of patients with cirrhosis? JHEP Rep. 2020 May 23;2(4):100122.

GBD 2017
GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020;5(3):245-66.

Gunarathne et al 2020
Gunarathne LS, Rajapaksha H, Shackel N, Angus PW, Herath CB. Cirrhotic portal hypertension: From pathophysiology to novel therapeutics. World J Gastroenterol. 2020;28;26(40):6111-40.

Heerspink et al 2020
Heerspink HJL, Kohan DE, de Zeeuw D. New insights from SONAR indicate adding sodium glucose co-transporter 2 inhibitors to an endothelin receptor antagonist mitigates fluid retention and enhances albuminuria reduction. Kidney Int. 2021;99(2):346-49.

Hsiang et al 2020
Hsiang JC, Wong VW. SGLT2 inhibitors in liver patients. Clin Gastroenterol Hepatol. 2020;18(10):2168-72.

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

Iwakiri 2014
Iwakiri Y. Pathophysiology of portal hypertension. Clin Liver Dis. 2014;18(2):281-91.

Kosiborod et al 2021
Kosiborod MN, Esterline R, Furtado RHM, Oscarsson J, Gasparyan SB, Koch GG, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2021;Sep;9(9):586-94.

Liu et al 2022
Liu YB, Chen MK. Epidemiology of liver cirrhosis and associated complications: Current knowledge and future directions. World J Gastroenterol. 2022 Nov 7;28(41):5910-30.

Montalvo-Gordon et al 2020
Montalvo-Gordon I, Chi-Cervera LA, García-Tsao G. Sodium-glucose cotransporter 2 inhibitors ameliorate ascites and peripheral edema in patients with cirrhosis and diabetes. Hepatology 2020;72(5):1880-2.

Morris et al 2005
Morris CD, Rose A, Curwen J, Hughes AM, Wilson DJ, Webb DJ. Specific inhibition of the endothelin A receptor with ZD4054: clinical and pre-clinical evidence. Br J Cancer. 2005;92(12):2148-52.

Nelson et al 2012
Nelson JB, Fizazi K, Miller K, Higano C, Moul JW, Akaza H, et al. Phase 3, randomized, placebo-controlled study of zibotentan (ZD4054) in patients with castration-resistant prostate cancer metastatic to bone. Cancer. 2012;118(22):5709-18.

Okamoto et al 2016
Okamoto T, Koda M, Miyoshi K, Onoyama T, Kishina M, Matono T, et al. Antifibrotic effects of ambrisentan, an endothelin-A receptor antagonist, in a non-alcoholic steatohepatitis mouse model. World J Hepatol. 2016; 8(22):933–41.

Poordad 2015
Poordad FF. Presentation and complications associated with cirrhosis of the liver. Curr Med Res Opin. 2015;31(5):925-37.

Preston et al 2020
Preston IR, Burger CD, Bartolome S, Safdar Z, Krowka M, Sood N, et al. Ambrisentan in portopulmonary hypertension: A multicenter, open-label trial. J Heart Lung Transplant. 2020;39(5):464-472.

Rockey and Chung 1996
Rockey DC, Chung JJ. Endothelin antagonism in experimental hepatic fibrosis. Implications for endothelin in the pathogenesis of wound healing. J Clin Invest. 1996;98(6):1381-8.

Romanelli and Stasi 2016
Romanelli RG, Stasi C. Recent advancements in diagnosis and therapy of liver cirrhosis. Curr Drug Targets. 2016;17(15):1804-17.

Sitbon et al 2019
Sitbon O, Bosch J, Cottreel E, Csonka D, de Groote P, Hoeper MM, et al. Macitentan for the treatment of portopulmonary hypertension (PORTICO): a multicentre, randomised, double-

blind, placebo-controlled, phase 4 trial. Lancet Respir Med. 2019;7(7):594-604.

Takahashi et al 2021
Takahashi H, Kessoku T, Kawanaka M, Nonaka M, Hyogo H, Fujii H, et al. Ipragliflozin improves the hepatic outcomes of patients with diabetes with NAFLD. Hepatol Commun. 2022;6(1):120-32.

Tsochatzis et al 2014
Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014;383(9930):1749-61.

Zibotentan Investigator's Brochure
Zibotentan Investigator's Brochure, Edition 21.2.

Zipprich et al 2021
Zipprich A, Gittinger F, Winkler M, Dollinger MM, Ripoll C. Effect of ET-A blockade on portal pressure and hepatic arterial perfusion in patients with cirrhosis: A proof of concept study. Liver Int. 2021;41(3):554-61.