Clinical Study Protocol	
Study Intervention	Zibotentan and Dapagliflozin
Study Code	D4326C00003
Version	4.0
Date	28 May 2024

Redacted for Public Disclosure

A Two Part Phase IIa/b Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Dose-ranging Study to Assess Efficacy, Safety, and Tolerability of the Combination of Zibotentan and Dapagliflozin, and Dapagliflozin Monotherapy Versus Placebo in Participants with Cirrhosis with Features of Portal Hypertension

Sponsor Name: AstraZeneca AB

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Regulatory Agency Identifier Number: IND 156901, EU CT 2023-505405-17-00

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

Protocol Number: D4326C00003

Study Intervention: Zibotentan and Dapagliflozin

Study Phase: Phase IIa/b

Short Title: Zibotentan and Dapagliflozin combination, EvAluated in Liver cirrhosis (ZEAL study)

Study Physician Name and Contact Information will be provided separately.

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SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
CSP Version 4.0	*28 May 2024*
CSP Version 3.0	*05 October 2023*
CSP Version 2.0	*20 June 2022*
CSP Version 1.0	*05 May 2022*

CSP Version 4.0: 28 May 2024

This modification to CSP version 3.0 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 right or safety of participants nor the scientific value of the study.

Overall Rationale for the Modification

The overall rationale for the non-substantial changes implemented in this version of the CSP is to correct inconsistencies and enhance readability.

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 v3.0 to produce v4.0.	To give details of changes made to the previous version of the CSP.
5.1 Inclusion Criteria	Text in bold below was added to inclusion criterion 3: "(b) HVPG recording of good enough quality and HVPG > 10 mmHg, as judged by a central reader **at Screening, Visit 2."**	To provide added clarity regarding timing
5.2 Exclusion Criteria	Text in bold below was added to exclusion criterion 19: "History or ongoing allergy/hypersensitivity, as judged by the investigator, to SGLT2i (eg, dapagliflozin, empagliflozin), zibotentan or **other ERAs (eg, ambrisentan, atrasentan, bosentan), or any of the excipients of the products**.", and "drugs with a similar chemical structure to zibotentan" was removed.	To include allergy/hypersensitivity to excipients of the products and to correct and clarify regarding similar products to zibotentan.

Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Text in bold added to exclusion criterion 37: "History of encephalopathy of West Haven grade 2 or higher **within 6 months prior to screening**".	To correct inconsistency with respect to allowing participants with history of decompensated cirrhosis in the trial.
6.5.1 Prohibited Medications	Rifaximin removed as a prohibited medication in Table 7.	Rifaximin is not absorbed so does not need to be prohibited
Appendix A1 Regulatory and Ethical Considerations	The following bullet was added: "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."	To comply with new CSP template and reporting requirements.
Appendix B1 Definition of Adverse Events	Edit in bold made to the following sentence: "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 ~~considered~~ related to the medicinal product."	To comply with new CSP template
Appendix I Protocol Version History	Appendix added to keep a record of the edits that were made to produce CSP version 2.0 from CSP version 1.0 and CSP version 3.0 from CSP version 2.0.	To capture the history of amendments to the global CSP. The summary of changes from version 1.0 to 2.0 was missing in CSP version 2.0 and CSP version 3.0.

CAPA=corrective action and preventative action; CTIS=clinical trials information system; CTR=clinical trials regulation; EU=European Union; CCI ; IMP=investigational medicinal product.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Two Part Phase IIa/b Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Dose-ranging Study to Assess the Efficacy, Safety and Tolerability of the Combination of Zibotentan and Dapagliflozin, and Dapagliflozin Monotherapy Versus Placebo in Participants with Cirrhosis with Features of Portal Hypertension

Short Title: Zibotentan and Dapagliflozin combination, EvAluated in Liver cirrhosis (ZEAL study)

Rationale:

The mechanisms of action of zibotentan and dapagliflozin are different and the outcome of combined treatment is expected to be complementary. The main biological effects of zibotentan are expected to block endothelin-1 driven changes in intrahepatic resistance (including elements of portal vein and sinusoidal vasoconstriction, and increased hepatic arterial blood flow), decrease vascular stiffness, improve endothelial function, reduce hepatic inflammation and, in the long-term, 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.

The study is designed to evaluate the effects of the combination of zibotentan and dapagliflozin and dapagliflozin monotherapy versus placebo on the hepatic venous pressure gradient (HVPG) response in participants with cirrhosis with features of portal hypertension at 6 weeks of treatment. The primary efficacy objective for Part A is to evaluate the absolute change in HVPG at 6 weeks from baseline in participants treated with [redacted] mg zibotentan combined with 10 mg dapagliflozin versus placebo. The primary efficacy objective for Part B is to evaluate the absolute change in HVPG at 6 weeks from baseline in participants treated with [redacted], [redacted], or [redacted] mg zibotentan combined with 10 mg dapagliflozin and 10 mg dapagliflozin monotherapy versus placebo. Secondary objectives in both Parts A and B include the percentage change in HVPG, the proportion of participants achieving $\geq$ 20% decrease in HVPG or a reduction to or below 12 mmHg (Part B only), and assessment of body weight, body fat mass, and body water volumes, total dosage of loop-diuretic equivalents, and blood pressure.

Part A Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination versus placebo.	Absolute change in HVPG from baseline to Week 6.
Secondary	
To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination versus placebo.	Percent change in HVPG from baseline to Week 6.
To evaluate the proportion of participants achieving HVPG < 10 mmHg or a reduction in HVPG of ≥ 1.5 mmHg on zibotentan and dapagliflozin versus placebo.	HVPG response, where a responder is defined as HVPG < 10 mmHg or a reduction in HVPG of ≥ 1.5 mmHg from baseline to Week 6.
To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on change in body weight.	• Evaluation of change in body weight (kg) over time course of study[a]. • Percentage and absolute change from baseline in body weight at Week 6[b].
To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on total loop-diuretic equivalents use.	Percentage and absolute change in total dosage of loop-diuretic equivalents[c] use from baseline to Week 6.
To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on body water volumes and body fat mass.	• Change in total body water, extracellular water, and intracellular water volumes from baseline to Week 6. • Change in total body fat mass from baseline to Week 6.
To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on changes in office-based systolic and diastolic blood pressure.	Change in systolic and diastolic blood pressure from baseline to Week 6.
Safety	
To assess the safety and tolerability of zibotentan and dapagliflozin in combination versus placebo.	• AEs, SAEs, and DAEs. • AESIs CCI [redacted] • Vital signs. • Clinical laboratory tests. • ECG assessments.

[a] Home-based balance.
[b] Office balance.
[c] 40 mg furosemide = 1 mg bumetanide = 20 mg torsemide = 50 mg ethacrynic acid.

AE = adverse event; AESI = adverse event of special interest; CCI [redacted]; DAE = discontinuation due to adverse event; ECG = electrocardiogram; CCI [redacted]; HVPG = hepatic venous pressure gradient; SAE = serious adverse event; CCI [redacted].

Part B Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo.	Absolute change in HVPG from baseline to Week 6.
Secondary	
To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo.	Percentage change in HVPG from baseline to Week 6.
To evaluate the proportion of participants achieving at least 20% decrease in HVPG or a reduction to or below 12 mmHg in HVPG on zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo.	HVPG response, where a responder is defined as at least 20% decrease or a reduction to or below 12 mmHg in HVPG from baseline to Week 6.
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on change in body weight.	• Evaluation of change in body weight (kg) over time course of study[a]. • Percentage and absolute change from baseline in body weight at Week 6 and Week 16[b].
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on total loop-diuretic equivalents use.	Absolute change in total dosage of loop-diuretic equivalents[c] use from baseline to Week 6 and Week 16.
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on body water volumes and body fat mass.	• Change in total body water, extracellular water and intracellular water volumes from baseline to Week 6 and Week 16. • Change in total body fat mass from baseline to Week 6 and Week 16.
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on changes in office-based systolic and diastolic blood pressure.	Change in systolic and diastolic blood pressure from baseline to Week 6 and Week 16.
Safety	
To assess the safety and tolerability of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo.	• AEs, SAEs, and DAEs. • AESIs CCI [redacted] • Vital signs. • Clinical laboratory tests. • ECG assessments.

[a] Home-based balance.
[b] Office balance.
[c] 40 mg furosemide = 1 mg bumetanide = 20 mg torsemide = 50 mg ethacrynic acid.

AE = adverse event; AESI = adverse event of special interest; CCI [redacted]; DAE = discontinuation due to adverse event; ECG = electrocardiogram; CCI [redacted]; HVPG = hepatic venous pressure gradient; SAE = serious adverse event; CCI [redacted].

For exploratory objectives and endpoints, see Section 3.

Overall Design

This is a two-part, Phase IIa/b, multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study to assess the efficacy, safety, and tolerability of the combination of zibotentan and dapagliflozin, and dapagliflozin monotherapy versus placebo in participants with cirrhosis with features of portal hypertension.

Part A will assess the efficacy, safety, and tolerability of the combination of [redacted] mg zibotentan and 10 mg dapagliflozin versus placebo in participants with Child-Pugh A cirrhosis with features of portal hypertension and with no history of decompensation events. If the safety profile is determined to be acceptable at the conclusion of Part A, Part B will investigate efficacy, safety, and tolerability of [redacted], [redacted], or [redacted] mg zibotentan combined with 10 mg dapagliflozin and of 10 mg dapagliflozin monotherapy versus placebo in participants with cirrhosis with features of portal hypertension. Part B will include a broader range of Child-Pugh A and Child-Pugh B cirrhosis participants, including those with more severe disease, a history of decompensation events, or current ascites.

The study will be conducted in approximately 30 to 45 study centres in North America, Asia, and Europe.

Part A will include the following periods:

- **Screening Period**: up to [redacted] weeks; to confirm participant eligibility and collect baseline data (Visits 1 and 2). Before randomisation, baseline HVPG recording (Visit 2) must be of good enough quality as judged by central reader of HVPG, to randomise the participant.
- **Treatment Period**: 6 weeks; at Visit 3 (Day 1), participants will be randomised and will take the first dose of the study intervention. At each study visit during the treatment period (except at days of HVPG assessment and VCTE/Fibroscan assessment), participants will take the once-daily dose at the study centre.
- **Follow-up Period**: [redacted] weeks; participants will return to the study centre for follow-up assessments approximately [redacted] weeks after their last dose of study intervention.

Disclosure Statement: This is a parallel group, 2-arm study that is blinded to the participants, investigators, and sponsor.

Part B will include the following periods:

- **Screening Period**: up to [redacted] weeks; to confirm participant eligibility and collect baseline data (Visits 1 and 2). Before randomisation, baseline HVPG recording (Visit 2) must be

of good enough quality and the HVPG must be > 10 mmHg, as judged by central reader of HVPG, to randomise the participant. Participants with compensated cirrhosis must have a liver stiffness [redacted] and a platelet count < 150 x10^9 in order to do the Visit 2 HVPG examination.

- **Treatment Period**: 16 weeks; at Visit 3 (Day 1), participants will be randomised and will take the first dose of the study intervention. At each study visit during the treatment period (except at days of HVPG assessment and VCTE/Fibroscan assessment, if visit procedures are separated on different days), participants will take the once-daily dose at the study centre.
- **Follow-up Period**: [redacted] weeks; participants will return to the study centre for follow-up assessments approximately [redacted] weeks after their last dose of study intervention.

Disclosure Statement: This is a parallel group, 5-arm study that is blinded to the participants, investigators, and sponsor.

Number of Participants:

In Part A, it is planned to randomise approximately 30 participants to 2 groups of [redacted] participants per treatment group. With an estimated [redacted]% premature treatment discontinuation, this will allow for [redacted] evaluable participants per treatment group.

In Part B, it is planned to randomise approximately 165 participants to 5 treatment groups of [redacted] participants per treatment group. With an estimated [redacted]% premature treatment discontinuation, this will allow for [redacted] evaluable participants per treatment group with evaluable HVPG measurements at baseline and Week 6 (primary endpoint).

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.

Intervention Groups and Duration:

Part A:
Participants who meet the eligibility criteria and agree to participate will be randomised to one of the following 2 treatment groups ([redacted] participants per group).

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

The study intervention will be a once-daily dose of the assigned study intervention (oral

capsules and tablets) for 6 weeks, in addition to their standard of care therapy. Total study duration for participants in Part A will be approximately [redacted] weeks (including the screening and follow-up period).

Part B:

Participants who meet the eligibility criteria and agree to participate will be randomised to one of the following 5 treatment groups ([redacted] participants per group).

- Treatment Group 1: placebo matching zibotentan capsule + placebo matching dapagliflozin tablet.
- Treatment Group 2: placebo matching zibotentan capsule + dapagliflozin tablet 10 mg.
- Treatment Group 3: zibotentan capsule [redacted] mg + dapagliflozin tablet 10 mg.
- Treatment Group 4: zibotentan capsule [redacted] mg + dapagliflozin tablet 10 mg.
- Treatment Group 5: zibotentan capsule [redacted] mg + dapagliflozin tablet 10 mg.

Participants in Part B will be stratified by the [redacted] at the time of randomisation to ensure an approximate balance between treatment groups within each sub-population.

The study intervention will be a once-daily dose of the assigned study intervention (oral capsules and tablets) for 16 weeks, in addition to their standard of care therapy.

Total study duration for participants in Part B will be approximately [redacted] weeks (including the screening and follow-up period).

Data Monitoring Committee

A DMC will monitor ongoing safety/tolerability data and may recommend stopping further recruitment and/or treatment of a treatment group at any time. The DMC will conduct regular safety reviews.

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

Statistical Methods

The primary efficacy endpoint is the absolute change in HVPG from baseline to Week 6 for both Part A and Part B, and it will be analysed using ANCOVA method. The model will include the fixed categorical effects of stratification factor (Part B only), treatment and baseline HVPG measurement as a continuous covariate for the pairwise comparisons between the active treatment groups and the placebo group.

Sample size for Part A is not determined based on statistical justification. For Part B, with

1-sided type I error of [CCI]%, [CCI] HVPG-evaluable participants per group will provide [CCI]% power to detect a difference of -2 mmHg in absolute change in HVPG from baseline to Week 6 for the active treatment groups versus the placebo group, assuming a common SD for change in HVPG of 3 mmHg (Bai et al 2021). Accounting for an estimated [CCI]% premature treatment discontinuation, it is planned to randomise [CCI] participants in each of the 5 treatment groups to have [CCI] participants ([CCI] participants per treatment group) with evaluable HVPG measurements at baseline and Week 6. Approximately 165 participants will therefore be randomised in Part B of this study.

In Part B, HVPG response at Week 6, where a responder is defined as a ≥ 20% decrease in HVPG or a reduction to or below 12 mmHg in HVPG from baseline to Week 6, will be analysed via Mantel-Haenszel test, accounting for the stratification factor. Pairwise comparisons will be made for the active treatment groups the versus placebo group.

An interim analysis is planned to be performed by an unblinded study team when all randomised participants have completed at least 6 weeks of treatment or have passed the planned Week 6 visit (ie, Visit [CCI]).

The change in body weight, body water volumes, body fat mass, total dosage of loop-diuretic equivalents, and blood pressure in Parts A and B will be analysed using MMRM methodology. The analytic model will include the fixed categorical effects of stratification factor (Part B only), treatment, visit, and treatment-by-visit interaction and continuous covariates of the baseline measurements. An unstructured covariance structure will be used for the within-participant errors.

Figure 1 [CCI]



Note that baseline HVPG is performed before randomisation at Visit 2.
Dapa = dapagliflozin; HVPG = hepatic venous pressure gradient; N = number of participants; Zibo = zibotentan.

1.2 Schedule of Activities

Table 1 Part A Schedule of Activities

	Screening period		Treatment period					Follow-up/ early termination
			Randomisation	Visits				
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Week	CCI							
Study day								
Visit window (days)		± 4		± 2	± 2	± 2	± 5	± 3
Informed consent	X							
Inclusion/exclusion criteria	X	X	X					
Alcohol breath test	X		X				X	
Screen for drugs of abuse	X							
AUDIT questionnaire	X							
Enrolment in IRT/RTSM	X							
Randomisation in IRT/RTSM [m]			X					
Routine clinical procedures								
Demography and baseline characteristics (including smoking history and alcohol consumption)	X							
Medical/surgical history	X							
Physical examination	X		X	X [c]	X [c]	X [c]	X [c]	X

Table 1 Part A Schedule of Activities

	Screening period		Treatment period					Follow-up/ early termination
			Randomisation	Visits				
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Week	CCI							
Study day								
Visit window (days)		**± 4**		**± 2**	**± 2**	**± 2**	**± 5**	**± 3**
Concomitant Medication	X		X	X	X	X	X	X
Body weight	X		X	X	X	X	X	X
Height, BMI calculation	X							
ECG	X	X [q]	X (predose, 2 hours postdose)	X	X	X	X [q]	X
FSH (females only)	X [d]							
Pregnancy tests (females only; serum or urine)	X (serum)		X					X
Study intervention								
Study intervention dispensed			X			X		
Study intervention accountability (counting remaining tablets and capsules)				X	X	X	X	
Study intervention intake [n]			X	X	X	X	X	
Efficacy assessments								
HVPG [o]		X [b, j]					X [b, j]	
VCTE/Fibroscan [p]			X [b]				X [b]	

Table 1 Part A Schedule of Activities

	Screening period		Treatment period					Follow-up/ early termination
			Randomisation	Visits				
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Week	CCI [redacted]							
Study day								
Visit window (days)		± 4		± 2	± 2	± 2	± 5	± 3
Daily digital body weight measurement		X	Daily home measurement using a digital device from baseline to end of follow-up.					
Bioimpedance spectroscopy		X	X	X	X	X	X	X
Safety assessments								
Adverse event review [k]	X SAEs only	X SAEs only	X	X	X	X	X	X
Pulse and orthostatic test (supine and standing blood pressure) (Section 8.2.2)	X	X	X (predose, 60, 120, 240 minutes)	X	X	X	X	X
Body temperature	X	X	X	X	X	X	X	X
Safety clinical chemistry, electrolyte, coagulation and haematology	X	X	X [f]	X [f]	X [f]	X [f]	X [f]	X
HIV Serology	X							
Other safety test: CCI [redacted] CCI [redacted] CCI [redacted]	X	X	X [f]	X [f]	X [f]	X [f]	X [f]	X
PK assessments								
Pre-dose PK plasma sample [o]				X	X	X	X	X [g]
PK profile						X [h,i]		

Table 1 Part A Schedule of Activities

	Screening period		Treatment period					Follow-up/ early termination
			Randomisation	Visits				
Visit number	1	2	3	4	5	6	7	8
Week	CCI							
Study day								
Visit window (days)		± 4		± 2	± 2	± 2	± 5	± 3
Exploratory assessments								
MELD score calculation	X	X	X	X	X	X	X	X
CCI	CCI							
Child-Pugh score calculation	X	X	X	X	X	X	X	X
Non-fasting plasma/serum biomarkers (see Section 8.1.3)		X				X [f]	X [f]	X
Fasting plasma/serum biomarkers (see Section 8.1.3)		X				X [f]	X [f]	X
Spot urine: CCI CCI	X	X	X [f]	X [f]	X [f]	X [f]	X [f]	X
Spot urine: CCI CCI CCI		X				X [f]	X [f]	X
		X					X [f]	X
Collect and store serum and plasma samples for exploratory assessment of biomarkers		X				X [f]	X [f]	
Collect and store urine samples for exploratory assessment of biomarkers		X				X [f]	X [f]	
Optional genetic sampling (blood)			X					

[a] Visit can take place during up to 3 different days.

[b] Participants must be fasted for at least 8 hours prior to study intervention administration until the HVPG and VCTE/Fibroscan assessments have taken place. If the participant is on a non-selective beta-blocker to reduce HVPG, the morning dose should not be taken, but taken after the HVPG and Fibroscan assessments.

[c] Brief physical examination.

[d] Results need to be available before the baseline visit.

[e] To be assessed CCI after study intervention administration. Note that randomisation should not take place before first HVPG recording at the study centre has been reviewed and concluded to be of good quality. If assessment of HVPG recording conclude that it is not of good enough quality, the study participant will not be randomised. See Appendix G for a detailed HVPG manual.

[f] To be done predose, unless otherwise stated.

[g] PK sample at early termination visit only. If no dosing takes place, sample at any time during the study centre visit and document exact date and time.

[h] Samples for PK profile collected over 5 hours at the study centre. Sampling times: predose, 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 postdose; exact clock times need to be documented. See Section 5.3.1 for further details on meal restrictions.

[i] PK profile can be done at Visit 7 if not possible at Visit 6. 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.

[j] Participants should abstain from using nicotine-containing products from the night prior to and during the visit.

[k] 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.

[l] CCI .

[m] Note that randomisation should not take place before first HVPG recording at the study centre has been reviewed by central reader.

[n] Study intervention intake will take place at the study centre, except at visits of HVPG assessment and VCTE/Fibroscan assessment when participants may take study intervention at home, visit procedures are separated on different days (but if a PK profile is performed at the visit, study intervention intake will take place at the study centre).

[o] Pre-dose sample if dosing at the study centre; when the study intervention is taken at home, a post-dose sample may be taken at any time during the visit instead (record both exact dosing and sampling time).

[p] VCTE/Fibroscan may take place on a separate day (Days 5 to 1) and assessed CCI after study intervention administration. VCTE/Fibroscan assessment of spleen stiffness should only be done if technically feasible to complete an accurate spleen stiffness measurement and is up to the discretion of the investigator at the study centre.

[q] ECG assessment will be done during the HVPG procedure.

AUDIT = Alcohol use Disorders Identification Test; BMI = body mass index; ECG = electrocardiogram; CCI ; FSH = follicle-stimulating hormone; h = hour; CCI A1c; HVPG = hepatic venous pressure gradient; IRT = Interactive Response Technology; MELD = model for end-stage-liver disease; MRI = magnetic resonance imaging; PK = pharmacokinetics; RTSM = Randomisation and Trial Supply Management; SAE = serious adverse event; VCTE = vibration-controlled transient elastography.

Table 2 Part B Schedule of Activities

	Screening period		Treatment period								Follow-up/ early termination
			Randomisation	Visits							
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Week	CCI										
Study day											
Visit window (days)		**± 4**		**± 2**	**± 2**	**± 2**	**± 5**	**± 3**	**± 3**	**± 4**	**± 3**
Informed consent	X										
Inclusion/exclusion criteria	X	X	X								
Alcohol breath test	X		X				X			X	
Screen for drugs of abuse	X										
AUDIT questionnaire	X										
Enrolment in IRT/RTSM	X										
Randomisation in IRT/RTSM [o]			X								
Routine clinical procedures											
Demography and baseline characteristics (including smoking history and alcohol consumption)	X										
Medical/surgical history	X										
Physical examination	X		X	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X	X
Concomitant Medication	X		X	X	X	X	X	X	X	X	X

Table 2 Part B Schedule of Activities

	Screening period		Treatment period								Follow-up/ early termination
			Randomisation	Visits							
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Week	CCI										
Study day											
Visit window (days)		**± 4**		**± 2**	**± 2**	**± 2**	**± 5**	**± 3**	**± 3**	**± 4**	**± 3**
Body weight	X		X	X	X	X	X	X	X	X	X
Height, BMI calculation	X										
ECG	X	X [s]	X (predose, 2 hours postdose)	X	X	X	X [s]	X	X	X	X
FSH (females only)	X [d]										
Pregnancy tests (females only; serum)	X										
Study intervention											
Study intervention dispensed			X			X	X	X	X [k]		
Study intervention accountability (counting remaining tablets and capsules)				X	X	X	X	X	X	X	
Study intervention intake [p]			X	X	X	X	X	X	X	X	
Efficacy assessments											
HVPG [e]		X [b,l]					X [b,l]				
VCTE/Fibroscan [r]	X[b]						X[b]				

Table 2 Part B Schedule of Activities

	Screening period		Treatment period								Follow-up/ early termination
			Randomisation	Visits							
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Week	CCI										
Study day											
Visit window (days)		**± 4**		**± 2**	**± 2**	**± 2**	**± 5**	**± 3**	**± 3**	**± 4**	**± 3**
ECHO [g]	X (any time during screening period)										
Daily digital body weight measurement		X	Daily home measurement using a digital device from baseline to end of follow-up.								
Bioimpedance spectroscopy		X	X	X	X	X	X	X	X	X	X
Safety assessments											
Adverse event review [m]	X SAEs only	X SAEs only	X	X	X	X	X	X	X	X	X
Pulse and orthostatic test (supine and standing blood pressure) (Section 8.2.2)	X	X	X (predose, 60, 120, 180 minutes)	X	X	X	X	X	X	X	X
Body temperature	X	X	X	X	X	X	X	X	X	X	X

Table 2 Part B Schedule of Activities

	Screening period		Treatment period								Follow-up/ early termination
			Randomisation	Visits							
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Week	CCI										
Study day											
Visit window (days)		**± 4**		**± 2**	**± 2**	**± 2**	**± 5**	**± 3**	**± 3**	**± 4**	**± 3**
Safety clinical chemistry, electrolyte, coagulation and haematology	X	X	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X
HIV Serology	X										
Other safety test: CCI CCI CCI CCI	X	X	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X
PK assessments											
Pre-dose PK plasma sample [q]				X	X	X	X				X [h]
PK profile						X [i,j]					

Table 2 Part B Schedule of Activities

	Screening period		Treatment period								Follow-up/ early termination
			Randomisation	Visits							
Visit number	1	2	3	4	5	6	7	8	9	10	11
Week	CCI										
Study day											
Visit window (days)		± 4		± 2	± 2	± 2	± 5	± 3	± 3	± 4	± 3
Exploratory assessments											
MELD score calculation	X	X	X	X	X	X	X	X	X	X	X
CCI	CCI										
Child-Pugh score calculation	X	X	X	X	X	X	X	X	X	X	X
Non fasting-plasma/serum biomarkers (see Section 8.1.3)		X					X [f]			X [f]	X
Fasting plasma/serum biomarkers (see Section 8.1.3)		X					X [f]			X [f]	X
Spot Urine: CCI CCI		X	X [f]	X [f]			X [f]			X [f]	X
Spot urine: CCI CCI CCI		X					X [f]			X [f]	X
Fasting lipid profile[n]			X							X[f]	X
CCI	X		X							X	

Table 2 Part B Schedule of Activities

	Screening period		Treatment period								Follow-up/ early termination
			Randomisation	Visits							
Visit number	1	2	3	4	5	6	7	8	9	10	11
Week	CCI										
Study day											
Visit window (days)		± 4		± 2	± 2	± 2	± 5	± 3	± 3	± 4	± 3
Collect and store serum and plasma samples for exploratory assessment of biomarkers		X					X [f]			X [f]	
Collect and store urine samples for exploratory assessment of biomarkers		X					X [f]			X [f]	
Optional genetic sampling (blood)			X								

[a] Visit can take place during up to 3 different days.

[b] Participants are preferably fasted overnight (> 8 hours) prior to study intervention administration before the HVPG and VCTE/Fibroscan assessments have taken place. However, if the HVPG or VCTE procedure must take place late in the morning or close to lunchtime, the participant can be served a light meal 3 to 4 hours before the procedure. At Visit 1, the VCTE procedure should take place at least 3 to 4 hours after breakfast or another light meal. If the participant is on a non-selective beta-blocker to reduce HVPG, the morning dose should not be taken, but taken after the HVPG and Fibroscan assessments. Also, diuretics are to be avoided before the HVPG procedure.

[c] Brief physical examination.

[d] Results need to be available before the baseline visit.

[e] To be assessed CCI after study intervention administration. Note that randomisation should not take place before first HVPG recording at the study centre has been reviewed and concluded to be of good quality and with a value of > 10 mmHg. If assessment of HVPG recording conclude that it is not of good enough quality or ≤ 10 mmHg, the study participant will not be randomised. See Appendix G for a detailed HVPG manual.

[f] To be done predose, unless otherwise stated.

[g] Only if historical data in the prior 12 months is not available.

[h] PK sample at early termination visit only. If no dosing takes place, sample at any time during the study centre visit and document exact date and time.

[i] Samples for PK profile collected over 5 hours at the study centre. Sampling times: predose, 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 postdose; exact clock times need to be documented. See Section 5.3.1 for further details on meal restrictions.

[j] PK profile can be done at Visit 5 if not possible at Visit 6. 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.

[k] Two bottles of study intervention to be dispensed.

[l] Participants should abstain from using nicotine-containing products from the night prior to and during the visit.

[m] 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.

[n] CCI .

[o] Note that randomisation should not take place before first HVPG recording at the study centre has been reviewed by central reader.

[p] Study intervention intake will take place at the study centre, except at visits of HVPG assessment (Visit 7) and VCTE/Fibroscan assessment (Visits 7) when participants may take study intervention at home, visit procedures are separated on different days (but if a PK profile is performed at the visit, study intervention intake will take place at the study centre).

[q] Pre-dose sample if dosing at the study centre; when the study intervention is taken at home, a post-dose sample may be taken at any time during the visit instead (record both exact dosing and sampling time).

[r] VCTE/Fibroscan may take place on a separate day and assessed CCI after study intervention administration at Visit 7. VCTE/Fibroscan assessment of spleen stiffness should only be done if technically feasible to complete an accurate spleen stiffness measurement and is up to the discretion of the investigator at the study centre. Liver stiffness at Visit 1 should be CCI and platelet count < 150 x10^9 among participants with compensated cirrhosis before an HVPG examination can be done at Visit 2.

[s] It is recommended to perform an ECG during the HVPG examination since there is a small risk of arrythmia during the procedure.

AUDIT = Alcohol use Disorders Identification Test; BMI = body mass index; ECG = electrocardiogram; ECHO = echocardiogram; CCI ; FSH = follicle-stimulating hormone; h = hour; CCI ; HVPG = hepatic venous pressure gradient; IRT = Interactive Response Technology; MELD = model for end-stage-liver disease; MRI = magnetic resonance imaging; PK = pharmacokinetics; RTSM = Randomisation and Trial Supply Management; SAE = serious adverse event; VCTE = vibration-controlled transient elastography.

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

Zibotentan is a selective endothelin (ET_A) receptor antagonist. The main biological effect of zibotentan in cirrhosis is antagonism of ET-1 mediated vasoconstriction in the portal vasculature and intrahepatic stellate cells, leading to a reduction in portal venous pressure in established portal hypertension. Studies of beta blockers in cirrhosis have established that reduced portal hypertension improves outcomes and reduces the risk of variceal haemorrhage and perhaps death. Zibotentan has potential to provide further benefit through its effect on hepatic vascular resistance (reduced) and improved endothelial function, and may also exhibit, in the longer term, anti-fibrotic effects in the liver, which would be expected to improve overall liver function. However, as a chronic monotherapy, the benefit: risk profile for zibotentan in cirrhosis may be unfavourable given the potential for ET-1 antagonism to cause fluid retention in some participants.

Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, was originally developed to improve glycaemic control in patients with T2DM and is approved for the treatment of T2DM in over 100 countries worldwide. Subsequent outcome studies have demonstrated that dapagliflozin is effective as a treatment for HF with reduced ejection fraction (DAPA-HF) and chronic kidney disease (DAPA-CKD) in patients with and without diabetes. As a result, many product labels also include indications for treatment of HF and CKD. SGLT2 inhibition blocks glucose and sodium reabsorption in the proximal tubule of the kidney leading to an osmotic diuresis without subsequent hyponatraemia or hyperkalaemia, while counteracting the effects of renin-angiotensin-aldosterone system activation. This mode of action has potential to be a useful therapy in cirrhotic ascites in reducing fluid overload, but unlike existing diuretic therapies, an SGLT2 inhibitor would be less likely to exacerbate pre-existing hyponatraemia or provoke renal impairment.

Dapagliflozin is expected to have limited effect on portal blood pressure, in contrast to zibotentan. In this study, dapagliflozin's main role is to mitigate any zibotentan mediated effects on sodium and water retention. In patients with pre-existing ascites, dapagliflozin may

have a role in improving symptoms, and in some participants, it may prevent the development of ascites over time. The main objectives of this Phase IIa/b study are to demonstrate the effect of zibotentan and dapagliflozin on HVPG and the safety and tolerability of this treatment in this population.

2.2 Disease Background

Patients with cirrhosis with features of portal hypertension have limited treatment options and significant risk of decompensation and death with limited pharmacological treatment options.

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 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 clinical complication. In decompensated patients, the liver is unable to perform vital metabolic, synthetic and storage functions (Tsochatzis et al 2014). 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 (Romanelli et al 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 Cirrhosis Collaborators 2020).

Portal hypertension is a major complication of chronic liver disease. The primary cause of portal hypertension in cirrhosis is an increase in intrahepatic vascular resistance due to structural changes associated with fibrosis and increased vascular tone in the hepatic microcirculation (Iwakiri 2014). As portal hypertension develops, the formation of collateral vessels and arterial vasodilation progress, which results in increased blood flow to the portal circulation (Iwakiri 2014). Eventually, a hyperdynamic circulatory syndrome develops, leading to oesophageal varices and/or ascites (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, antiviral 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 cirrhosis with portal hypertension (Gunarathne et al 2020). Accordingly, there is an enormous unmet need for new treatments in patients with cirrhosis with features of portal hypertension. 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 developed for prostate cancer, but 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. A study of zibotentan and dapagliflozin in combination in chronic kidney disease (ZENITH-CKD, NCT04724837), investigator-sponsored studies with zibotentan in microvascular angina (PRIZE; NCT04097314) (10 mg, 8 weeks; n = 356), and a Phase II study with zibotentan in systemic scleroderma CKD- ZEBRA (NCT02047708) (10 mg; 52 weeks; n = 23) have all now 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 SGLT2i (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 is currently being studied in patients with heart failure with preserved ejection fraction (DELIVER, NCT03619213) and has recently completed a study 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 generally safe and well tolerated. The potential and identified risks of dapagliflozin treatment have been well characterised through the dapagliflozin clinical development programme 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, diabetic ketoacidosis was commonly seen in T1DM patients treated with dapagliflozin but was rare in clinical trials with T2DM patients.

The adverse clinical effects of zibotentan observed in healthy volunteers and oncology populations were largely due to its pharmacologically mediated effects on ET receptor antagonism resulting in vasodilation: 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 leads to a reduction in the concentration of the cellular elements of blood: reduction in Hb, anaemia. Reduction in Hb tends to develop within a month of commencing the drug and in most patients is mild (CTC Grade 1/2), nonprogressive and tends to reverse on stopping 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 castration-resistant prostate cancer 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.

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

Table 3 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 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 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.	Patients with T1DM are excluded from the study (see exclusion criteria). DKA including euglycemic DKA have been reported with use of dapagliflozin. Consider temporary interrupting study treatment if DKA is suspected. The patient should be promptly evaluated. If diabetic ketoacidosis is confirmed, study intervention should be discontinued permanently. If diabetic ketoacidosis is not confirmed, restart of study intervention should be considered (see Section 7.1).

Table 3 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	In clinical trials in subjects with heart failure (DAPA-HF) or chronic kidney disease (DAPA-CKD) with and without T2DM, events of ketoacidosis were only observed in subjects 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. Type 1 diabetes mellitus: In the 2 placebo-controlled clinical studies of dapagliflozin in T1DM, patients were advised to monitor blood ketones in case of suspected symptoms of DKA and seek medical advice/attention if their self-measured blood ketone reading was ≥ 0.6 mmol/L. In the pooled 24-week data, events of DKA were reported in 11 (1.9%) patients in the dapagliflozin 10 mg group and 3 (0.6%) patients in the placebo group. DKA events occurred evenly distributed over the study period. Inadequate insulin doses (missed insulin dose or insulin pump failure) were the most common precipitating factors. Three of the 11 patients with DKA in the dapagliflozin 10 mg group had blood glucose in the euglycemic range (< 14 mmol/L or 250 mg/dL). Patients with DKA events responded to conventional treatment for DKA. In addition, there have been post marketing reports of ketoacidosis, including diabetic ketoacidosis, in patients with T1DM and T2DM taking dapagliflozin or other SGLT2i.	
Zibotentan (in context of dapagliflozin combination treatment)		
Fluid retention	Fluid retention is a class effect of ERAs. Peripheral oedema has been very commonly reported in patients receiving zibotentan in previous oncology trials 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 [redacted]

Table 3 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		Monitoring of CCI and CCI will be performed.
Heart failure	ERAs 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 adverse events 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.	Patients 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 CCI Monitoring of CCI will be performed.
Hypotension	The adverse clinical effect of hypotension is largely due to zibotentan's pharmacologically mediated effects of ET receptor antagonism resulting in vasodilation. Hypotension (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 an osmotic diuresis, which may lead to reduced blood pressure.	CCI according to the SoA (Table 1 and Table 2). Patients with CCI are excluded from the study (Section 5.2). Discontinuation from study intervention if criteria for hypotension are met (see criteria in Section 7.1). CCI
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 1 mg/kg/day and above, consistent with other ERAs (zibotentan IB Section 4.3.9.12). 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.	WOCBP must not be included in the study, (inclusion criterion 7). For restrictions for male participants, see Sections 5.1, 5.3.4, and 5.3.5. Participants must not donate or bank blood (both male and females) or sperm, see Section 5.3.5 and 5.3.6. Negative pregnancy test at the time of enrolment (serum). 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 criteria, Section 7.1.

Table 3 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	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.	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.
Other		
COVID-19 pandemic risks	There is currently an outbreak of respiratory disease (COVID-19) caused by a novel SARS-CoV-2, for which the WHO declared a pandemic situation on 12 March 2020. The mechanism of action of either zibotentan and/or dapagliflozin is unlikely to impact the course of infection with SARS-CoV-2. Therefore, the risk to participants of exposure to SARS-CoV-2 or of suffering from COVID-19 is expected to be similar to the background population with the same co-morbidities as those in the study, in particular cirrhosis. The risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (eg, during commuting to the study centre) and have additional human contact (eg, with study centre staff and other participants of the clinical study).	Exclusion of participants with symptoms of COVID-19 infection or a recent positive test in the 14 days prior to enrolment in the study. Additional COVID risk mitigation measures are detailed in Appendix F.

AE = adverse event; CCI ; CKD = chronic kidney disease; COVID-19 = coronavirus disease 2019; CRPC = castration-resistant prostate cancer; DAPA = dapagliflozin; DKA = diabetic ketoacidosis; ECG = electrocardiogram; ERA, endothelin receptor antagonist; ET = endothelin; CCI ; HF = heart failure; NYHA = New York Heart Association; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; WHO = World Health Organization.

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 local 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 endothelin A

receptor antagonist BQ123 (Zipprich et al 2021) in patients with cirrhosis, local hepatic artery infusion of BQ123 resulted in a significant decrease in HVPG with no effect on systemic haemodynamic parameters. The same report demonstrated that the effect of a single oral dose of ambrisentan resulted in a significant decrease in HVPG. In that 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 SGLT2i in Cirrhosis and Features of Portal Hypertension

Several studies have evaluated the impact of SGLT2i on liver biomarkers in patients with T2DM, NASH and NAFLD. A review of results from 7 studies and 11 cohort studies (Hsiang et al 2020) demonstrated consistent decreases in liver aminotransferase levels, liver fat, and FIB-4 index after treatment with an SGLTi. A recently published pilot study indicated that 72 weeks of treatment with an SGLT2i 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 series of case studies evaluated the effect of SGLT2i on body weight in patients with ascites (Gordon-Montalvo et al 2020). All 3 patients showed a decrease in body weight ranging between 4.9 kg (7.8%) and 11.2 kg (13.8%) across 6 months indicative of decreased ascites and fluid overload whilst hyponatraemia was corrected or sodium levels unchanged and no hyperkalaemia observed. SGLT2i have also been shown to improve endothelial function and decrease vascular stiffness which may bring additional benefit to the portal hypertension population.

2.3.4.3 Possible Complementary Actions of Zibotentan and Dapagliflozin

The combination of zibotentan and dapagliflozin is expected to target two distinct steps in the pathogenesis of cirrhotic disease: portal hypertension and ascites accumulation. 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 and perhaps death. Fluid retention is a class effect of ERAs, which may limit their potential use as monotherapy in cirrhosis. Clinical data and scientific rationale support a zibotentan/dapagliflozin fixed dose combination that combines two different and complementary mechanisms of action. The reduction in portal hypertension afforded by zibotentan and dapagliflozin also 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 AND ENDPOINTS

Table 4 Part A Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination versus placebo.	Absolute change in HVPG from baseline to Week 6.
Secondary	
To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination versus placebo.	Percent change in HVPG from baseline to Week 6.
To evaluate the proportion of participants achieving HVPG < 10 mmHg or a reduction in HVPG of ≥ 1.5 mmHg on zibotentan and dapagliflozin versus placebo.	• HVPG response, where a responder is defined as HVPG < 10 mmHg or a reduction in HVPG of ≥ 1.5 mmHg from baseline to Week 6.
To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on change in body weight.	• Evaluation of change in body weight (kg) over time course of study[a]. • Percentage and absolute change from baseline in body weight at Week 6[b].
To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on total loop-diuretic equivalents use.	Absolute change in total dosage of loop-diuretic equivalents[c] use from baseline to Week 6.
To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on body water volumes and body fat mass.	• Change in total body water, extracellular water, and intracellular water volumes from baseline to Week 6. • Change in total body fat mass from baseline to Week 6.
To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on changes in office-based systolic and diastolic blood pressure.	Change in systolic and diastolic blood pressure from baseline to Week 6.
Exploratory	
To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on spleen stiffness as measured with VCTE/Fibroscan[d].	Percentage and absolute change in spleen stiffness from baseline to Week 6.
To assess the plasma exposure of zibotentan and dapagliflozin in the participant population.	Plasma concentrations of zibotentan and dapagliflozin per treatment, visit and timepoint.
To determine the effect of zibotentan and dapagliflozin in combination versus placebo on CCI.	Change in CCI from baseline to Week 1 and Week 6.
To assess the effect of zibotentan and dapagliflozin in combination versus placebo on plasma/serum CCI	Evaluation of changes in blood and urine biomarkers across time course of the study.

Table 4 Part A Objectives and Endpoints

Objectives	Endpoints
CCI [redacted]	
To collect and store plasma, serum and urine samples for potential exploratory research aimed at exploring biomarkers involved in PK, PD, safety and tolerability related to zibotentan and dapagliflozin in combination versus placebo or related to liver diseases.	Evaluation of changes in blood and urine biomarkers across time course of the study.
Collect and store blood samples for genetic research (according to each country's local and ethical procedures) (optional).	Exploratory research into genes/genetic variation that may influence response to treatment.
Safety	
To assess the safety and tolerability of zibotentan and dapagliflozin in combination versus placebo.	• AEs, SAEs, and DAEs. • CCI [redacted] • Vital signs. • Clinical laboratory tests. • ECG assessments.

[a] Home-based balance.
[b] Office balance.
[c] 40 mg furosemide = 1 mg bumetanide = 20 mg torsemide = 50 mg ethacrynic acid.
[d] VCTE/Fibroscan assessment of spleen stiffness should only be done if technically feasible to complete an accurate spleen stiffness measurement and is up to the discretion of the investigator at the study centre.

AE = adverse event; AESI = adverse event of special interest; CCI [redacted]
CCI [redacted]
DAE = discontinuation due to adverse event; ECG = electrocardiogram; CCI [redacted]
rate; CCI [redacted]
CCI [redacted] CCI [redacted] CCI [redacted]; HE = hepatic encephalopathy; HVPG = hepatic venous pressure gradient;
PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; CCI [redacted];
VCTE = vibration-controlled transient elastography.

Table 5 Part B Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo.	Absolute change in HVPG from baseline to Week 6.
Secondary	
To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo.	Percentage change in HVPG from baseline to Week 6.
To evaluate the proportion of participants achieving at least 20% decrease in HVPG or a reduction to or below 12 mmHg in HVPG on zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo.	HVPG response, where a responder is defined as at least 20% decrease or a reduction to or below 12 mmHg in HVPG from baseline to Week 6.
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on change in body weight.	• Evaluation of change in body weight (kg) over time course of study[a]. • Percentage and absolute change from baseline in body weight at Week 6 and Week 16[b].
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on total loop-diuretic equivalents use.	Absolute change in total dosage of loop-diuretic equivalents[c] use from baseline to Week 6 and Week 16.
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on body water volumes and body fat mass.	• Change in total body water, extracellular water and intracellular water volumes from baseline to Week 6 and Week 16. • Change in total body fat mass from baseline to Week 6 and Week 16.
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on changes in office-based systolic and diastolic blood pressure.	Change in systolic and diastolic blood pressure from baseline to Week 6 and Week 16.
Exploratory	
To evaluate the proportion of participants who exhibit 10%, 20%, and 30% decrease in HVPG in response to zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo.	HVPG response, where a responder is defined as a 10%, 20% and 30% decrease in HVPG.
To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination versus dapagliflozin monotherapy.	Absolute change in HVPG from baseline to Week 6.
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on liver and/or spleen stiffness as measured with VCTE/Fibroscan[d].	Percentage and absolute change in liver and/or spleen stiffness from baseline to Week 6.

Table 5 Part B Objectives and Endpoints

Objectives	Endpoints
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on CCI and CCI CCI	• Percentage and absolute change from baseline in AST and ALT from baseline to Week 6 and Week 16. • Absolute change from baseline in CCI ratio, CCI , and CCI from baseline to Week 6 and Week 16. • Absolute change from baseline in MELD score from baseline to Week 6 and Week 16.
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on proportion of participants experiencing a CCI defined as any of the following: CCI	Composite of time to first event of: CCI
To assess the plasma exposure of zibotentan and dapagliflozin in the participant population.	Plasma concentrations of zibotentan and dapagliflozin per treatment, visit and timepoint.
To determine the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on CCI .	Change in CCI from baseline to Week 1, Week 3, Week 6 and Week 16.
To assess the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on plasma/serum CCI	Evaluation of changes in blood and urine biomarkers across time course of the study.
To collect and store plasma, serum and urine samples for potential exploratory research aimed at exploring biomarkers involved in PK, PD, safety and tolerability related to zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo or related to liver diseases.	Evaluation of changes in blood and urine biomarkers across time course of the study.

Table 5 Part B Objectives and Endpoints

Objectives	Endpoints
Collect and store blood samples for genetic research (according to each country's local and ethical procedures) (optional).	Exploratory research into genes/genetic variation that may influence response to treatment.
Safety	
To assess the safety and tolerability of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo.	• AEs, SAEs, and DAEs. • CCI • Vital signs. • Clinical laboratory tests. • ECG assessments.

[a] Home-based balance.
[b] Office balance.
[c] 40 mg furosemide = 1 mg bumetanide = 20 mg torsemide = 50 mg ethacrynic acid.
[d] VCTE/Fibroscan assessment of spleen stiffness should only be done if technically feasible to complete an accurate spleen stiffness measurement and is up to the discretion of the investigator at the study centre. Spleen stiffness should only be measured if an appropriate measuring device (Fibroscan Model 630) is available at site.
[e] CCI
[f] Clinical grading of ascites:
Grade 1; "mild" ascites, defined as ascites only detectable by imaging/ultrasound examination.
Grade 2; "moderate" ascites, defined as ascites detected by moderate symmetrical distension of abdomen.
Grade 3; "large" ascites, defined as obvious or gross ascites that manifests as marked abdominal distension.
[g] West Haven criteria on HE:
No HE.
Minimal HE; psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change.
Grade 1; trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction, altered sleep rhythm.
Grade 2; lethargy or apathy, disorientation for time, obvious personality change, inappropriate behaviour, dyspraxia, asterixis.
Grade 3; somnolence to semi-stupor, responsive to stimuli, confused, gross disorientation, bizarre behaviour.
Grade 4; coma.

AE = adverse event; AESI = adverse event of special interest; CCI CCI CCI DAE = discontinuation due to adverse event; ECG = electrocardiogram; CCI CCI CCI CCI HE = hepatic encephalopathy; HVPG = hepatic venous pressure gradient; MELD = model for end-stage liver disease; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; CCI ; VCTE = vibration-controlled transient elastography.

4 STUDY DESIGN

4.1 Overall Design

This is a two-part, Phase IIa/b, multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study to assess the efficacy, safety, and tolerability of the combination of zibotentan and dapagliflozin, and dapagliflozin monotherapy versus placebo in participants with cirrhosis with features of portal hypertension.

The study will be conducted in approximately 30 to 45 study centres in North America, Asia, and Europe.

Part A will assess the efficacy, safety, and tolerability of the combination of [redacted] mg zibotentan and 10 mg dapagliflozin versus placebo in participants with Child-Pugh A cirrhosis with features of portal hypertension and with no history of decompensation events. If the safety and tolerability profile is determined to be acceptable at the conclusion of Part A, Part B will investigate efficacy, safety, and tolerability of the combination of [redacted], [redacted], or [redacted] mg zibotentan and 10 mg dapagliflozin and of 10 mg dapagliflozin monotherapy versus placebo in participants with cirrhosis with features of portal hypertension. Part B will include a broader range of participants with more severe disease including Child-Pugh B and participants with a history of decompensation events or current ascites.

Part A and Part B will consist of the following periods:

Screening Period: up to [redacted] weeks; to confirm participant eligibility and collect baseline data on vital signs; clinical chemistry, haematology, and urinalysis; and ECHO (for Part B only). Participants will visit the study centre twice (Visits 1 and 2). At Visit 2, eligibility criteria will be assessed, safety laboratory data reverified and participants will be provided digital medical devices to measure their body weight starting before the randomisation visit and every day at home. At Visit 1, liver stiffness must be [redacted] and platelet count $< 150 \times 10^9$ in participants with compensated cirrhosis in order to perform the HVPG examination at Visit 2. At Visit 2, baseline HVPG recording will be done and must be of good enough quality (and with HVPG > 10 mmHg in Part B) as judged by central reader of HVPG, in order to randomise the participant.

Treatment Period: during the treatment period (6 weeks in Part A, 16 weeks in Part B), participants will visit the study centre 5 (Part A) or 8 (Part B) times. At Visit 3, participants will be randomised and will take the first dose of the study intervention. At each study visit during the treatment period (except at days of HVPG assessment and VCTE/Fibroscan assessment, if visit procedures are separated on different days), participants will take the once-daily dose at the study centre and will provide a predose blood sample for PK analysis and other laboratory samples before intake of study intervention. At Part A Visit 6 (or Visit 7) and Part B Visit 6 (or Visit 5), participants will provide pre- and post-dose blood samples for

PK analysis over about 5 hours.

Follow-up Period: [redacted] weeks; participants will not be taking the study intervention and will return to the study centre for follow-up assessments approximately [redacted] weeks after their last dose of study intervention.

In Part A, it is planned to randomise approximately 30 participants to 2 groups of [redacted] participants per treatment group. With an estimated [redacted]% premature treatment discontinuation, this will allow for [redacted] evaluable participants per treatment group.

In Part B, it is planned to randomise approximately 165 participants to 5 treatment groups of [redacted] participants per treatment group. With an estimated [redacted]% premature treatment discontinuation, this will allow for [redacted] evaluable participants per treatment group with evaluable HVPG measurements at baseline and Week 6 (primary endpoint).

The study intervention will be a once-daily dose of the assigned study intervention (oral capsules and tablets) during the treatment period (6 weeks for Part A, 16 weeks for Part B), in addition to their standard of care therapy. Total study duration for participants (including the screening and follow-up period) will be approximately [redacted] weeks for Part A and [redacted] weeks for Part B.

In Part A, participants who meet the eligibility criteria and agree to participate will be randomised to one of the following 2 treatment groups ([redacted] participants per group).

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

In Part B, participants who meet the eligibility criteria and agree to participate will be randomised to one of the following 5 treatment groups ([redacted] participants per group).

- Treatment Group 1: placebo matching zibotentan capsule + placebo matching dapagliflozin tablet.
- Treatment Group 2: placebo matching zibotentan capsule + dapagliflozin tablet 10 mg.
- Treatment Group 3: zibotentan capsule [redacted]mg + dapagliflozin tablet 10 mg.
- Treatment Group 4: zibotentan capsule [redacted] mg + dapagliflozin tablet 10 mg.
- Treatment Group 5: zibotentan capsule [redacted]mg + dapagliflozin tablet 10 mg.

Participants in Part B will be stratified by the [redacted] at the time of randomisation to ensure an approximate balance between treatment groups within each sub-population. For details on randomisation and stratification, refer to

Section 6.3.

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. The main biological effects of zibotentan are expected to block endothelin-1 driven changes in intrahepatic resistance (including elements of portal vein and sinusoidal vasoconstriction, and increased hepatic arterial blood flow), decrease vascular stiffness, improve endothelial function, reduce hepatic inflammation and, in the long-term, 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.

4.3 Justification for Dose

Study participants will receive either:

Part A:

- placebo matching zibotentan capsules + placebo matching dapagliflozin tablets.
- zibotentan [redacted] mg + dapagliflozin 10 mg.

Part B:

- placebo matching zibotentan capsules + placebo matching dapagliflozin tablets.
- placebo matching zibotentan capsule + dapagliflozin 10 mg monotherapy.
- zibotentan [redacted] mg + dapagliflozin 10 mg.
- zibotentan [redacted] mg + dapagliflozin 10 mg.
- zibotentan [redacted] mg + dapagliflozin 10 mg.

In the previous Phase III programme in oncology, zibotentan 10 mg was used and extensive safety data are available for this dose. Based on the zibotentan hepatic impairment study (Tomkinson et al 2011), exposure is expected to be 1.45 times higher in participants with moderate hepatic impairment compared to healthy control participants. The planned study will include participants with mild or moderate hepatic impairment and with normal renal function or mild renal impairment (MELD score < 15 and eGFR [redacted]) and dosing will be adjusted as described below.

Part A of this study is designed to give proof of concept. Participants with less severe disease, defined as Child-Pugh A and no history of decompensation events, will receive [redacted] mg zibotentan in combination with 10 mg dapagliflozin or placebo. If the combination therapy is

determined to be safe in these participants, then Part B will commence and will also include participants with Child-Pugh B, a history of decompensation events, or ascites. In Part B, [redacted] mg, [redacted] mg, and [redacted] mg zibotentan will be studied in combination with dapagliflozin, [redacted] representing [redacted], [redacted] and [redacted] of the zibotentan dose in the previous oncology programme.

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). Doses of dapagliflozin 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 with features of portal hypertension (Dapagliflozin Investigator's Brochure).

4.4 End of Study Definition

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

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

A participant is considered to have completed the study if they have completed all phases of the study including the last scheduled procedure shown in the SoA.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

Age (all participants)

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 (Part A only)

2 **Part A** participants who have the following:

(a) Clinical and/or histological diagnosis of cirrhosis with either (i) features of portal hypertension or (ii) CCI [redacted]

(b) MELD score < 15.

(c) Child-Pugh score ≤ 6.

(d) No clinically evident ascites.

(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.

(f) HVPG recording of good enough quality as judged by a central reader.

Type of Participant and Disease Characteristics (Part B only)

3 **Part B** participants who have the following:

(a) Clinical and/or histological diagnosis of cirrhosis and either history of decompensation or compensated cirrhosis with signs of clinically significant portal hypertension such as varices at endoscopy **or** collaterals at imaging (detected within the last 12 months prior to screening) **or** a liver stiffness measurement using vibration-controlled elastography of either CCI [redacted] together with platelet count < 150 $x10^9$ at Screening, Visit 1.

(b) HVPG recording of good enough quality and HVPG > 10 mmHg, as judged by a central reader at Screening, Visit 2.

(c) MELD score < 15.

(d) Child-Pugh score < 10.

(e) No ascites or ascites up to grade 2 without change in diuretic treatment within the last month prior to first dose and no paracentesis within the last month or planned paracentesis in the next 4 months at screening.

(f) 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 (all participants)

4 No current or prior (within 1 month of enrolment) medical treatment with an SGLT2 inhibitor or ERAs.

5 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

6 Males or Females of nonchildbearing potential.

a) **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 study participants must not donate or bank sperm during the same period (see Sections 5.3.5 and 8.3.10.2). 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 (see Section 5.3.4).

b) **Female participants must be of nonchildbearing potential** confirmed at screening by fulfilling one of the following criteria:

i. 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 postmenopausal range by central laboratory (note: the postmenopausal range must be checked against the specific FSH assay used). In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to define postmenopausal 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.

ii. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation.

Must have a negative pregnancy test at screening and must not be lactating.

Informed Consent (all participants)

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

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

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

5.2 Exclusion Criteria

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

Medical Conditions (all participants)

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 Liver cirrhosis caused by chronic cholestatic liver disease.

3 ALT or AST $\geq$ 150 U/L and/or total bilirubin $\geq$ 3 × ULN.

4 Any history of hepatocellular carcinoma.

5 Any history of portal venous thrombosis.

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

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

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

9 Ongoing or history of significant use of alcohol expected to preclude correct adherence to study procedures.

10 Active treatment for HCV within the last 1 year or HBV antiviral therapy for less than 1 year.

11 Active urinary tract infection or genital infection.

12 Uncontrolled diabetes mellitus (CCI [redacted]).

13 Participants with T1DM.

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

15 eGFR CCI [redacted]

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

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

18 Participants treated with strong CCI [redacted] of study intervention administration (Table 7); this CCI [redacted]

19 History or ongoing allergy/hypersensitivity, as judged by the investigator, to SGLT2i (eg, dapagliflozin, empagliflozin), zibotentan or other ERAs (eg, ambrisentan, atrasentan, bosentan), or any of the excipients of the products.

20 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, for example:

(a) Anaemia defined as haemoglobin (Hb) levels < 100 g/L or 10 g/dL.

(b) Wernicke's encephalopathy or Korsakoff's syndrome.

(c) History of HIV.

21 Any of the following regarding COVID19:

(a) Symptoms of COVID-19 infection or a recent positive test in the 14 days prior to enrolment in the study.

(b) Participants hospitalised with COVID-19 infection within the last 3 months who required in hospital medical care (oxygen therapy, mechanical ventilation, intensive care unit admission, etc.).

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

Medical Conditions (Part A only)

23 INR > 1.5.

24 Serum/plasma levels of albumin ≤ 35 g/L.

25 Platelet count < 75×10^9/L.

26 History of ascites.

27 History of hepatic hydrothorax.

28 History of portopulmonary syndrome.

29 History of hepatic encephalopathy.

30 History of variceal haemorrhage.

31 History of acute kidney injury.

32 History of heart failure, including high output heart failure (eg, due to hyperthyroidism or Paget's disease).

Medical Conditions (Part B only)

33 INR > 1.7.

34 Serum/plasma levels of albumin ≤ 28 g/L.

35 Platelet count < 50 × /10^9L.

36 Acute kidney injury within 3 months of screening.

37 History of encephalopathy of West Haven grade 2 or higher within 6 months prior to screening.

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

39 NYHA functional heart failure class III or IV or 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.

40 Heart failure due to cardiomyopathies that would primarily require specific other treatment: eg, cardiomyopathy due to pericardial disease, amyloidosis or other infiltrative diseases, cardiomyopathy related to congenital heart disease, primary hypertrophic cardiomyopathy, cardiomyopathy related to toxic or infective conditions (ie, chemotherapy, infective myocarditis, septic cardiomyopathy).

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

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

Prior/Concurrent Clinical Study Experience (all participants)

43 Participation in another clinical study with an investigational product administered in the last 3 months prior to randomisation.

Other Exclusions (all participants)

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

45 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.

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

47 Hypersensitivity to contrast agents.

48 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 (all participants)

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

49 Previous allogeneic bone marrow transplant.

50 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.

On the days of the HVPG and VCTE/Fibroscan assessments, participants have preferably fasted overnight (≥ 8 hours) prior to study intervention administration until the assessments have taken place. However, if the HVPG or VCTE procedure must take place late in the morning or close to lunchtime the participant can be served a light meal 3 to 4 hours before the procedure. At Visit 1, the VCTE procedure should take place at least 3 to 4 hours after breakfast or another light meal.

On the day of the PK profile, 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 will be asked not to CCI [redacted] during the course of the study.

5.3.2 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.

Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted from the night prior to and during Visit 2 and Visit 7.

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 see Section 5.1).

Male participants

It is important that WOCBP, 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:

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

Periodic abstinence (eg, calendar, ovulation, symptom-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 should 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 Blood Donation

Patients should not donate blood during therapy and for 1 month following discontinuation of the IMP because of the potential risk to the foetus of a pregnant transfusion recipient.

5.3.7 Pregnancy

Women of childbearing potential are not eligible for inclusion 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. The investigator should also be notified of any pregnancy occurring during the study but confirmed after completion of the study. 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.

5.4 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 analyst criteria for participation in this study (screen failure) may have these parameters tested up to 2 times during the screening period. Participants may be re-screened once, at the discretion of the investigator, if they have reason to believe they may be eligible. However, participants who are enrolled in Part A but fail screening can be re-screened for inclusion in Part B.

Re-screened participants should be assigned the same participant number as for the initial screening. Participants screened in Part A who are rescreened in Part B may be assigned a new participant number.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

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) at every dosing. Study intervention should ideally be taken between approximately 08:00 and 10:00 each morning. If later than 12:00 midday, dosing should be delayed until the following day.

Table 6 Study Intervention

Part A	**Treatment group 1**	**NA**	**NA**	**Treatment group 2**	**NA**
Part B	**Treatment group 1**	**Treatment group 2**	**Treatment group 3**	**Treatment group 4**	**Treatment group 5**
Intervention name	Placebo	dapagliflozin	zibotentan + dapagliflozin	zibotentan + dapagliflozin	zibotentan + dapagliflozin
Type	Placebo	Drug/placebo	Drug	Drug	Drug
Dose formulation	placebo capsule (matching zibotentan capsule) placebo tablet (matching dapagliflozin tablet)	placebo capsule (matching zibotentan capsule) dapagliflozin tablet	zibotentan capsule dapagliflozin tablet	zibotentan capsule dapagliflozin tablet	zibotentan capsule dapagliflozin tablet
Dose levels	NA	10 mg: dapagliflozin	CCI mg: zibotentan 10 mg: dapagliflozin	CCI mg: zibotentan 10 mg: dapagliflozin	CCI mg: zibotentan 10 mg: dapagliflozin
Route of administration	Oral	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Experimental	Experimental
IMP and NIMP	IMP	IMP	IMP	IMP	IMP
Sourcing	zibotentan, dapagliflozin, and their respective matching placebo treatments will be supplied centrally through AstraZeneca.				

Table 6 Study Intervention

Part A	**Treatment group 1**	**NA**	**NA**	**Treatment group 2**	**NA**
Part B	**Treatment group 1**	**Treatment group 2**	**Treatment group 3**	**Treatment group 4**	**Treatment group 5**
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.				

GMP = Good Manufacturing Practice; HDPE = high-density polyethylene; IMP = investigational medicinal product; NA = not applicable; NIMP = non-investigational medicinal product.

6.1.2 Medical Devices

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

Home-based devices for measurement of body weight (all participants), blood pressure measurements (participants with low blood pressure or symptoms of low blood pressure), and glucose measurements (glucometer provided to T2DM participants treated with insulin or sulfonylurea only) not manufactured by or for AstraZeneca will be provided.

Instructions for medical 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 medical 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 (see Appendix A). In this study any deficiency observed with a third-party medical device will be collected and reported to the manufacturer. A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer. The manufacturers medical device complaint report will be used to collect the deficiency.

6.2 Preparation/Handling/Storage/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 enrolled in the study may receive study intervention and only authorised study centre staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in

accordance with the 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 Measures to Minimise Bias: Randomisation and Blinding

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.

In Part A, eligible participants will be randomised to receive either zibotentan CCI mg/dapagliflozin 10 mg or placebo at a ratio of 1:1. No stratification factor will be applied to Part A.

Participants in Part B will be randomised CCI and stratified by the CCI CCI at the time of randomisation to ensure an approximate balance between treatment groups within each sub-population.

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

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.
- 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 blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind.

6.4 Study Intervention Compliance

At visits specified in Table 1 and Table 2, participants will receive study intervention at the study centre directly from the investigator or designee, under medical supervision or will take the study intervention at home. The date and time of the dose administered at the study centre 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 intervention capsules and tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded in the eCRF.

6.5 Concomitant Therapy

As ET-1 has a potential role in the maintenance of blood pressure, hypotension may be encountered following ET blockade. Although only minor reductions in blood pressure were seen in patients it is possible that more marked changes might occur in hypertensive patients especially those taking hypotensive therapy such as angiotensin-converting enzyme 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).

Midazolam is the preferred medication for sedation during the HVPG procedure (see Section 8.1.1.1 and Appendix G). In study D4320C00010, co-administration of zibotentan 10 mg (steady-state conditions) with midazolam resulted in a 20% increase in midazolam AUC (treatment ratio: 1.20; 90% CI: 1.05, 1.34); no marked change in plasma clearance, t½ or in volume of distribution; unchanged tmax and unchanged Cmax (treatment ratio: 1.05; 90% CI: 0.84, 1.31). For a substance to act as a weak CCI substrates an increase in AUC of at least 1.25-fold would be expected. Concomitant administration of zibotentan with CCI is likely to cause a small increase in exposure that is unlikely to be sufficient to cause a clinically significant effect on the safety profile.

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

6.5.1 Prohibited Medications

The medications and supplements listed below are prohibited from the time of randomisation and for the duration of the study. Participants taking any of these medications at the time of randomisation cannot be included into the study.

- SGLT2i.
- ERAs.

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

Other prohibited medications are CCI , within 14 days CCI CCI prior to dose of zibotentan (Table 7) 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 1, 8, 15, 22, 43, and 65).

Table 7 CCI

Medication	Rationale
CCI	

The list is not intended CCI , and the CCI
CCI
CCI

6.5.2 Permitted Procedures and Medications

6.5.2.1 Paracentesis

Paracentesis is permitted during the study if required for safety.

6.5.2.2 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; Section 6.1.2) since more frequent blood glucose monitoring should be considered in participants receiving insulin and/or SU, especially with baseline CCI at baseline. 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 8.2.5.1 for details about hypoglycaemia).

6.6 Dose Modification

Dose modification of study intervention is not permitted. All participants will receive the assigned dosage of study intervention.

6.7 Intervention After the End of the Study

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

6.8 Treatment of Overdose

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. For more information regarding reporting of overdose, see Section 8.3.12.

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 8.3.12 for details of AE/SAE reporting related to overdose.
- Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Study Clinical Lead (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

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

- CCI [redacted]; Section 8.3.7).
- New diagnosis of CCI or CCI [redacted] of the existing CCI condition.

- New or worsening of symptoms of CCI other than CCI that is not managed by CCI of CCI.
- Recurrent encephalopathy grade 2 or higher, CCI and hepatocellular cancer.
- Serious/severe CCI.
- Serious/severe CCI.
- DKA including euglycaemic DKA has 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, restart of study intervention should be considered.
- When CCI (CCI) is suspected and restart of the study intervention is not permitted based on the algorithm outlined in Section 7.1.2.
- eGFR CCI
- Development of CCI or other causes of CCI
- Liver transplantation.
- TIPS.
- 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 noncompliance 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.

Participants who prematurely discontinue study intervention should remain in the study and attend all planned study visits including the Follow-up Visit (Table 1 and Table 2).

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.

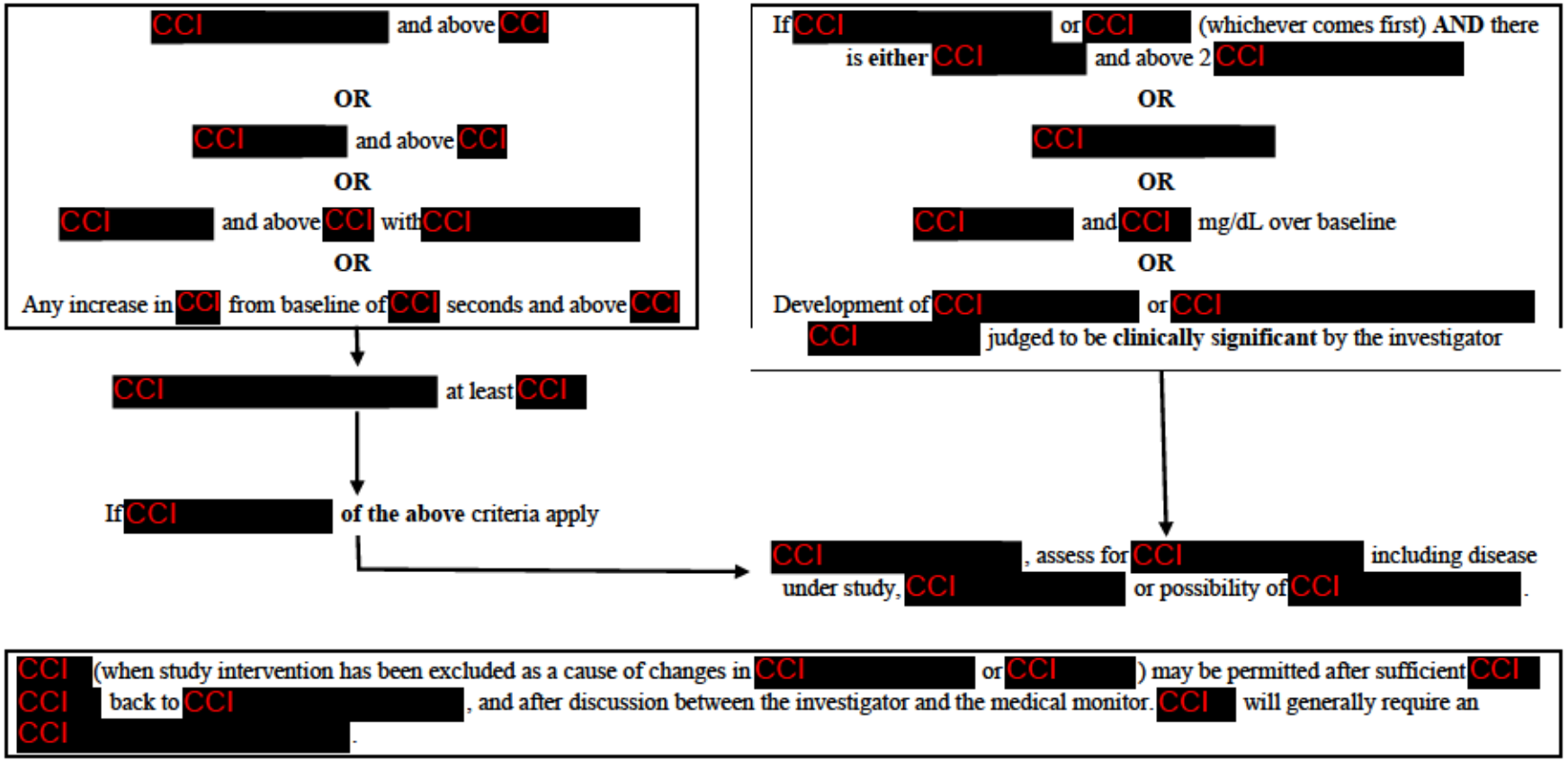
Participants on investigational treatment who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is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

7.1.2 Management of Treatment-emergent Abnormalities in Liver Function Tests

In order to identify cases of suspected CCI, the following algorithm must be followed (also see Appendix E for actions required for evaluation of modified Hy's Law). The CCI algorithm accounts for CCI of the CCI value (defined as the CCI of the CCI CCI during the CCI period) or a CCI value, whichever comes first, and not solely on CCI of the CCI. The algorithm also accounts the status of participant at CCI as CCI as well as takes into consideration normal or abnormal baseline ALT for participants with 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 CCI is defined as CCI with presence at baseline of CCI, or 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 mg/dL over CCI, **AND**
- CCI (if normal at CCI) or CCI increase 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 (with CCI) **OR** CCI if abnormal at CCI,
- CCI mg/dL over baseline,
- CCI (if CCI) OR increased by CCI CCI)

OR

CCI (whichever comes first)

OR

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 excluded 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, 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 is sustained.

CCI (when study intervention has been excluded 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 Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Termination visit should be conducted, that will comprise of the same assessments as shown for the Follow-up Visit as shown in the SoA (Table 1 and Table 2).
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation the investigator must document the decision on use of existing samples in the 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 he or she 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Table 1 and Table 2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Table 1 and Table 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures such as ECHO (to exclude valvular disease and/or significant cardiomyopathy as defined in Section 5.2), clinical chemistry, haematology, urinalysis conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 2).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Repeat/unscheduled samples may be tested at the local laboratory. 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 400 mL in Part A and 450 mL in Part B.

8.1 Efficacy Assessments

8.1.1 Primary Variable

8.1.1.1 Hepatic Venous Pressure Gradient

HVPG assessments will be performed at timepoints specified in Table 1 and Table 2, according to the HVPG training manual in Appendix G. Importantly, study site must be able to store a recording according to the HVPG training manual for assessment by the central reader.

HVPG assessment can take place on a separate day of the visit day according to the study

plan. On the day of the HVPG assessment, participants must be fasted and must avoid nicotine-containing products until the HVPG assessment has taken place. The participants will preferably fast overnight (≥ 8 hours) or if the procedure cannot take part before late in the morning or close to lunchtime, a light meal can be served 3 to 4 hours before the procedure. At Visit 1, the VCTE procedure should take place at least 3 to 4 hours after breakfast or another light meal. If the participant is on a non-selective beta-blocker, the CCI [redacted]. Also, changes in diuretics dosing the day before the HVPG procedure must be avoided. HVPG assessment CCI [redacted] after administration of study intervention. Therefore, the timing of HVPG assessment and intake of study intervention at Visit 7 should be carefully planned. Study intervention administration before HVPG assessment can take place either at the study centre or at home.

Recordings of HVPG must be kept to be evaluated by a central reader blinded to treatment allocation. The baseline recordings must be reviewed and found to be of good enough quality and with HVPG > 10 mmHg by the central reader before the participant can be randomised. A good enough HVPG recording is the result of a recording that adheres to all the requirements set up in the HVPG manual (Appendix G). An acceptable tracing that can be used to derive HVPG data although not totally satisfactory, still allows to derive the CCI [redacted] measurements of WHVP, FHVP, and HVPG, with consistent results even if the tracings have artefacts, or if some ancillary measurement is lacking (ie, right atrial pressure, inferior vena cava pressure).

As per Appendix G, a balloon catheter will be introduced via the transjugular approach into the hepatic vein under ultrasound/fluoroscopic guidance. Light sedation for participant comfort will be provided. CCI [redacted] is the preferred medication for sedation since it does not influence HVPG. Note that zibotentan leads to a CCI [redacted] which is, however, unlikely to be clinically relevant with CCI [redacted] (see Section 6.5). Once the catheter is in situ in the hepatic vein, an initial free venous pressure measurement should be undertaken, followed by a wedge pressure measurement. HVPG is calculated from these two values. Measurements of HVPG should be performed in triplicate.

8.1.2 Secondary Variables

8.1.2.1 Electronic Scale Measurement of Body Weight

Body weight will be measured at the study centre at study visits. In addition, participants will measure their body weight every morning using a digital device provided (Table 1, Table 2, and Section 8.2.1).

8.1.2.2 Bioimpedance Spectroscopy

Bioimpedance spectroscopy (BIS) will be performed at the study centre at the timepoints specified in the SoA (Table 1 and Table 2) 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 and 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.

8.1.3 Exploratory Variables

8.1.3.1 Vibration-controlled Transient Elastography

Vibration-controlled transient elastography (VCTE) will be performed at the timepoints specified in Table 1 and Table 2 in the fasting state (overnight ≥ 8-hour fast or if the procedure cannot take part before late in the morning or close to lunchtime, a light meal can be served 3 to 4 hours before the procedure) as well as CCI after study intervention administration at Visit 7. At Visit 1, the VCTE procedure should take place at least 3 to 4 hours after breakfast or another light meal. If the participant is on a non-selective beta-blocker, the dose should not be taken in the morning before VCTE, but right after the VCTE assessment. Spleen stiffness will be measured only if Fibroscan Model 630 is available, while liver stiffness will be measured using any Fibroscan/VCTE model. Liver and/or spleen stiffness is collected as an exploratory endpoint to investigate to what extent it may be used as a surrogate for changes in hepatic portal venous pressure gradient. The measurement should preferably be done by the same examiner on all occasions.

Liver stiffness will also be done at Screening (Visit 1), using the criteria of liver stiffness of CCI together with platelet count < 150 x10^9, before an HVPG is carried out in participants with compensated cirrhosis, in order to reduce the chance of performing an HVPG examination in participants with HVPG ≤ 10 mmHg.

VCTE/Fibroscan assessment of spleen stiffness should only be done if technically feasible to complete an accurate spleen stiffness measurement and is up to the discretion of the investigator at the study centre.

8.1.3.2 Serum Analysis of Creatinine and Cystatin C (eGRF)

The participant's eGFR will be calculated 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. 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. Note that eGFR1 will be used throughout the study to monitor safety/ kidney function, while eGFR2 will be calculated after the study is completed.

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

CCI $= 142 \times \min(S_{cr}/\kappa,1)^{-0.241\ (\text{if female})/-0.302\ (\text{if male})} \times \max(S_{cr}/\kappa,1)^{-1.200} \times 0.994^{Age} \times 1.012$ [if female]

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

8.1.3.3 Laboratory Assessments for Exploratory Analysis

Blood and urine samples will be collected as shown in the SoA (Table 1 and Table 2) to measure levels of the following biomarkers for analysis of exploratory variables:

- Plasma/serum CCI are derived from safety variables (Table 9; Part B only).
- MELD 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.
- Plasma/serum CCI and CCI are the non-fasting plasma biomarkers in the SoA.
- Fasting plasma/serum CCI are the fasting plasma biomarkers in the SoA. CCI and CCI (ie, lipid profile) are additional fasting plasma biomarkers in the SoA.
- CCI test for CCI, and for CCI, CCI, and CCI, are measured at visits specified in the SoA.
- CCI at every visit.

Above samples will be handled by the central laboratory.

Table 8 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
International normalised ratio	< 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)			

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1 and Table 2).

8.2.1 Physical Examinations

Physical examination, and measurement of weight and height will be conducted at the timepoints outlined in the SoA (Table 1 and Table 2).

- A full physical examination will include assessments of general appearance, respiratory (respiratory rate and breath sounds), cardiovascular (heart rate, 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 (heart rate, 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 8.3.5.

In addition, body weight will be monitored at home using an electronic scale throughout the interventional period as part of the efficacy measurements (Table 1 and Table 2; Section 8.1.2.2). For measurement, the participant should wear indoor, daytime clothing with no shoes and no coats/jackets and removal of heavy objects from pockets.

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA (Table 1 and Table 2).

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 and Table 2), 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 have hypotension and/or symptoms suggestive of low blood pressure during the course of the study will be provided with a home blood pressure device (Sections 6.1.2 and 8.3.7).

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 1 pulse, 1 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, a CCI [redacted]. These assessments should preferably be done in the morning. If CCI [redacted] is confirmed during the test, it should be CCI [redacted] including symptoms related to the measurement of CCI [redacted] if present (Section 8.3.7).

For information on how AEs based on vital sign results should be recorded and reported, see Section 8.3.5.

There will be safety monitoring of CCI [redacted], or as an alternative, paper diaries can be used for capturing the information. A body CCI CCI [redacted] is regarded as a significant 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 CCI [redacted], 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 CCI .

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

8.2.3 Electrocardiograms

Single 12-lead ECGs will be performed after the participant has been resting in a supine position for at least 10 minutes, at the visits outlined in the SoA (Table 1 and Table 2).

Throughout the study, clinically relevant new findings or worsening of a pre-existing finding in the ECGs (parameters or abnormal findings in the tracing) must be considered an AE and must be recorded in the AE CRF form.

For information on how AEs based on ECG results should be recorded and reported, see Section 8.3.5.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis for safety analysis will be taken at the visits indicated in Table 1 and Table 2. Laboratory assessments for exploratory analysis are presented in Section 8.1.3.3.

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.

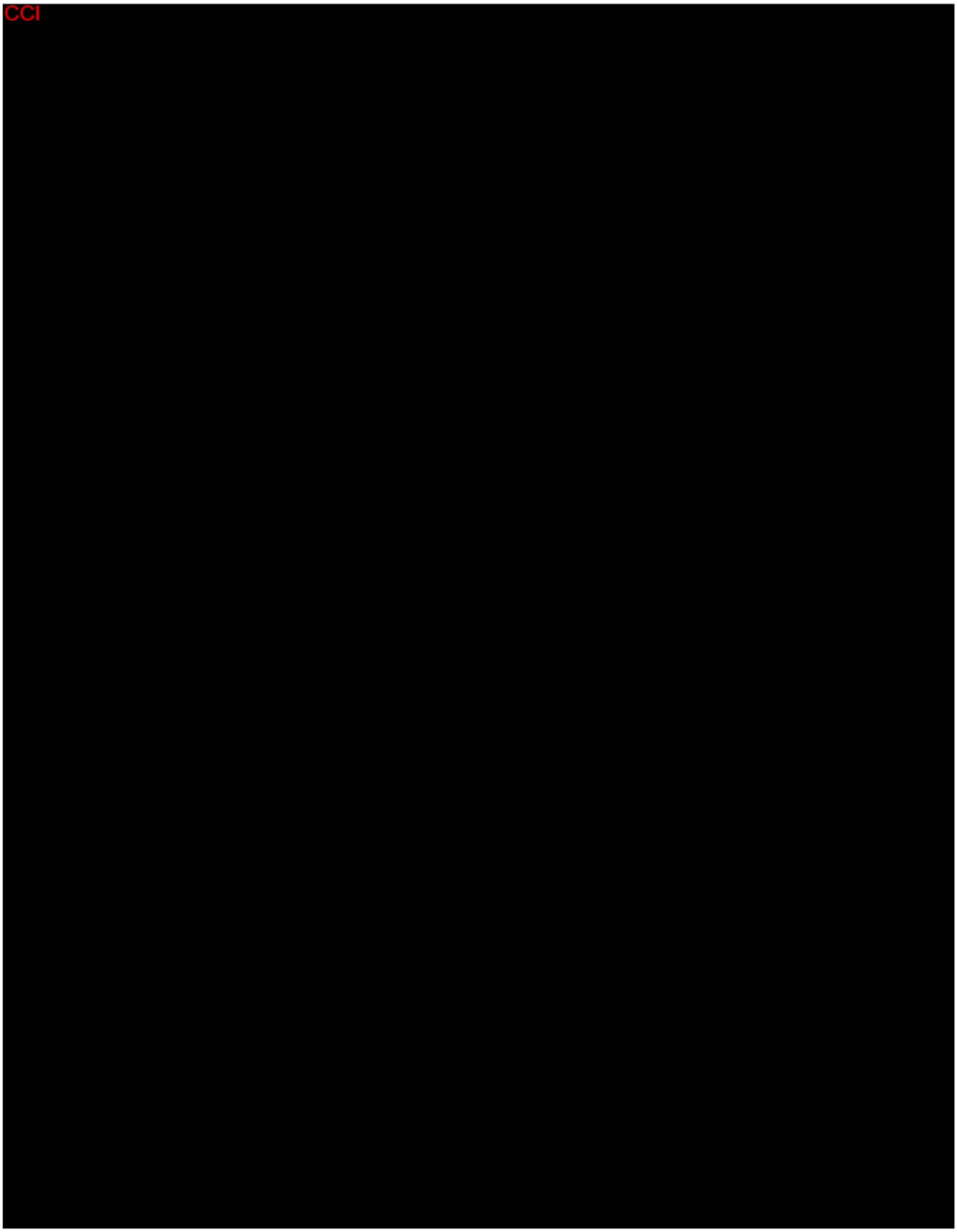
The laboratory assessments for clinical chemistry, haematology and urinalysis will be performed at a central laboratory.

The laboratory safety variables that will be measured are listed in Table 9.

NB. 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.

Table 9 Laboratory Safety Variables



8.2.5 Other safety assessments

8.2.5.1 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 when they develop symptoms suggestive of hypoglycaemia and 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, 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 Section 8.3).

8.2.5.2 Alcohol Use Disorders Identification Test Questionnaire

The Alcohol Use Disorders Identification Test (AUDIT) questionnaire to assess alcohol use habits will be completed at screening only. 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.

8.3 AEs, SAEs, and Other Safety Reporting

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

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

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

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

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality 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
- AE description
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

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

All adverse events 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 IMP that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs 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.

8.3.3 Causality Collection

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

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study 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.

8.3.5 Adverse Events Based on Examinations and Tests

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

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and ECGs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption) (Sections 8.2.2 and 8.3.7).

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 versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s) (Section 8.2.5.1).

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.

8.3.6 Adverse Events Related to Specific Study Procedures

Any event caused by the HVPG procedure (refer to Section 8.1.1) should be reported if it meets the SAE criteria.

8.3.7 Adverse Events of Special Interest

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

- New diagnosis of CCI of the existing CCI . 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 etc.).
- CCI defined as a CCI of CCI in CCI or a CCI in CCI . Participants will be educated about the symptoms of CCI and will be provided with a CCI and asked to contact the investigator if symptoms occur or if their CCI
- CCI . In the event of symptoms of CCI , a CCI CCI should be performed.
- CCI .
- CCI , including the following: increase in CCI CCI within 48 hours; or increase in CCI times 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 for 6 hours.

8.3.8 Hy's Law

Cases where a participant shows elevations in LFTs or relevant clinical manifestations as defined in Section E 2 and identified in Section E 3 of Appendix E 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.

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other study centre 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 1 calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other study centre 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.

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

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

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

8.3.10 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.

8.3.10.1 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 Section 4.3.9.12). 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). Pregnant or breastfeeding women must not receive the compound.

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 course of 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 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.10.2 Paternal Exposure

To prevent potential exposure via semen, men receiving zibotentan who are sexually active with a WOCBP 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 (see 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 study follow-up visit.

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 immediately. The investigator or other study centre personnel should inform the appropriate AstraZeneca representatives about the pregnancy within the timelines specified in Section 8.3.10.1. The investigator should also be notified of pregnancies occurring during the study but confirmed after completion of the study.

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 three 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.

8.3.11 Medication Error, Drug Abuse, and Drug Misuse

8.3.11.1 Timelines

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other events.

8.3.11.2 Medication Error

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

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

8.3.11.3 Drug Abuse

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

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

8.3.11.4 Drug Misuse

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

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

8.3.12 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.

The maximum well-tolerated daily dose of zibotentan in oncology patients was considered to be 15 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 8.3.9) and **within 30 days** for all other overdoses.

8.4 Human Biological Samples

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

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

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier).
  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.4.1 Pharmacokinetics

Plasma samples will be collected for measurement of concentrations of zibotentan and dapagliflozin as specified in the SoA (Table 1 and Table 2).

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. The timing of sampling may be altered during the course of the study (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring. PK samples that are not collected in line with scheduled assessments may not be reported in the CSR.

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

8.4.1.1 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.

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.

8.4.2 Immunogenicity Assessments

Immunogenicity analysis will not be done in this study.

8.4.3 Pharmacodynamics

Plasma/serum parameters will be measured during the study for the evaluation of the exploratory endpoints. Parameters will be measured from the blood samples collected for safety analysed at a central core laboratory (see Section 8.2.4).

8.4.3.1 Collection of Samples

Blood samples will be collected as described in the SoA (Table 1 and Table 2) and analysed by a central laboratory. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

For storage, re-use and destruction of pharmacodynamic samples see Section 8.4.

8.5 Human Biological Sample Biomarkers

8.5.1 Collection of Mandatory Samples for Biomarker Analysis

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 as specified in the SoA (Table 1 and Table 2):

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

8.6 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA (Table 1 and Table 2) and is subject to agreement in the ICF addendum.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

For storage and destruction of genetic samples see Appendix D.

8.7 Medical Resource Utilisation and Health Economics

Medical resource utilisation and health economics are not planned for this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

There is no formal hypothesis testing for the primary efficacy endpoint in Part A. The absolute change in HVPG from baseline to Week 6 in the combination of zibotentan and dapagliflozin groups and placebo group will be analysed via estimation approach.

For Part B, the primary efficacy hypothesis is that the combination of zibotentan and dapagliflozin will reduce HVPG compared with placebo.

9.2 Sample Size Determination

Part A is a proof-of-concept study, the sample size is not determined based on a formal statistical hypothesis testing. Assuming a difference of CCI in mean absolute change in HVPG at Week 6 for the zibotentan/dapagliflozin group versus the placebo group, and a common standard deviation (SD) for difference in HVPG of CCI (Bai et al 2021), CCI HVPG-evaluable participants per group will provide CCI % power to detect the difference at Week 6 with a type I error of CCI % (1-sided). With an estimated CCI % premature treatment discontinuation, it is planned to randomise a total of 30 participants (CCI per group) in Part A.

For Part B, with a 1-sided type I error of CCI %, CCI HVPG-evaluable participants per group will provide CCI % power to detect a difference of CCI in absolute change in HVPG from baseline to Week 6 for the zibotentan and dapagliflozin in combination group and the dapagliflozin monotherapy group versus placebo group, assuming a common SD for change in HVPG of 3 mmHg (Bai et al 2021). Accounting for an estimated CCI % premature treatment discontinuation, it is planned to randomise 33 participants in each of the 5 treatment groups in order to have CCI participants (CCI participants per treatment group) with evaluable HVPG measurements at baseline and Week 6. Approximately 165 participants will therefore be randomised in Part B of this study.

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.

9.3 Populations for Analyses

The following populations are defined:

Table 10 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.
Full Analysis Set (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 primary analysis set for efficacy endpoints analyses and all analyses of demographic, baseline characteristics.
Per Protocol Analysis Set (PPS)	A subset of the FAS consisting of all participants who completed at least 6 weeks of treatment and do not violate the terms of the protocol in a way that may affect the primary efficacy endpoint significantly. All decisions to exclude participants from the per protocol analysis set will be made and documented prior to the unblinding of the study. Participants are evaluated according to the treatment assigned at randomisation. The PPS will be used for supplementary analysis of efficacy endpoints.
Safety Analysis Set (SAS)	All participants who are randomised and receive at least one dose of the study intervention. Participants are evaluated according to the actual treatment they received. If a participant received a different treatment dose than randomised throughout the study, they will be analysed according to the treated dose, not the randomisation dose. If a participant received study intervention from the wrong kit for only part of the treatment duration, they will be analysed according to their randomisation dose. The SAS will be used for all safety analyses.
Pharmacokinetic Analysis Set (PKS)	All participants in the FAS who have at least one detectable zibotentan or dapagliflozin plasma concentration measurement post-treatment. PK samples that are not collected in line with scheduled assessments may not be reported in the CSR. The Pharmacokinetic Analysis Set will be used for all PK analyses.

Additional analysis sets may be defined in the Statistical Analysis Plan (SAP) for exploratory analyses.

9.4 Statistical Analyses

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 statistical analyses described in this section.

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

All results will be presented by treatment group and overall (where specified) for Part A and Part B separately, 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 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.

9.4.2 Efficacy

All the primary and secondary objectives will be assessed through an estimand defined by the following attributes:

- Population: Patients with compensated or decompensated cirrhosis (see Section 5.1 and 5.2 for details of the inclusion and exclusion criteria, respectively).
- Treatment: Zibotentan and dapagliflozin in combination, dapagliflozin monotherapy (Part B) or placebo, in addition to their SoC.
- Intercurrent events: For premature treatment discontinuation due to any reason, the treatment policy strategy will be applied. Terminal events (eg, death) are expected to be few and will be handled via while-alive strategy.
- Variables: See Table 4 and Table 5.
- Population level summary: Treatment difference in absolute change in HVPG from baseline to Week 6 for zibotentan and dapagliflozin in combination and dapagliflozin monotherapy (Part B) versus placebo.

This estimand is intended to estimate the treatment difference that reflect the effect of the initially assigned randomised study intervention, irrespective of exposure to study intervention, concomitant treatment as well as subsequent treatment after discontinuation of study intervention. This estimand is in alignment with the primary and secondary efficacy

endpoints. Measurements of primary and secondary endpoints will be collected regardless of intercurrent events (eg, discontinue treatment due to any reason). Missing value will be imputed at missing visits using multiple imputation methods. Details on estimand regarding attributes will be provided in the SAP.

The analysis of all efficacy variables will be performed on the FAS. Sensitivity analyses and supplementary analyses (eg, PPS analysis) will be conducted for the primary efficacy endpoint; details will be stated in the SAP.

9.4.2.1 Primary Endpoint

The primary efficacy endpoint is the absolute change in HVPG from baseline to Week 6 for both Part A and Part B, and it will be analysed using ANCOVA method. The model will include the fixed categorical effects of stratification factor (Part B only), treatment and baseline HVPG measurement as a continuous covariate for the pairwise comparisons between the active treatment groups versus the placebo group.

Details will be provided in the SAP.

9.4.2.2 Secondary Endpoints

The percentage change in HVPG from baseline to Week 6 will be analysed using ANCOVA model similar to the primary efficacy analysis.

In Part B, HVPG response at Week 6, where a responder is defined as a $\geq$ 20% decrease in HVPG or a reduction to or below 12 mmHg in HVPG from baseline at Week 6, will be analysed via Mantel-Haenszel test, accounting for the stratification factor.

The change in body weight, body water volumes, body fat mass, total dosage of loop-diuretic equivalents, and blood pressure at Week 6 and Week 16 will be analysed using MMRM methodology. The analytical model will include the fixed categorical effects of stratification factor (Part B only), treatment, visit, and treatment-by-visit interaction, and continuous covariates of the baseline measurements. An unstructured covariance structure will be used for the within participant errors.

All secondary efficacy endpoints will be assessed for the active treatment groups versus placebo via pairwise comparisons.

An interim analysis is planned to be conducted in Part B by an unblinded study team when all participants have completed at least 6 weeks of treatment or have passed the planned Week 6 visit (ie, Visit 7). A blinded study team will oversee the study conduct until the final clinical database lock. Further details will be provided in the SAP and Study Integrity Plan.

9.4.3 Safety

Safety analyses will be performed using the SAS. Safety data will be presented using descriptive statistics unless otherwise specified. In general, the baseline value for statistical analysis is the last non-missing 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 1 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. Serious AEs 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 AEs leading to withdrawal from study.

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, other significant AEs, and timing of events.

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 SAS 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 (office/clinic 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; clinically significant) 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 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.

Details of laboratory findings for urinalysis a shift table will present the baseline assessment against the maximum on-treatment category.

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

Details of laboratory analyses including definition of abnormality criteria (eg, definition of low, normal, high; clinically significant) and project-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 predose on Day 1.

9.4.4 Other Analyses

9.4.4.1 Exploratory Efficacy Endpoints

For Part A, percentage and absolute change in spleen stiffness at Week 6 and for part B, percentage and absolute change in liver and/or spleen stiffness at Week 6 will be analysed.

Change in CCI will be measured at Week 1, Week 3, Week 6, and Week 16 (Part B only), and evaluation of changes in blood and urine biomarkers across the time course of the study will be analysed. Absolute change in HVPG from baseline to Week 6 for zibotentan and dapagliflozin in combination compared with dapagliflozin monotherapy will be evaluated via pairwise comparisons. For details on exploratory objectives and endpoints, see Section 3.

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

9.4.4.2 Exploratory Pharmacokinetic Endpoints

Plasma concentration of zibotentan and dapagliflozin will be summarised by treatment group, per visit, and timepoint 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.

9.4.4.3 Exploratory Pharmacodynamic and Biomarker Endpoints

The exploratory PD and biomarker endpoints described in Section 8.1.3.3 will be summarised by treatment group and timepoint based on the PPS.

Further details on this will be provided in the SAP. Results for exploratory PD and biomarker endpoints may be captured separately from the CSR.

9.4.4.4 Exploratory Vibration-controlled Transient Elastography Endpoints

The following exploratory endpoints will be summarised by treatment group based on the FAS:

- For Part A: Percentage and absolute change from baseline in spleen stiffness, assessed using VCTE/Fibroscan, at Week 6.
- For Part B: At Visit 1, liver stiffness should be investigated to understand if participants with compensated cirrhosis fulfil the liver stiffness criteria to be investigated. Percentage and absolute change from baseline (Visit 1) in liver and/or spleen stiffness, assessed using VCTE/Fibroscan, at Visit 7.

Further details on this will be provided in the SAP.

9.4.4.5 Potential Exploratory Research and Optional Genetic Research

The following analyses will not be part of the CSR:

- Evaluation of changes in blood and urine biomarkers 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 Data Monitoring Committee

A DMC will regularly monitor safety/tolerability data (including monitoring of modified CCI [redacted] cases and CCI [redacted] including CCI [redacted]) and have the authority to unblind a participants' intervention assignment due to safety concerns, if warranted. The DMC may recommend to stop further recruitment and/or treatment of a treatment group at any time after comprehensive assessment of safety data. The recommendation from DMC will be sent to an unblinded senior manager who will submit a decision based on the DMC recommendation to the study team.

Further details about planned regular safety meetings will be provided in the DMC charter.

9.6 Interim Analyses

An interim analysis is planned to be conducted in Part B by an unblinded study team when all participants have completed at least 6 weeks of treatment or passed the planned Week 6 visit (ie, Visi[redacted]). The objective of the interim analysis is to facilitate the programme-development planning for zibotentan and dapagliflozin in combination. The SAP will describe the planned interim analyses in detail.

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 International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required 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 study centre and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- 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.
  - Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

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

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators

are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant 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, Health Insurance Portability and Accountability Act 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.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Participants who are re-screened 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 the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, 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. AstraZeneca 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[1] 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:

- Allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.

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

- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (email 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 of 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.

A 7 Data Quality Assurance

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

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised study centre personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of 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 study centre.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in source data agreement and computerised data checklist for electronic source data.

A 9 Study and Study Centre 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.

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

The investigator may initiate study centre 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 centre by the sponsor or investigator may include but are not limited to:

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any 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 the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual study centre data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any 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 can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

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

- Results in death.
- Is immediately life-threatening.
- Requires in-participant 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 tumour**s and breast cancer with lumpectomy identified and reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. 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 product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

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

Important Medical Event or Medical Treatment

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

- Angioedema not severe enough to require intubation but requiring intravenous 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.

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

Intensity Rating Scale:

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

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

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in this appendix. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in this appendix.

B 3 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another 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 disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

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

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study centre 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, for example, wrong route or wrong site of administration.
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature.
- Wrong participant received the medication (excluding IRT/RTSM errors).
- Wrong drug administered to participant (excluding IRT/RTSM errors).

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

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

- Participant failed to return unused medication or empty packaging.
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product.

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

Drug Abuse

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

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the 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 data entry site 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 study centre.

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 centres, auditing or process checks, and contractual requirements of external laboratory providers.

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

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

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in 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 analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

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

Inclusion Criteria

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

Exclusion Criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant.
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

Withdrawal of Consent for Genetic Research

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

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

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants at Visit 3. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

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

Ethical and Regulatory Requirements

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

Informed Consent

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

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

Participant Data Protection

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

Data management

- Data will be reported separately from the CSR.
- Any genetic 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 research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

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

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report PHL cases and 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 Hy's Law 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 Liver Function Tests.

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

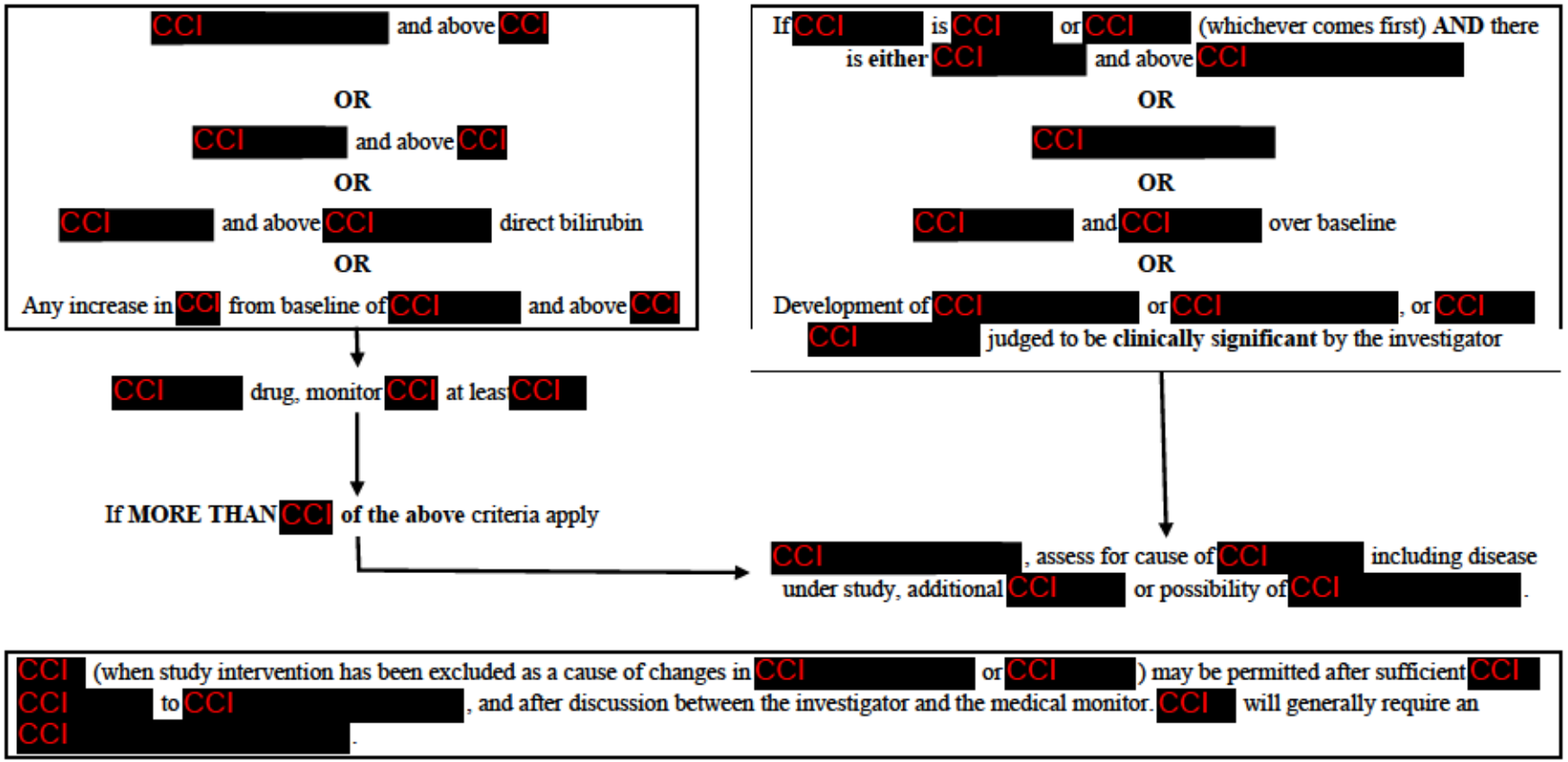
Potential Hy's Law
Elevation in LFTs or relevant clinical manifestations defined in Section 3 flowcharts that lead to hold of the study intervention to assess the cause of these changes.

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 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 × 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 CCI).

CCI , monitor CCI

CCI or CCI (whichever comes first)

AND AT LEAST ONE OF THE FOLLOWING

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

OR

CCI (whichever comes first)

OR

CCI over baseline

OR

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

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

CCI (when study intervention has been excluded 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 nadir values

OR

CCI × 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 or CCI judged to be **clinically significant** by the investigator.

↓

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

Due to variability in CCI, patients with CCI meeting requirement for hold of study drug based solely on CCI, 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 is sustained.

CCI (when study intervention has been excluded as a cause of changes in CCI elevation 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 & IgG anti-CMV IgM & IgG anti-HSV IgM & 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

[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.
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; RNA = ribonucleic acid.

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Appendix F COVID-19 Specifics

F 1 Background to COVID-19

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

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

F 2 Risk Assessment for COVID-19 Pandemic

The mechanism of action of zibotentan is unlikely to impact the course of infection with SARS-CoV-2. Zibotentan is an ET_A receptor antagonist and is not expected to cause immune suppression.

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

- This study is going to start enrolling only when the sponsor deems it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID19 pandemic imposed by the local authorities are compatible with safe conduct of the study.
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Participants will be closely monitored for any signs and symptoms of COVID19, including fever, dry cough, dyspnoea, sore throat and fatigue throughout the study during the pandemic. Once clinical signs of infection are reported by participants, the investigator needs to determine whether samples can be collected, and safety data can be recorded at the study centre. If not, AEs and concomitant medications will be obtained via

phone calls. The decision to continue with dosing the participant with the study intervention in the event of him/her showing symptoms of COVID19 infection will be per investigator's discretion.

F 3 Data Quality Assurance Related to COVID-19

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

F 4 References

EMA Guidance on the Management of Clinical Trials During the COVID 19 (Coronavirus) Pandemic
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Appendix G HVPG Measurements

G 1 Obtaining Accurate and Reliable HVPG Measurements

Required equipment

CCI

[redacted]

Adequate calibration and recording

CCI

[redacted]

CCI

[redacted]

Actual measurement

CCI

[redacted]



ECG = electrocardiogram; FHVP = free hepatic venous pressure; HVPG = hepatic venous pressure gradient; IVC = inferior vena cava; WHVP = wedged hepatic venous pressure.

G 2 Reference

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Appendix H Abbreviations

Abbreviation or special term	Explanation
ABV	alcohol by volume
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
ANCOVA	analysis of covariance
AUDIT	Alcohol Use Disorders Identification Test
BIS	bioimpedance spectroscopy
CCI	CCI
BSL	baseline
CCI	CCI
AST	aspartate aminotransferase/transaminase
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology collaboration
COVID-19	coronavirus disease 2019
CRO	Contract Research Organisation
CRPC	castration resistant prostate cancer
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	clinical trial information system
CCI	CCI
CCI	CCI
DAE	discontinuation due to adverse event
DAPA	dapagliflozin
CCI	CCI
DKA	diabetic ketoacidosis
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
EDC	electronic data capture

Abbreviation or special term	Explanation
CCI	CCI
CCI	CCI
EMA	European Medicines Agency
ERA	endothelin receptor antagonist
ET	endothelin
ET-1	endothelin-1
ET_A	endothelin A
ET_B	endothelin B
FAS	full analysis set
FDA	United States Food and Drug Administration
FHVP	free hepatic venous pressure
CCI	CCI
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HF	heart failure
HVPG	hepatic venous pressure gradient
IB	Investigator's Brochure
IATA	International Airline Transportation Associations
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
CCI	CCI
LH	luteinising hormone
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage-liver disease
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NIMP	non-investigational medicinal product

Abbreviation or special term	Explanation
NYHA	New York Heart Association
PD	pharmacodynamic(s)
PHL	potential Hy's Law
PK	pharmacokinetic(s)
PKS	pharmacokinetic analysis set
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected using Fridericia's formula
RTSM	Randomisation and Trial Supply Management
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SGLT2	sodium-glucose cotransporter 2
SGLT2i	sodium-glucose cotransporter 2 inhibitor
SoA	schedule of activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TIPS	transjugular intrahepatic portosystemic shunt
ULN	upper limit of normal
US	United States
CCI	CCI
WHO	World Health Organization
WHVP	wedged hepatic venous pressure
WOCHP	women of childbearing potential

Appendix I Protocol Version History

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

CSP Version 2.0: 20 June 2022

This modification to 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 impacts the right or safety of participants nor the scientific value of the study.

Overall Rationale for the Modification (version 1.0 to 2.0)

The overall rationale for the non-substantial changes implemented in CSP version 2.0 was to make minor edits to the protocol and provide additional clarifications.

Summary of Changes (version 1.0 to 2.0:

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis Section 4.1 – Overall Design Section 5.2 – Exclusion Criteria	Removed the text stating that *"Participants in Part A cannot participate in Part B. Participants who are enrolled in Part A but fail screening can be re-screened for inclusion in Part B."* Removed the associated exclusion criterion (exclusion Criterion #46).	To allow for subjects to participate in both parts of the study based on investigator discretion, assuming the subject has completed the study intervention's washout period.
Section 3 – Objectives and Endpoints Table 4 (Part A Objectives) Table 5 (Part B Objectives)	Replaced mention of "cardiorenal diseases" with "liver diseases" for Exploratory Endpoints	To clarify the purpose of collecting and storing plasma, serum and urine samples for potential exploratory research.
Section 1.2 – Schedule of Activities Table 1 (Part A Schedule of Activities) Table 2 (Part B Schedule of Activities)	Clarified sample collection by changing *"Fasting plasma biomarkers"* to *"fasting plasma/serum biomarkers"*	To align the Schedules of Activities with the body text in the Protocol which describes samples to be collected in Section 8.
Section 1.2 – Schedule of Activities Table 1 (Part A Schedule of Activities) Table 2 (Part B Schedule of Activities)	Clarified that Visit 1 should take place [redacted] days before randomisation. Protocol previously stated [redacted] days.	To align the 'Study Days' with the amount of weeks before randomisation for Visit 1 (6 weeks).

Section Number and Name	Description of Change	Brief Rationale
Section 1.2 – Schedule of Activities Table 1 (Part A Schedule of Activities) Table 2 (Part B Schedule of Activities) Section 3 – Objectives and Endpoints	Clarified that biological samples will be collected and stored for exploratory assessment of biomarkers, instead of for *"future exploratory assessments"*	To ensure that exploratory analyses are appropriately detailed in the Protocol.
Section 1.2 – Schedule of Activities Table 1 (Part A Schedule of Activities) Table 2 (Part B Schedule of Activities)	Removed the following text from footnote 'b': *"Participants will be allowed to drink water until 1 hour before and from 2 hours after study intervention administration and after completion of HVPG and VCTE/Fibroscan examinations"*	After review, it was determined that this restriction is not required prior to HVPG and VCTE/Fibroscan assessment.
Section 5.1 – Inclusion Criteria	Added *"tubal occlusion"* to inclusion criterion #8 regarding acceptable birth control methods.	To further clarify which subjects would fit the study's reproduction-related inclusion criteria.
Section 8.3.7 – Adverse Events of Special Interest	Removed "CCI [redacted]" from the Protocol's definition of CCI [redacted].	To provide objective guidance for identifying CCI [redacted]
Section 8.3.9 – Reporting of Serious Adverse Events	Clarified that *"email or other local approved processes"* may be used to report Serious Adverse Events (SAEs) in case the EDC is not available.	To ensure Protocol alignment with internal policies regarding SAE reporting in case of EDC unavailability.
Section 9.1 – Statistical Hypotheses Section 9.2 – Sample Size Determination	Clarified that Part A primary efficacy endpoint will not have formal hypothesis testing. Endpoint will be *"analysed via estimation approach."* Also clarified that Part A sample size was *"not determined based on formal statistical hypothesis testing"*.	To clarify the Sponsor approach for sample size determination and analysis of Part A primary efficacy endpoint.
Section 9.4.4.5 - Potential Exploratory Research and Optional Genetic Research	Changed subsection title from "Potential Future Exploratory Research…" to "Potential Exploratory Research…" and removed the term "future". Changed text to state that analyses of blood and urine biomarkers relevant to "liver diseases and drug mechanisms" will not be included in CSR. Original was "cardiorenal diseases".	To align with this Protocol's changes to exploratory endpoints.

Section Number and Name	Description of Change	Brief Rationale
Section 9.5 – Data Monitoring Committee	Clarified that the IDMC will not review "potential" Hy's Law cases; they will only review Hy's Law cases.	To align with expected IDMC role during study conduct, and planned IDMC Charter contents.

CSP Version 3.0: 05 October 2023

This modification to CSP version 2.0 was 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 (version 2.0 to 3.0)

The overall rationale for the substantial changes implemented in CSP version 3.0 was to increase the power of the study to evaluate the effect of treatment on HVPG. Additional changes were made to clarify safety monitoring, facilitate the patient journey, reduce patient burden, and to enhance readabilty of the protocol. This protocol amendment was produced following completion of Part A, so the changes made were relevant to Part B only.

Summary of Changes (version 2.0 to 3.0):

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schedule of Activities 3 Objectives and Endpoints 4.1 Overall Design 5.1 Inclusion Criteria 8.1.1.1 Hepatic Venous Pressure Gradient	Inclusion criterion 3 has been updated to include that baseline HVPG must be > 10 mmHg.	The change has been made based on Part A results, to ensure that all included participants have clinically significant portal hypertension, a key feature of the target population for treatment.
1.1 Synopsis 2.3.3 Risk Assessment 4.1 Overall Design 4.3 Justification for Dose 6.3 Measures to Minimise Bias: Randomisation and Blinding	CCI [redacted] scheme will not be applied.	Part A results showed that CCI [redacted] mg zibotentan in combination with 10 mg dapagliflozin did not result in safety or tolerability issues, and CCI [redacted] would increase the complexity of the study.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and Endpoints 4.2 Scientific Rationale for Study Design 9.1 Statistical Hypotheses 9.4.2 Efficacy	Part B primary endpoint changed to absolute change in HVPG from baseline to week 6, and original Part B primary endpoint moved to secondary objectives.	Based on Part A results and to increase the power of the study
1.1 Synopsis 3 Objectives and Endpoints 8.1.3.1 Vibration-controlled Transient Elastography 9.4.4.1 Exploratory Efficacy Endpoints 9.4.4.4 Exploratory Vibration-controlled Transient Elastography Endpoints	For exploratory objective "To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on liver and/or spleen stiffness as measured with VCTE/Fibroscan", the endpoints of percentage and absolute change in liver and/or spleen stiffness from baseline to Week 16 (Visit 10) was removed.	To reduce patient burden.
1.1 Synopsis 4.1 Overall Design	Number of potential study centres increased to 45 and centre locations changed from North America and Europe to North America, Asia, and Europe	Number of sites and countries involved need to be increased because of the increased number of participants
1.1 Synopsis 4.1 Overall Design 9.2 Sample Size Determination	The number of participants CCI from CCI to CCI per arm	Based on the Part A results and to CCI of the study
1.2 Schedule of Activities 4.1 Overall Design 5.1 Inclusion Criteria 8.1.3.1 Vibration-controlled Transient Elastography 9.4.4.4 Exploratory Vibration-controlled Transient Elastography Endpoints	Text updated to capture the requirement in Part B for the measurement of liver and spleen stiffness to take place at Visit 1 and the requirement of a liver stiffness of CCI CCI and platelets < 150 x 10^9 to be observed in participants with compensated cirrhosis before an HVPG examination can be done at Visit 2.	The liver stiffness criteria are added to reduce the risk of carrying out an HVPG examination in a participant with HVPG ≤ 10 mmHg.
1.2 Schedule of Activities 5.3.1 Meals and Dietary Restrictions 8.1.1.1 Hepatic Venous Pressure Gradient 8.1.3.1 Vibration-controlled Transient Elastography	Added "At Visit 1, the VCTE procedure should take place at least 3 to 4 hours after breakfast or another light meal".	VCTE/Fibroscan examinations must not be done close to a meal.

Section Number and Name	Description of Change	Brief Rationale
1.2 Schedule of Activities 5.3.1 Meals and Dietary Restrictions 8.1.1.1 Hepatic Venous Pressure Gradient 8.1.3.1 Vibration-controlled Transient Elastography	Fasting requirements on the days of HVPG and VCTE/Fibroscan assessments were clarified. Participants will preferably fast overnight ≥ 8 hours prior to study intervention administration until the assessments have taken place; however, if the HVPG or VCTE procedure is in the late morning, the participant can be served a light meal 3 to 4 hours before the procedure.	Overnight fast (≥ 8 hours) is not needed and is difficult to adhere to if the examinations will take place later in the morning. Patients with cirrhosis may be sensitive to prolonged fasting (risk for hypoglycaemia).
3 Objectives and Endpoints 9.4.4.1 Exploratory Efficacy Endpoints	New exploratory endpoint added. "To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination versus dapagliflozin monotherapy".	To capture, as an objective and endpoint, the analysis of the effect of zibotentan on HVPG.
5.1 Inclusion Criteria 5.3.4 Reproductive Restrictions 8.3.10.2 Paternal Exposure	Original inclusion criteria 7, 8, and 9 deleted and the information incorporated into inclusion criterion 6. Details of highly effective birth control methods moved from both Section 5.1 and Section 8.3.10.2 to Section 5.3.4.	Alignment with company standards, for better clarity of information.
5.2 Exclusion Criteria	Edited CCI values in exclusion criterion CCI to CCI mmol/mol.	Based on Part A data with few cases of hyper- or hypoglycaemia.

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Throughout document	Minor edits and section content reordering throughout that do not affect study conduct.	To improve readability and clarity.
1.1 Synopsis 9.4.2 Efficacy 9.6 Interim Analyses	Change of listed responsibility for interim analysis from DMC to unblinded study team.	The interim is better done by an unblinded study team since all participants at the time have done all HVPG examinations.
1.2 Schedule of Activities	CCI to be measured first time at Visit 1 instead of Visit 2.	To obtain results for potential exclusion criteria before invasive HVPG procedure on Visit 2 to minimise patient burden.
1.2 Schedule of Activities	Pulse and CCI are to be done in Visit 3 at 180 minutes (as well as predose, 60, and 120 minutes), rather than at 240 minutes.	Due to Part A results and to increase feasibility.

Section Number and Name	Description of Change	Brief Rationale
1.2 Schedule of Activities	Removal of urine pregnancy test from post-randomisation visit and at follow-up.	Participants are women of nonchildbearing potential.
1.2 Schedule of Activities	Reduction in the of samples to be taken from participants for PK, non-fasting and fasting plasma/serum biomarkers, spot urine, and 'collect and store' serum/plasma/urine samples for exploratory assessment of biomarkers.	To reduce patient burden.
2.3.3 Risk Assessment 8.3.10.1 Maternal Exposure	Details of teratogenicity risk added.	This is not new information but added to emphasise the necessity to exclude women of childbearing potential from participating, by adding teratogenicity information to the risk table.
4.4 End of Study Definition	Clarified definition of the end of study according to EU and FDA requirements.	For consistency and alignment in terms of posting study results
5.1 Inclusion Criteria	Additional details of the postmenopausal requirements for female participants added.	To add clarity
5.3.6 Blood Donation	Section on 'Blood Donation' added, to state that patients should not donate blood during therapy and for 1 month following discontinuation of the IMP.	This is due to the potential risk to the foetus of a pregnant transfusion recipient.
6.1.1 Study Intervention	Moved information on the timing of study intervention to Section 6.1.1 from 5.3.1 and added the additional detail that beyond 12:00 midday, dosing should be delayed until the following day.	Previously, the dosing timing of IP was in the wrong section. The additional detail about the cut-off time is to enhance reproducibility of exposure.
6.1.2 Medical Devices	Additional details added regarding which participants should use medical devices to measure body weight, blood pressure, and glucose.	To add clarity
6.8 Treatment of Overdose	Section added on treatment of overdose.	In line with changes to company standards.
7.1.2 Management of Treatment-emergent Abnormalities in Liver Function Tests Appendix E3 Identification of Potential Hy's Law Cases	Text added to the management guidelines for participants with decompensated cirrhosis to say that "Due to variability in CCI, patients with CCI meeting requirement for CCI study drug based solely on CCI, and not meeting any other criteria for drug hold, may have one CCI with 1-2 days at the discretion of the investigator to determine whether the CCI is sustained".	Due to variability in CCI, avoid unnecessary triggering of the CCI CCI .

Section Number and Name	Description of Change	Brief Rationale
8 Study Assessments and Procedures	Text added to say "Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Repeat/unscheduled samples may be tested at the local laboratory".	In the case of safety issues, the investigator will get the analysis result faster if the samples are sent to the local laboratory.
8.3 AEs, SAEs, and Other Safety Reporting	Removal of "time when AE started and stopped" and "AE leading to participant's withdrawal from study (yes/no)" from list of AE variables that will be collected, and addition of "AE description" for SAE variables.	In line with changes to company standards.
8.3.11 Medication Error, Drug Abuse, and Drug Misuse	Added information on drug abuse and drug misuse.	Update required due to EU CTR regulation and corporate safety CAPA
8.4.1 Pharmacokinetics 9.3 Populations for Analysis	Text added to say that PK samples that are not collected in line with scheduled assessments may not be reported in the CSR.	To avoid delays because of individual late PK samples.
Appendix A1	Added sub-heading "Regulatory Reporting Requirements for Serious Breaches"	Update required to comply with regulatory requirement (eg, EU CTR) and global company requirement
Appendix A4	Data protection information regarding GDPR and personal data breaches was added.	According to company standards to comply with health authority requirements.
Appendix A6	Updated information about timelines for submission of trial results summaries to EU CTIS	Update required to comply with EU CTR
Appendix A7	Updated information about retention timelines of records and documents to [25 years after study archiving or as required by local regulations]	Update required to comply with EU CTR and global company requirement
Appendix B4	Added detailed drug abuse and drug misuse definition and examples	Update required due to EU CTR Regulation and corporate safety CAPA

CAPA=corrective action and preventative action; CTIS=clinical trials information system; CTR=clinical trials regulation; EU=European Union; FDA; Food and Drug Administration; CCI [redacted]; IMP=investigational medicinal product.

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