STATISTICAL ANALYSIS PLAN

Study Code	D4326C00003
Edition Number	5.0
Date	13 June, 2025

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

Redacted for Public Disclosure

TABLE OF CONTENTS

TITLE PAGE 1
TABLE OF CONTENTS 2
LIST OF ABBREVIATIONS 5
AMENDMENT HISTORY 7
1 INTRODUCTION 33
1.1 Study Design 33
1.2 Randomisation 35
1.3 Number of Subjects 35
2 CHANGES TO PROTOCOL PLANNED ANALYSES 36
3 DATA ANALYSIS CONSIDERATION 36
3.1 Timing of Analyses 36
3.2 General Considerations 37
3.2.1 General Study Level Definitions 37
3.2.1.1 Baseline 37
3.2.1.2 Study periods 37
3.2.1.3 Study Day 38
3.2.1.4 Imputation of Incomplete Dates 38
3.2.1.5 Descriptive Statistics 39
3.2.1.6 Subject Convention 40
3.2.2 Visit Window 40
3.2.3 COVID-19 44
3.2.4 Multiplicity/Multiple Comparisons 44
4 STATISTICAL ANALYSIS 44
4.1 Study Population 44
4.1.1 Subject Disposition and Complete Status 44
4.1.1.1 Definitions and Derivations 44
4.1.1.2 Presentation 45
4.1.2 Analysis Sets 45
4.1.2.1 Definitions and Derivations 45
4.1.2.2 Presentation 46
4.1.3 Stratifications Factors at Randomisation 46
4.1.3.1 Definitions and Derivations 46
4.1.3.2 Presentation 46
4.1.4 Study Recruitment 47
4.1.4.1 Definitions and Derivations 47
4.1.4.2 Presentation 47
4.1.5 Protocol Deviations 47
4.1.5.1 Definitions and Derivations 47
4.1.5.2 Presentation 48

4.1.6 Demographics 48
4.1.6.1 Definitions and Derivations 48
4.1.6.2 Presentation 48
4.1.7 Baseline Characteristics 48
4.1.7.1 Definitions and Derivations 48
4.1.7.2 Presentation 49
4.1.8 Baseline Disease Characteristics 49
4.1.8.1 Definitions and Derivations 49
4.1.8.2 Presentation 51
4.1.9 Medical History and Concomitant Disease 51
4.1.9.1 Definitions and Derivations 51
4.1.9.2 Presentation 51
4.1.10 Prior and Concomitant Medications 52
4.1.10.1 Definitions and Derivations 52
4.1.10.2 Presentation 52
4.1.11 Study Drug Compliance 52
4.1.11.1 Definitions and Derivations 52
4.1.11.2 Presentation 53
4.2 Efficacy Analyses 53
4.2.1 Primary Endpoint 66
4.2.1.1 Definition 66
4.2.1.2 Handling of Dropouts and Missing Data 66
4.2.1.3 Primary Analysis of Primary Endpoint 67
4.2.1.4 Sensitivity Analyses of the Primary Endpoint 67
4.2.1.5 Supplementary Analysis of the Primary Endpoint 67
4.2.1.6 Subgroup Analysis of the Primary Endpoint 67
4.2.2 Secondary Endpoint 69
4.2.2.1 Handling of Dropouts and Missing Data 69
4.2.2.2 Percentage change in HVPG 69
4.2.2.3 HVPG response 69
4.2.2.4 Change in body weight, total body water, extracellular water, intracellular water volumes, body fat mass, total dosage of loop-diuretic equivalents, systolic blood pressure, diastolic blood pressure 70
4.2.3 Exploratory Endpoint 71
4.2.3.1 Handling of Dropouts and Missing Data 71
4.2.3.2 Different HVPG response 71
4.2.3.3 Absolute change in HVPG compared to dapagliflozin monotherapy 72
4.2.3.4 Percentage and absolute change in liver and/or spleen stiffness 72
4.2.3.5 Liver health and portal hypertension biomarkers 72
4.2.3.6 Decompensation event 73
4.2.3.7 Change in CCI 74
4.2.3.8 Change in blood and urine biomarkers 74
4.2.3.9 Plasma concentration 75
4.2.3.10 HVPG further understanding 75

4.3 Pharmacodynamic Endpoint(s) 75
4.4 Pharmacokinetics 75
4.5 Immunogenicity 75
4.6 Safety Analyses 75
4.6.1 Exposure 76
4.6.1.1 Definitions and Derivations 76
4.6.1.2 Presentation 77
4.6.2 Adverse Event 77
4.6.2.1 Definitions and Derivations 77
4.6.2.2 Presentation 79
4.6.3 Clinical Laboratory, Blood Sample 81
4.6.3.1 Definitions and Derivations 81
4.6.3.2 Presentation 82
4.6.4 Clinical Laboratory, Urinalysis 83
4.6.4.1 Definitions and Derivations 83
4.6.4.2 Presentation 83
4.6.5 Vital Signs 84
4.6.5.1 Definitions and Derivations 84
4.6.5.2 Presentation 84
4.6.6 Electrocardiogram 85
4.6.6.1 Definitions and Derivations 85
4.6.6.2 Presentation 85
5 INTERIM ANALYSIS 85
6 REFERENCES 86
7 APPENDIX 87
7.1 Laboratory Safety Variables 87

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AE	Adverse event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASH	Alcoholic Steatohepatitis
AST	Aspartate Aminotransferase
AZ	AstraZeneca
BMI	Body Mass Index
CCI	CCI
CCI	CCI
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CCI	CCI
DMC	Data Monitoring Committee
CCI	CCI
eCRF	Electronic Case Report Form
CCI	CCI
EOS	End of Study
CCI	CCI
ET-1	Endothelin-1
FAS	Full Analysis Set
FHVP	Free Hepatic Venous
CCI	CCI
CCI	CCI
HR	Hazard Ratio

HVPG	Hepatic Venous Pressure Gradient
ICF	Informed Consent Form
IP	Investigational Product
IPD	Important Protocol Deviation
LLN	Lower Limit Normal
LSMD	Least Square Mean Difference
MELD	Model For End-Stage Liver Disease
MMRM	Mixed Model for Repeated Measures
NASH	Non-Alcoholic Steatohepatitis
NSBB	Non-selective beta-blockers
CCI	CCI
PD	Protocol Deviation
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PT	Preferred Term
PPS	Per Protocol Analysis Set
RDMS	Regulatory Document Management System
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SE	Standard Error
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System Organ Class
ULN	Upper Limit Normal
WHVP	Wedged Hepatic Venous Pressure

AMENDMENT HISTORY

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	10/26/2022	Initial approved SAP.	N/A	N/A
Statistical analysis method for primary endpoints	4/4/2023	Section 4.2.1.4. Added sensitivity analysis for the primary endpoint in Part B regarding handling of terminal events.	Yes, version 2.0	Relevant analysis, to facilitate interpretation.
Statistical analysis method for primary or secondary endpoints	4/4/2023	Section 4.2. For the primary estimand added a intercurrent event strategy for handling of terminal events (e.g. death)	Yes, version 2.0	Clarification of definition.
Data presentation	4/4/2023	Section 1.1. Added Asia as a possible region for Part B since China could participate in Part B.	Yes, version 2.0	Clarification for scenarios not previously handled.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	4/4/2023	Section 4.1.1.1. Changed reasons for withdrawal from the study to be presented.	Yes, version 2.0	To facilitate interpretation.
Data presentation	4/4/2023	Section 4.1.8.1. Added non-selective beta blocker usage as a category in basline disease characteristics. Added ascites group 3 as a category in baseline disease characteristics.	Yes, version 2.0	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	4/4/2023	Section 4.2.3.8. Added CCI [redacted], as exploratory biomarkers for the exploratory analysis, removed CCI [redacted] Added ANCOVA as model to analyse CCI [redacted].	Yes, version 2.0	To facilitate interpretation.
Data presentation	4/4/2023	Section 4.2.3.8. Added copeptin levels as a variable that is outside of the scope of the CSR and will be reported separately.	Yes, version 2.0	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	4/4/2023	Section 4.2.3.5. Changed analysis model from ANCOVA to MMRM for the exploratory endpoint of liver health and portal hypertension biomarkers, will be analysed to Week 6 and Week 16	Yes, version 2.0	To align with CSP.
Data presentation	4/4/2023	Section 4.2.3.10. Added WHVP, FHVP and right atrial pressure as additional analysis.	Yes, version 2.0	To facilitate interpretation.
Data presentation	4/4/2023	Section 4.6.2.1. Added definition of [redacted]	Yes, version 2.0	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	4/4/2023	Section 4.6.2.1. Removed subsection about AE leading to withdrawal from study, since it is not collected in Part A.	Yes, version 2.0	To facilitate interpretation.
Data presentation	4/4/2023	Section 4.6.2.1. Removed subsection about interruption of IP due to treatment-emergent abnormalities in liver function test.	Yes, version 2.0	To facilitate interpretation.
Data presentation	4/4/2023	Section 4.6.2.2. Added clarity that AESIs will be presented in overall summary.	Yes, version 2.0	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	4/4/2023	Section 4.6.3.1. Changed abnormality criteria for INR from ULN to be based of baseline values instead	Yes, version 2.0	To facilitate interpretation.
Data presentation	4/4/2023	Section 4.6.3.2. Changed from percentage to absolute when presenting change from baseline in clinical laboratory parameters.	Yes, version 2.0	To facilitate interpretation.
Data presentation	4/4/2023	Section 4.6.3.2. Added that laboratory data can be presented in SI or conventional units, if applicable.	Yes, version 2.0	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	4/4/2023	Section 4.6.3.2. Added that shift tables from baseline can be presented either maximum or minimum value during the on-treatment period.	Yes, version 2.0	To facilitate interpretation.
Data presentation	4/4/2023	Section 4.6.6.2. Clarified details that no quantative ECG parameters are collected and how these will be presented.	Yes, version 2.0	To facilitate interpretation.
Other	4/4/2023	Section 3.2.1.1. Added that baseline definition will include the same day as administration of first dose.	Yes, version 2.0	Clarification of definition.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Other	4/4/2023	Section 4.2. For the primary estimand added a while-on-treatment intercurrent event strategy for handling of PK data.	Yes, version 2.0	Clarification of definition
Other	4/4/2023	Section 4.2. In the safety estimand, removed PKS from the population attribute and moved it to primary estimand.	Yes, version 2.0	Correction of errors.
Other	4/4/2023	Section 4.2.2, Section 4.2.3. Added clarification of how terminal events will be handled for primary, secondary and exploratory endpoints.	Yes, version 2.0	To align with the primary estimand.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Other	4/4/2023	Section 4.6. Moved safety estimand to safety section.	Yes, version 2.0	To align with Safety estimand.
Other	4/4/2023	Fixed typos, abbreviations and other language-related issues.	Yes, version 2.0	Corrections of errors.
Statistical analysis method for primary endpoints	22/8/2023	Section 4.2. Changed primary analysis method in Part B from common risk ratio to common risk difference due to the possibility of zero responders in a treatment group.	Yes, version 2.0	Relevant analysis, to handle scenarios not previous taken into account.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Statistical analysis method for primary or secondary endpoints	22/8/2023	Section **Error! Reference source not found.**. Changed secondary analysis method in Part A from risk ratio to risk difference due to the possibility of zero responders an a treatment group.	Yes, version 2.0	Relevant analysis, to handle scenarios not previous taken into account.
Data presentation	22/8/2023	Section 4.2.2.4. Changed accumulated dosage to total dosage and of loop-diuretic equivalents will only be presented in absolute change from baseline due to the possibility of having zero loop-diuretic use at baseline.	No, version 2.0. CSP will be updated.	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	22/8/2023	Section 4.2.2.4. Body water volumes and body fat mass will be presented in absolute and percentage change from baseline. Blood pressure will only be presented in absolute change from baseline.	Yes, version 2.0	To facilitate interpretation.
Data presentation	22/8/2023	Section 4.2.2.4. Descriptive statistics will be used for presented CCI CCI due to the possibility of very few baseline values, the previous proposed MMRM model may not converge.	Yes, version 2.0	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	22/8/2023	Section 4.2.3.2. Changed analysis method to common risk difference due to the possibility of zero responders in a treatment group.	Yes, version 2.0	Relevant analysis, to handle scenarios not previous taken into account.
Data presentation	22/8/2023	Section 4.6.3. Added clarity that coagulation abnormalities key subject information table will also be presented.	Yes, version 2.0	To facilitate interpretation.
Other	22/8/2023	Section 4.2.1.6. Added clarity how mean arterial pressure is derived.	Yes, version 2.0	To facilitate interpretation.
Other	22/8/2023	Fixed typos, abbreviations and other language-related issues.	Yes, version 2.0	Corrections of errors.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Statistical analysis method for primary endpoints	14/2/2024	Section 4.2. Changed primary analysis method in Part B from common risk difference to absolute change and the original Part B primary endpoint moved to secondary objective. Removed imputation approach from Section 4.2.3.2.	Yes, version 3.0	Due to Part A results and to increase the power of the study.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Statistical analysis method for primary endpoints	14/2/2024	Section 4.2. Removed sensitivity analysis for the primary endpoint that assumed terminal events as non-responders. Added supplemental analysis for Part B where deaths are handled using a composite strategy.	Yes, version 3.0	To facilitate interpretation.
Statistical analysis method for primary endpoints	14/2/2024	Section 4.2. Subgroup analysis for primary endpoint in Part B updated.	Yes, version 3.0	Due to Part A results, changed inclusion criteras.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Statistical analysis method for primary or secondary endpoints	14/2/2024	Section 4.2 and Section 1.2. Staggered randomisation scheme will not be applied in Part B, thus removed covariate of cohort from the models	Yes, version 3.0	Due to Part A results, no safety or tolerability issues showed.
Data presentation	14/2/2024	Section 1.3. The number of subjects increased from 22 to 33 per arm.	Yes, version 3.0	Due to Part A results and to increase the power of the study.
Data presentation	14/2/2024	Section 3.1 and Section 5. Removed interim analyses conducted by the DMC in Part A instead an internal Part B interim analysis will be conducted by AZ, clarified the scope of the interim.	Yes, version 3.0	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	14/2/2024	Section 4.1.2 and Section 4.6. Updated the analysis sets, FAS will be used for all safety analyses in Part B instead of the SAS. Part A will still use SAS for all safety analyses.	Yes, version 3.0	To adhere to as randomised principle. Same analysis set for efficacy and safety.
Data presentation	14/2/2024	Section 4.1.6. Altered age group categories to reflect if subjects have an age of below 18 or above 80.	Yes, version 3.0	To facilitate interpretation.
Data presentation	14/2/2024	Section 4.1.8. Updated disease characteristics due to inclusion criteras for Part B changed. Added baseline liver stiffness for Part B	Yes, version 3.0	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	14/2/2024	Section 4.2.3.3. Added exploratory endpoint of absolute change in HVPG on zibotentan and dapagliflozin in combination versus dapagliflozin monotherapy.	Yes, version 3.0	To facilitate interpretation.
Data presentation	14/2/2024	Section 4.2.3.4. Removed Week 16 timepoint since no liver/spleen stiffness data is collected for that visit in Part B. Added liver stiffness analysis for Part B	Yes, version 3.0	To facilitate interpretation.
Data presentation	14/2/2024	Section 4.2.3.6. Clarified the presentation of decompensation events using survival analysis.	Yes, version 3.0	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	14/2/2024	Section 4.2.3.7. CCI	Yes, version 3.0	Corrections of errors.
Data presentation	14/2/2024		Yes, version 3.0	To facilitate interpretation.
Other	14/2/2024	Section 1.2. Clarified that the randomisation will be performed in balanced blocks in Part A and Part B.	Yes, version 3.0	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Other	14/2/2024	Section 3.2.1.1. Clarified baseline definition for compensated cirrhosis.	Yes, version 3.0	To facilitate interpretation.
Other	14/2/2024	Section 3.2.1.2. Moved study periods definition from 4.6.	Yes, version 3.0	To facilitate interpretation.
Other	14/2/2024	Section 4.1.5.Updated the definition of IPD to be more aligned with the SOP's.	Yes, version 3.0	To facilitate interpretation.
Other	14/2/2024	Section 4.2 and Section 4.6. Updated the population attribute wording for the primary estimand and the safety estimand, to be more aligned with the CSP.	Yes, version 3.0	To facilitate interpretation.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Other	14/2/2024	Section 4.2.3.5. CCI CCI	Yes, version 3.0	To facilitate interpretation.
Other	14/2/2024	CCI	Yes, version 3.0	To facilitate interpretation.
Other	14/2/2024	Section 4.6.3. Clarified how treatment emergent laboratory abnormalities are defined.	Yes, version 3.0	To facilitate interpretation.
Other	14/2/2024	Section 7.1. Table updated to reflect the latest CSP.	Yes, version 3.0	To facilitate interpretation.
Other	14/2/2024	Fixed typos, abbreviations and other language-related issues.	Yes, version 3.0	Corrections of errors.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Statistical analysis method for primary endpoints	13/6/2025	Section 4.2.1, 4.2.2 Excluded the fixed categorical effects of stratification factor, affecting primary endpoint of HVPG as well as secondary endpoints of HVPG, body weight, body water volumes, body fat mass, total dosage of loop-diuretic equivalents, and blood pressure	Clarify the changes to protocol planned analyses, version 4.0	Due to limited number of patients with clinically detectable (grade 2) ascites recorded in the IRT.
Statistical analysis method for primary endpoints	13/6/2025	Section 4.2.1.6 Added details of model-based subgroup analyses	Yes, version 4.0	To provide details and facilitate interpretation

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	13/6/2025	Section 4.2.2.4 Added descriptive statistics of observed values as well as change from baseline for secondary endpoints	Yes, version 4.0	To facilitate interpretation
Other	13/6/2025	Section 2. Clarified the changes to protocol planned analyses	Clarify the changes to protocol planned analyses, version 4.0	To clarify gaps and facilitate interpretation
Other	13/6/2025	Section 3.2.1.1 Clarified the details of baseline as well as the definition of decompensated cirrhosis patient at baseline	Yes, version 4.0	To provide details and facilitate interpretation
Other	13/6/2025	Section 3.2.1.2 Clarified the analysis periods	Yes, version 4.0	To facilitate interpretation

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Other	13/6/2025	Section 3.2.1.4 Clarified the imputation of missing dates and for interim	Yes, version 4.0	To facilitate interpretation
Other	13/6/2025	Section 3.2.2 Added details of visit window for [redacted] and loop diuretics	Yes, version 4.0	To provide details and facilitate interpretation
Other	13/6/2025	Section 3.2.4 Added clarification of multiplicity and multiple comparison for key endspoints	Yes, version 4.0	To provide details and facilitate interpretation
Other	13/6/2025	Section 4.1.2.1 Added details of Pharmacokinetic Analysis Set	Yes, version 4.0	To facilitate interpretation
Other	13/6/2025	Section 4.1.8 Clarified details of baseline HVPG category for Part B based on the inclusion criteria	Yes, version 4.0	To facilitate interpretation

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Other	13/6/2025	Section 4.1.10 Clarified the definitions of prior and concomitant medication	Yes, version 4.0	To facilitate interpretation
Other	13/6/2025	Section 4.2.2.3, 4.2.3.2 Updated responder analysis risk difference instead of Mantel-Haenszel test	Clarify the changes to protocol planned analyses, version 4.0	To facilitate interpretation
Other	13/6/2025	Section 4.2 Clarified the treatment in Efficacy analyses as an attribute to primary estimand	Yes, version 4.0	To facilitate interpretation
Other	13/6/2025	Section 4.2.2.3 Clarified the HVPG responder in Part B	Yes, version 4.0	Due to Part A results and to facilitate interpretation

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Other	13/6/2025	Section 4.2.2.4 Added analyses for subgroup of compensated and decompensated Cirrhosis as well as clarified loop diuretic equivalents analyses	Yes, version 4.0	To inform drug project and facilitate interpretation
Other	13/6/2025	Section 4.2.3.9 Added details of Pk profile summary.	Yes, version 4.0	To facilitate interpretation
Other	13/6/2025	Section 4.6 Clarified the intercurrent event strategy for safety endpoints	Yes, version 4.0	To facilitate interpretation
Other	13/6/2025	Section 4.6.2.2 Clarified the AE listing, added AE for potential proarrhythmic effect and updated scope for narratives.	Yes, version 4.0	To facilitate interpretation and inform drug project

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Other	13/6/2025	Section 4.6.3 Added INR in the shift table, updated presentation for key subject information and CCI [redacted] CCI [redacted]	Yes, version 4.0	To facilitate interpretation
Other	13/6/2025	Section 4.6.5 Added definition of treatment emergent abnormality for vital signs CCI [redacted] CCI [redacted]	Yes, version 4.0	To facilitate interpretation
Other	13/6/2025	Section 4.6.6 Added definition of QTcF and its abnormality	Yes, version 4.0	To facilitate interpretation
Other	13/6/2025	Section 5 Added details of interim analysis	Yes, version 4.0	To facilitate interpretation and inform drug project

1 INTRODUCTION

Cirrhosis is the end-stage result of chronic liver injury/disease and patients with features of portal hypertension have limited treatment options and significant risk of decompensation and death. Zibotentan and dapagliflozin have different mechanisms of action and the outcome of combined treatment is expected to be complementary.

This study is a two part study. In Part A, patient population with Child-Pugh A cirrhosis with features of portal hypertension and no history of decompensation events will be assessed to evaluate efficacy, safety and tolerability of the combination of CCI zibotentan and 10 mg dapagliflozin versus placebo. If the safety profile is determined to be acceptable at the conclusion of Part A, Part B will investigate efficacy, safety and tolerability of CCI zibotentan combined with 10 mg dapagliflozin and of 10 mg dapagliflozin monotherapy versus placebo in subjects with compensated or decompensated cirrhosis. In contrast to part A, Part B will include subjects with a broader range of Child-Pugh A and Child-Pugh B, including those with more severe disease, a history of decompensation events, or current ascites up to grade 2.

This Statistical Analysis Plan (SAP) document describes the details for the statistical analysis supporting the Clinical Study Report (CSR) and the planned interim analysis.The SAP is based on the CSP D4326C00003 version 4.0 dated 28 May 2024.

1.1 Study 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 primary efficacy objective in Part A and Part B is to estimate the absolute change in hepatic venous pressure gradient (HVPG) at Week 6 from baseline. The secondary objectives in both Part A and Part B include the assessment of the percentage change in HVPG at Week 6 from baseline, HVPG response at Week 6 and change of body weight, body fat mass, and body water volumes, total dosage of loop-diuretic equivalents and blood pressure.

The study will be conducted in approximately 30 to 45 sites across North America, Europe and Asia (Part B), and will randomise approximately CCI subjects to 2 treatment groups (approximately CCI per group) for Part A and approximately CCI subjects to 5 treatment groups (approximately CCI per group) for Part B.

Part A:

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

Part B:

- 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 CCI + dapagliflozin tablet 10 mg.
- Treatment Group 4: zibotentan capsule CCI + dapagliflozin tablet 10 mg.
- Treatment Group 5: zibotentan capsule CCI + dapagliflozin tablet 10 mg.

For an overview of the study design, see Figure 1.

The total study duration for Part A will be approximately CCI weeks, the screening period can be up to CCI weeks prior to randomisation and follow-up period is approximately CCI weeks after subjects last dose of study intervention. Total study duration for subjects in Part B will be approximately CCI weeks, with same duration for the screening period and for the follow-up period as in Part A. The first dose will be taken at Visit 3 (Day 1) after randomisation in both Part A and Part B, once-daily of the assigned study intervention in addition to their standard of care.

A data monitoring committee (DMC) will monitor ongoing safety/tolerability data for Part A and Part B. The role and responsibilities of the DMC, and stopping criteria for the study, will be described in detail in the DMC charter.

An interim analysis is planned to be performed in Part B by an internal AstraZeneca (AZ) unblinded team when all randomised subjects have completed at least 6 weeks or have passed the planned Week 6 visit (ie, Visit CCI.

Figure 1 Study Design



1.2 Randomisation

All subjects in both Part A and Part B will be centrally assigned to randomised, blinded study intervention using an interactive response technology/randomisation and trial supply management (IRT/RTSM).

In Part A, subjects will be randomised to combination of zibotentan CCI and dapagliflozin tablet 10 mg or matching placebo (Treatment Group 1-2) in blocks to ensure approximate balance (1:1) between the treatment groups.

Subjects in Part B will be randomised to Treatment Group 1-5 in blocks stratified by the CCI at the time of randomisation. Subjects will be randomised to ensure approximate balance (1:1:1:1:1) across the treatment groups within each stratum.

The baseline HVPG measurement must be of good enough quality as judged by the central reader of HVPG in order to randomise subject for both Part A and Part B, in addition in Part B subjects HVPG at baseline must be >10 mmHg for inclusion.

1.3 Number of Subjects

Part A is a proof-of-concept study, the sample size is not determined based on formal statistical hypothesis testing. Assuming a difference of CCI in mean absolute change in HVPG at Week 6 for the combination of zibotentan and dapagliflozin group versus placebo group, and a common standard deviation (SD) of CCI HVPG evaluable subjects per group will provide CCI power to detect the difference in the primary endpoint with a Type I error of CCI% (one-sided). Accounting for an approximately CCI premature

treatment discontinuations, a total of CCI subjects (CCI per treatment group) is planned to be randomised in Part A to have CCI subjects with evaluable HVPG measurement at baseline and Week 6. For Part B, to detect a difference of CCI in mean absolute change in HVPG from baseline to Week 6 assuming a common SD of CCI HVPG-evaluable subjects per group will provide CCI% power to detect the difference at Week 6 with a Type I error of CCI% (one-sided). Accounting for an estimated CCI premature treatment discontinuation, a total of CCI subjects (CCI per treatment group) is planned to be randomised in Part B in order to have CCI subjects (CCI per treatment group) with evaluable HVPG measurements at baseline and Week 6. Approximately CCI subjects will therefore be randomised in Part B.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

For Part B, there is a change of endpoint regarding determining the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on CCI (efficacy). Due to the non-fasting biomarker samples only collected at Visit CCI(Screening), Visit CCI (Week 6), Visit CCI (Week 16) and Follow-up (Week CCI CCI CCI CCI CCI

For Part B, there is a change of modelling excluding the fixed categorical effects of stratification factor, affecting primary endpoint of HVPG as well as secondary endpoints of HVPG, body weight, body water volumes, body fat mass, total dosage of loop-diuretic equivalents, and blood pressure. The reason for this change is limited number of patients with clinically detectable (grade 2) ascites recorded in the IRT.

For Part B, there is a change of responder analysis using Fisher's exact test of risk difference instead of Mantel-Haenszel test. The primary reason was the change made to move the previous responder analysis from primary endpoint to secondary endpoint in SAP V4.0 (14 Feb 2024) and Fisher's exact test was considered more conservative as well as more suitable to the sample size of Part B study.

3 DATA ANALYSIS CONSIDERATION

3.1 Timing of Analyses

An interim analysis is planned to be conducted in Part B by an unblinded study team when all subjects have completed at least 6 weeks of treatment or passed Week 6 visit (ie, Visit CCI. The objective of the interim analysis is to facilitate the programme-development planning for zibotentan and dapagliflozin in combination.

The final clinical data lock for writing the CSR will occur once all subjects have completed their full study participation or withdrawn from study in Part B.

3.2 General Considerations

3.2.1 General Study Level Definitions

3.2.1.1 Baseline

Baseline is defined as the mean of the values obtained during the screening period for the following safety labs, CCI

- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, alkaline phosphatase (ALP) and international normalized ratio (INR).

For formulas using components of the above mentioned safety labs (e.g., AST/ALT ratio, AST/platelet ratio and CCI) baseline is the last non-missing value prior to or on the same date as the administration of the first dose of study intervention when all components of the formula is available at the same timepoint.

For all other measurements, baseline is defined as the last non-missing value prior to or on the same date as the administration of the first dose of study intervention, unless values on the same date are known to be both pre- and post-dose assessments in which case the pre-dose assessment will be used as baseline, for all analysis sets.

In Zeal, a patient with decompensated cirrhosis at baseline is defined as having either a history of or current ascites (grade 2 or 3) or having a history of Hepatic encephalopathy or Variceal hemorrhage, Acute kidney injury, Hepatorenal syndrome, Acute-on-chronic liver failure, Spontaneous bacterial peritonitis and complication unknown, collected on the LIVHIS form.

3.2.1.2 Study periods

For Part A and Part B the following study periods are defined:

Prior treatment

The event occurred during screening period and before the first administration of study intervention. Only applicable for SAE. Only be presented for listings.

On + off treatment

The event occurred on the same date or after the first administration of study intervention and ends on the earliest of: date of withdrawal of consent; date of death; and date of end of study.

On treatment

The event occurred on the same date or after the first administration of study intervention until the earliest of: 28 days following the date of last dose of study intervention; date of withdrawal of consent; date of death; and date of end of study.

Off treatment

The event occurred more than 28 days after the last dose of study intervention.

3.2.1.3 Study Day

Study day will be calculated from the date of first dose of study intervention. Day 1 is the day of first dose, Day -1 is the day prior to the date of first dose, there is no Day 0.

- If Assessment Date < Date of First Dose of Study Treatment then,

  $$Study\ day = Assessment\ Date - Date\ of\ First\ dose\ of\ Study\ Treatment.$$

- If Assessment Date ≥ Date of First Dose of Study Treatment then,

  $$Study\ Day = Assessment\ Date - Date\ of\ First\ dose\ of\ Study\ Treatment + 1.$$

3.2.1.4 Imputation of Incomplete Dates

The following imputed dates will only be used for analysis purpose and will remain as reported (partially or completely missing) in subject listings. Missing safety data will not be imputed.

Incomplete prior medication, concomitant medication and adverse event dates

Partially or completely missing medication or adverse event (AE) start dates will be imputed as follows:

- If medication started prior to study start, marked as taken prior to study start in the CM electronic case report form (eCRF), start date of medication may not be imputed. If not ticked in the case report form (CRF), the bullets below will be applied.
- If year is missing the year should be imputed as the year that the subject received the first dose of study treatment.
- If the year is available and the month and day is missing, then impute the month as January and the day as 01.
- If the year and month is available and the day is missing, impute the day as 01 (the first day of the month).
- If the AE/medication partial missing date is matching date of first dose of study treatment i.e. year and month matches year and month of first dose of study treatment, the date of first dose of treatment will be used.

- If the AE/medication start date is completely missing, the date of first dose of treatment will be used

Partially or completely missing medication or AE end dates will be imputed as follows:

- If the year is missing the year should be imputed as the year of end of study.
- If the year is available and the month and day is missing, then impute the month as December and the day as 31.
- If the year and month is available and the day is missing, impute the day as the last of the month (e.g. 28, 29, 30 or 31).
- If any of the above puts the date after the date of end of study, impute date as same as date of end of study.
- If the AE/medication end date is completely missing, the date of end of study will be used.

If the medication is marked as "Ongoing " the stop date will not be imputed. If the AE is still ongoing, AE not reported as resolved then the date will not be imputed.

Incomplete treatment end date (interim)

For interim analysis, missing treatment end date will be imputed as follows:

- If IP permanently discontinued or if IP interrupted but not yet restarted, then impute as the date of permanently discontinuation or as the date of IP interrupted

- If IP did not permanently discontinue or if IP was interrupted but restarted, then impute as the date of clinical data lock for the interim analysis.

3.2.1.5 Descriptive Statistics

Summary data will be presented by treatment group and analysis visit when applicable.

Quantitative data will be summarised by descriptive statistics, unless otherwise stated, including n, mean, SD, minimum, Q1, median, Q3 and maximum as appropriate. Geometric mean and CV will be calculated in addition to arithmetic mean and SD, if appropriate. Categorical data will be summarised as the number and percentage of subjects in each treatment group for each category. Percentages will not be presented for zero counts. Percentages will be presented to one decimal place. When appropriate, number of missing observations will be presented, and these will be included in the denominator when calculating percentages, unless otherwise specified.

A general rule is to present descriptive summary statistics (mean, SD, median, Q1, Q3, Confidence intervals (CI) and standard error (SE)) to 1 more decimal place than the individual values. The minimum and maximum values should be reported to the same number of decimal places as the individual values. In general, the maximum number of decimal places reported shall be three for any summary statistics.

If not otherwise stated testing at a one-sided CCI % significance level will be used and a two-sided CCI % CI will be reported.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Change from baseline will be presented similarly to summary data, with the absolute change from baseline and percent change from baseline summarised by descriptive statistics at the same timepoints, with the exception of baseline itself, in addition to the absolute values. The absolute change from baseline will be defined as the value post-dose minus the baseline value. Percent change from baseline at each timepoint will be calculated as:

$$change\ from\ baseline\ (\%) = \left(\frac{visit\ value - baseline\ value}{baseline\ value}\right) * 100.$$

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

3.2.1.6 Subject Convention

The term "participant" is generally used to refer to the language on the clinical study protocol (CSP), vendor technology, patient-reported outcomes and publication titles. The word "subject" is more commonly encountered in the statistical sections of this SAP for consistency. Participant, patient and subject are used interchangeably.

3.2.2 Visit Window

For the purpose of analysing visit based data, analysing visit windows will be used and are based on the target date for the planned visit, except for assessments which should only be collected once post-baseline (e.g. HVPG, VCTE/fibroscan, CCI vital signs collected pre-post HVPG procedure or measurements collected with regards to HVPG procedure) where visit reported by the investigator is used instead. All post-randomisation scheduled and unscheduled visits (including Early Termination visit), will be mapped to an appropriate visit unless specified otherwise shown in Table 1 for Part A, and for Part B as shown in Table 4.

Table 1 Part A Visit windows

CRF Visit	Target Day[a]	Protocol Visit Window[a]	Analysis visit window[b]	Analysis Visit
Visit CCI (Week 1)	Day 8	Day 6-10	Day 2-11	Week 1
Visit CCI (Week 2)	Day 15	Day 13-17	Day 12-18	Week 2
Visit CCI (Week 3)	Day 22	Day 20-24	Day 19-32	Week 3
Visit CCI (Week 6)	Day 43	Day 38-48	Day 33-50	Week 6
Visit CCI (Week 9)	Day 57	Day 54-60	Day 51-88	Follow-up

[a] Relative to the date of randomisation.
[b] Relative to the date of first dose of study treatment.

Data that has been collected daily (CCI) will be summarized using visit windowing presented in Table 2, for Part A.

Table 2 Part A CCI visit window

Analysis visit	Analysis visit window start day (day included) [a]	Analysis visit window end day (day included) [a]
Week 1	Day 2	Day 8
Week 2	Day 9	Day 15
Week 3	Day 16	Day 22
Week 4	Day 23	Day 29
Week 5	Day 30	Day 36
Week 6	Day 37	Day 43
Follow-up	Day 44	Each subject EOS[b]

[a] Relative to the date of first dose of study treatment.
[b] Given EOS occurs on or after study day 44.

Total dosage of loop-diuretics equivalents taken will be summarized using visit windowing presented in Table 3, for Part A. For analyses of loop-diuretic equivalents Day 1 is included for calculating cumulative actual loop-diuretics equivalents taken.

Table 3 Part A Loop-diuretic visit windowing

Analysis visit	Analysis visit window start day (day included) [a]	Analysis visit window end day (day included) [a]
Week 1	Day 1	Day 8

Table 3 Part A Loop-diuretic visit windowing

Analysis visit	Analysis visit window start day (day included) [a]	Analysis visit window end day (day included) [a]
Week 2	Day 9	Day 15
Week 3	Day 16	Day 22
Week 6	Day 23	Day 43

[a] Relative to the date of first dose of study treatment.

Table 4 Part B Visit Windows

CRF Visit	Target Day[a]	Protocol Visit Window[a]	Analysis visit window[b]	Analysis Visit
Visit CCI (Week 1)	Day 8	Day 6-10	Day 2-11	Week 1
Visit CCI (Week 2)	Day 15	Day 13-17	Day 12-18	Week 2
Visit CCI (Week 3)	Day 22	Day 20-24	Day 19-32	Week 3
Visit CCI (Week 6)	Day 43	Day 38-48	Day 33-53	Week 6
Visit CCI (Week 9)	Day 64	Day 61-67	Day 54-74	Week 9
Visit CCI (Week 12)	Day 85	Day 82-88	Day 75-99	Week 12
Visit CCI (Week 16)	Day 113	Day 109-117	Day 100-120	Week 16
Visit CCI (Week 18)	Day 127	Day 124-130	Day 121-158	Follow-up

[a] Relative to the date of randomisation.
[b] Relative to the date of first dose of study treatment.

Data that has been collected daily (CCI) will be summarized using visit windowing presented in Table 5, for Part B.

Table 5 Part B CCI visit window

Analysis visit	Analysis visit window start day (day included) [a]	Analysis visit window end day (day included) [a]
Week 1	Day 2	Day 8
Week 2	Day 9	Day 15
Week 3	Day 16	Day 22
Week 4	Day 23	Day 29
Week 5	Day 30	Day 36
Week 6	Day 37	Day 43

Table 5 Part B [redacted] visit window

Analysis visit	Analysis visit window start day (day included) [a]	Analysis visit window end day (day included) [a]
Week 7	Day 44	Day 50
Week 8	Day 51	Day 57
Week 9	Day 58	Day 64
Week 10	Day 65	Day 71
Week 11	Day 72	Day 78
Week 12	Day 79	Day 85
Week 13	Day 86	Day 92
Week 14	Day 93	Day 99
Week 15	Day 100	Day 106
Week 16	Day 107	Day 113
Follow-up	Day 114	Each subject EOS[b]

[a] Relative to the date of first dose of study treatment.
[b] Given EOS occurs on or after study day 114.

Total dosage of loop-diuretics equivalents taken will be summarized using visit windowing presented in Table 6 for Part B. For analyses of loop-diuretic equivalents Day 1 is included for calculating cumulative actual loop-diuretics equivalents taken.

Table 6 Part B Loop-diuretic visit windowing

Analysis visit	Analysis visit window start day (day included) [a]	Analysis visit window end day (day included) [a]
Week 1	Day 1	Day 8
Week 2	Day 9	Day 15
Week 3	Day 16	Day 22
Week 6	Day 23	Day 43
Week 9	Day 44	Day 64
Week 12	Day 65	Day 85
Week 16	Day 86	Day 113

[a] Relative to the date of first dose of study treatment.

For visit based-summaries, if there is more than one value per subject within a visit window, the closest assessment to the target date is assigned, or the earliest in the event the values are equidistant from the nominal visit date. For measurements where investigators reported visit are used, if there is more than one value per subject the same rule as above for

visit based-summaries will be used. The listings will highlight the value for that subject that went into the summary table, wherever feasible.

3.2.3 COVID-19

Subjects experiencing COVID-19 events will be captured on the AE case report form (CRF) and any dosing interruption due to COVID-19 will be captured on the exposure CRF, if a subject is terminated from the study due to COVID-19 it will be captured on the disposition CRF. The impact of COVID-19 pandemic is captured as a general question on each of these report forms pages on whether it was impacted as a global/country situation.

Subjects affected by the COVID-19 pandemic, such as efficacy or safety assessments not per CSP, will be recorded as protocol deviations (PD).

3.2.4 Multiplicity/Multiple Comparisons

The formal hypotheses tests will focus on the treatment effect of Zibo/dapa versus placebo on the efficacy endpoint related to HVPG. No multiplicity will be adjusted.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant medication and study drug compliance.

4.1.1 Subject Disposition and Complete Status

4.1.1.1 Definitions and Derivations

- Subjects screened will be defined as a subject who signed the informed consent form (ICF).
- Randomised will be defined as a subject who has been randomised to a treatment group.
- Screen failures are defined as subjects who signed the informed consent form but are not subsequently randomised to a treatment group.
- Subjects started treatment will be defined as a subject who has received at least one dose of study intervention.
- Completed treatment will be defined as a subject who has not permanently prematurely discontinued study intervention during the study. A subject who dies during follow-up

without having permanently discontinued study intervention prior to date of death, will be considered to have completed treatment.

- Subjects who discontinued treatment is defined as subjects who have permanently prematurely discontinued study intervention, the reasons for discontinuation as collected on the DOSDISC eCRF will be presented. For reason collected as "other", the specify field will be presented in listings but not in the disposition table.
- Completed study will be defined as a subject who has completed all phases of the study including the follow-up visit.
- Subjects who withdraw from the study are defined as subjects who have stopped the study medication permanently and are not willing to participate in the study further. The reason for withdrawal will be listed on Disposition form.
- Subjects who discontinued treatment due to global/country situation, if applicable.
- Subjects who withdraw from the study due to global/country situation, if applicable.

4.1.1.2 Presentation

For both Part A and Part B of the study, subject disposition and completion status will be described by treatment group for the total number of subjects and all subjects who have signed ICF. The reason for subjects who discontinued treatment will also be reported.

Number of subjects in each disposition status category will be presented, when applicable, percentages will also be presented.

A summary of global/country situation disposition table for the full analysis set (FAS) for both Part A and Part B will be provided.

By-subject listings of disposition details for discontinued subjects and subjects affected by the global/country situation will be provided. In addition by-subject listing of the randomisation scheme and codes will be provided.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Full Analysis Set

All subjects who are randomised and receive any study intervention will be included in the FAS. Subjects will be evaluated according to their randomised study intervention assignment, irrespective of the treatment actually received. For Part A and Part B the FAS will be used to analyse all efficacy endpoint analyses and all analyses of demographic, baseline characteristics, in addition for Part B the FAS will be used for all safety analyses.

Per Protocol Analysis Set

All subjects who are randomised and receive any study intervention and 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 will be included in the per protocol analysis set (PPS). All decisions to exclude subjects from the PPS will be made and documented prior to the unblinding of the study for Part A and prior to interim unblinding for Part B. The PPS will be used for supplementary analysis of efficacy endpoints.

Safety Analysis Set

All subjects who are randomised and receive at least one dose of the study intervention will be included in the safety analysis set (SAS). Subjects are evaluated according to the actual treatment they received. If a subject 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 subject received study intervention from the wrong kit for only a part of the treatment duration, they will be analysed according to their randomisation dose. The SAS will be used for all safety analyses in Part A.

Pharmacokinetic Analysis Set

All subjects who are randomised and receive any study intervention for whom have at least one detectable zibotentan or dapagliflozin plasma concentration measurement post-treatment will be included in the pharmacokinetic analysis set. Subjects are evaluated according to the actual treatment they received in Part A, and by their randomised study intervention assignment, irrespective of the treatment actually received in Part B. The pharmacokinetic analysis set (PKS) will be used for all pharmacokinetic (PK) analyses.

4.1.2.2 Presentation

For both Part A and Part B of the study, analysis sets will be presented by number of subjects in each analysis set for all randomised subjects, by treatment group and total number of subjects. The reason for exclusion from an analysis set will be presented.

By-subject listings of subjects excluded from each analysis set and the reason for exclusion from each analysis set will be provided.

4.1.3 Stratifications Factors at Randomisation

4.1.3.1 Definitions and Derivations

For Part B the stratifications factors are defined as clinically detectable (grade 2) ascites presence or non-presence at randomisation. Part A has no stratification factor.

4.1.3.2 Presentation

Subjects randomised to each of the stratification categories will be presented for the FAS by treatment group and total number of subjects for Part B.

4.1.4 Study Recruitment

4.1.4.1 Definitions and Derivations

Regions will be categorised by North America, Europe and Asia.

4.1.4.2 Presentation

Subject recruitment by region, country and site will be summarised for all enrolled subjects, FAS, PKS, PPS and SAS by treatment group and total number of subjects for Part A and Part B.

4.1.5 Protocol Deviations

4.1.5.1 Definitions and Derivations

Important protocol deviations (IPDs) are defined as protocol deviations which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a patient's rights, safety or well-being. They will include (but are not limited to):

- Inclusion Criteria Deviations.
- Exclusion Criteria Deviations.
- Discontinuation Criteria for study product met but patient not withdrawn from study treatment.
- Discontinuation Criteria for overall study withdrawal met but patient not withdrawn from study.
- Investigational Product Deviation.
- Excluded Medications taken.
- Deviations to study procedure.
- Other Important Protocol Deviations.

All IPDs will be identified and documented by the study team prior to unblinding of the trial. The number and percentage of subjects with any IPD will be summarised for each IPD category. Subjects with more than one deviation in the same IPD category will be counted once for that IPD category. Any subjects who have more than one IPD category will be counted once in the overall summary.

All decisions to exclude subjects from the PPS due to IPD will be made and documented prior to the unblinding of the study.

IPD handling depends on detection method and are verified with site and entered/reconciled with Clinical trial management system. Further details will be described in the protocol deviation plan.

4.1.5.2 Presentation

IPDs will be summarised for the FAS by randomised treatment group and total number of subjects for both Part A and Part B. The number and percentage of subjects with at least one IPD category as well as the number and percentage of subjects, meeting each IPD category will be provided by treatment group and in total.

A by-subject listing of IPD will be provided.

4.1.6 Demographics

4.1.6.1 Definitions and Derivations

Demographics characteristics based on the FAS includes:

- Age (years).
- Age group (<30, ≥30-<50, ≥50-<65, ≥65).
- Sex (male, female).
- Race (Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, White, Other).
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino).

4.1.6.2 Presentation

Demographics will be presented for the FAS, by treatment group and total number of subjects for both Part A and Part B.

Age will be presented as a continuous variable with descriptive statistics and categorically by age group. Sex, race and ethnicity will be presented as categorical variables.

4.1.7 Baseline Characteristics

4.1.7.1 Definitions and Derivations

Baseline patient characteristics includes:

- Body weight (kg).
- Body weight group:
  - <50 kg.
  - ≥50 kg and <75 kg.
  - ≥75 kg and <90 kg.

  - ≥90 kg and <120 kg.
  - ≥120 kg.
- Height (cm).
- BMI (kg/m²).
- BMI group:
  - Underweight (<18.5 kg/m²).
  - Normal weight (≥18.5 kg/m² and <25 kg/m²).
  - Overweight (≥25 kg/m² and <30 kg/m²).
  - Obese (≥30 kg/m²).

4.1.7.2 Presentation

Baseline patient characteristics will be presented descriptively by randomised treatment group and overall and will be based on FAS for Part A and Part B. Height, body weight and BMI will be presented as continuous variables with descriptive statistics. Body weight and BMI will also be presented categorically by group.

By-subject listings of demographic data (including age, race, baseline body weight, baseline height and baseline BMI) will be provided.

4.1.8 Baseline Disease Characteristics

4.1.8.1 Definitions and Derivations

The following disease characteristics will be presented at baseline:

- Baseline MELD score.
- Baseline Child-Pugh score.
- Baseline ascites:
  - No ascites or Grade 1.
  - Grade 2.
  - Grade 3.
  - Unknown
- Baseline HVPG (mmHg).
- Baseline HVPG (Part A), grouped by:
  - <10 mmHg.
  - ≥10 mmHg.
- Baseline HVPG, grouped by:

  - <12 mmHg.
  - ≥12 mmHg.
- Baseline HVPG (Part B), grouped by:
  - <16 mmHg.
  - ≥16 mmHg.
- Alcohol usage at baseline (current, former, never, defer).
- Baseline AUDIT score.
- Nicotine usage at baseline (current, former, never).
- CCI
- 
- Baseline spleen stiffness (kPa).
- Baseline liver stiffness (kPa) (Part B).
- Baseline systolic blood pressure (mmHg).
- Baseline diastolic blood pressure (mmHg).
- Baseline total body fat mass (kg).
- Baseline total body water volume (L).
- Baseline total extracellular water volume (L).
- Baseline total intracellular water volume (L).
- Baseline loop-diuretic usage (yes, no).
- Baseline decompensated cirrhosis (yes, no).
- Baseline compensated cirrhosis (yes, no).
- Baseline Type 2 diabetes (yes, no).

- CCI
- Baseline non-selective beta blockers usage (yes, no).

4.1.8.2 Presentation

Disease characteristics will be presented for the FAS, by treatment group and total number of subjects for Part A and Part B.

Baseline MELD score, Child-Pugh score, HVPG, CCI CCI alcohol use disorders identification test (AUDIT) score, CCI spleen stiffness, liver stiffness (Part B), systolic blood pressure, diastolic blood pressure, total body fat mass, total body water volume, total extracellular water volume and total intracellular water volume will be presented as continuous variables with descriptive statistics. Baseline ascites, alcohol usage, nicotine usage, CCI Type 2 diabetes, HVPG, decompensated cirrhosis, compensated cirrhosis, and loop-diuretics usage will be presented categorically by group.

A separate table of cirrhosis etiology (including Alcohol, Hepatitis B, Hepatitis C, NASH, Hemochromatosis, Autoimmune hepatitis, Wilson's Disease, A1AD, Sarcoid, etc) will be presented for the FAS, by treatment group and total number of subjects for Part A and Part B.

4.1.9 Medical History and Concomitant Disease

4.1.9.1 Definitions and Derivations

Medical history as well as surgical history will be coded according to MedDRA and will be summarized by system organ class (SOC) and preferred term (PT).

4.1.9.2 Presentation

Medical and surgical history will be presented descriptively for the FAS, by treatment group and total number of subjects for Part A and Part B. Percentages will be calculated with number of subjects in the FAS as denominator. Subjects are only counted once per SOC and PT regardless of the number of occurrences within each category.

PT will be presented within the relevant SOC and the table will be sorted firstly by international order of SOC and then alphabetically by PT.

4.1.10 Prior and Concomitant Medications

4.1.10.1 Definitions and Derivations

Prior medication is defined as any medication taken by the participant prior to the date of first dose of randomised treatment, regardless of when the medication ended. If medication is marked as taken to prior to study start in the CRF the medication will be prior medication.

A medication will be classified as concomitant if the medication end date is on or after the date of first dose of randomised treatment, or if the medication is ongoing at the study end.

Medications with completely missing end dates will be classified as concomitant.

Disallowed concomitant medication are defined in Section 6.5.1, Prohibited Medications of the CSP. All other concomitant medications are classified as allowed.

Prior and concomitant medications will be reported by ATC classification and generic drug name (according to WHODrug).

4.1.10.2 Presentation

Prior, allowed concomitant and disallowed medications will be presented descriptively by treatment group and total number of subjects for Part A and Part B, for the FAS. Percentages will be calculated with the number of subjects in the FAS as denominator. Subjects are only counted once per ATC classification and generic drug name regardless of the number of medication within each category. Generic drug name will be presented nested within the relevant ATC classification and sorted alphabetically by ATC and then generic drug name.

Prior medications, disallowed concomitant medications, and allowed concomitant medications will be presented separately.

4.1.11 Study Drug Compliance

4.1.11.1 Definitions and Derivations

The percentage of treatment compliance for zibotentan/placebo will be calculated from the number of capsules returned as:

$$\frac{Capsules\ dispensed - Capsules\ returned}{Capsules\ expected\ to\ be\ taken} * 100$$

The percentage treatment compliance for dapagliflozin/placebo will be calculated from the number of tablets returned as:

$$\frac{Tablets\ dispensed - Tablets\ returned}{Tablets\ expected\ to\ be\ taken} * 100$$

The overall percentage compliance will be calculated from the number of capsules and tablets returned as:

$$\frac{Capsules\ and\ Tablets\ dispensed - Capsules\ and\ Tablets\ returned}{Capsules\ and\ Tablets\ expected\ to\ be\ taken} * 100$$

A record of the number of capsules/tablets dispensed and returned during the site visits will be documented in the source documents and eCRF. The number of capsules and/or tablets expected to be taken is based on the number of study days between every set of clinical visits from Visit 3 to the end of treatment/early termination visit, excluding days of dose interruption.

Percent of compliance will also be categorized into three groups, these are:

- <80%.
- ≥80% to <120%.
- ≥120%.

For all calculations of compliance, dispensed and returned refers to capsules/tablets taken at clinic and at home.

4.1.11.2 Presentation

Compliance will be presented for the FAS by treatment group and total number of subjects for Part A and Part B. Compliance will be presented for zibotentan/placebo, dapagliflozin/placebo and overall as a continuous variable with descriptive statistics and categorically by compliance group where the number of subjects with missing compliance will also be presented.

By-subject listings of administration of investigational product (IP) will be provided.

4.2 Efficacy Analyses

This section covers details related to the efficacy endpoint analyses such as primary, secondary, other endpoints including sensitivity and exploratory.

The primary estimand of this study will be defined by the following attributes:

- Population: Patients with cirrhosis with signs of clinically significant portal hypertension due to any etiology except from chronic cholestatic liver disease. Details of the study population are defined by the inclusion and exclusion criteria in the CSP Section 5 and will be implemented through the use of the FAS and PKS (see Section 4.1.2).
- Treatment: Part A: treated with CCI zibotentan combined with 10 mg dapagliflozin versus placebo, in addition to their standard of care therapy; Part B: treated with CCI zibotentan combined with 10 mg dapagliflozin and 10 mg dapagliflozin monotherapy versus placebo, in addition to their standard of care therapy.
- Intercurrent events:
  - Premature treatment discontinuation due to any reason: The treatment policy strategy will be applied. Measurements for the variables of interest will be collected and analysed regardless of intercurrent events. This strategy requires that to the extent possible, randomised subjects are followed up regardless of the study intervention compliance.
  - Terminal events (i.e. death): A while-alive strategy will be applied. Terminal events expected to be few without substantial impact on the efficacy estimate and measurements of the variables of interest collected prior the terminal events will be used for analysis, unless other specified.
  - For PK data a while-on-treatment strategy will be used to address intercurrent events. Values after intercurrent events will not be used for analysis.
- Variables: Table 7 and Table 8.
- Population level summary: Treatment difference (measured by mean difference and risk difference) for zibotentan and dapagliflozin in combination and dapagliflozin monotherapy (Part B) versus placebo.

Table 7 Part A Efficacy and PK Objectives Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary Efficacy Objectives:					
Objective 1:					
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.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, ANCOVA)	4.2.1
Secondary Efficacy Objectives:					
Objective 2:					
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	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, ANCOVA)	4.2.2.2
Objective 3:					
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 if HVPG ≥ 10 mmHg at baseline or a reduction in HVPG of ≥ 1.5 mmHg from baseline to Week 6.	FAS	Treatment policy	Risk difference	**Error! Reference source not found.**
Objective 4:					
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].	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.2.4

Table 7 Part A Efficacy and PK Objectives Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 5:					
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.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.2.4
Objective 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.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.2.4
Objective 7:					
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.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.2.4

Table 7 Part A Efficacy and PK Objectives Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Exploratory Efficacy Objectives:					
Objective 8:					
To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on spleen stiffness as measured with VCTE/Fibroscan.	Percentage and absolute change in spleen stiffness from baseline to Week 6.	FAS	Treatment policy	MSean difference between treatment groups (LSMD from change from baseline, ANCOVA)	4.2.3.4
Objective 9:					
To determine the effect of zibotentan and dapagliflozin in combination versus placebo on CCI	Change in CCI from baseline to Week 3 and Week 6.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.3.7
Objective 10:					
To assess the effect of zibotentan and dapagliflozin in combination versus placebo on plasma/serum CCI , CCI	Evaluation of changes in blood and urine biomarkers across time course of the study.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, ANCOVA or MMRM)	4.2.3.8
Exploratory PK Objectives:					
Objective 11:					

Table 7 Part A Efficacy and PK Objectives Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
To assess the plasma exposure of zibotentan and dapagliflozin in the participant population.	Plasma concentrations of zibotentan and dapagliflozin per treatment, visit and timepoint.	PKS	While-on-treatment	Descriptive statistics	4.2.3.9
Exploratory Biomarkers and Genetics Objectives:					
Objective 12:					
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. Will be reported outside this study's CSR.	NA	NA	NA	NA
Objective 13:					
(Optional) Collect and store blood samples for genetic research (according to each country's local and ethical procedures).	Exploratory research into genes/genetic variation that may influence response to treatment. Will be reported outside this study's CSR.	NA	NA	NA	NA

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

Table 8 Part B Efficacy and PK Objectives Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary Efficacy Objectives:					
Objective 1:					
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.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, ANCOVA)	4.2.1
Secondary Efficacy Objectives:					
Objective 2:					
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.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, ANCOVA)	4.2.2.2
Objective 3:					
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 if baseline HVPG > 12 mmHG from baseline to Week 6.	FAS	Treatment policy	Risk difference	**Error! Reference source not found.**4.2.2.3

Table 8 Part B Efficacy and PK Objectives Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 4:					
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].	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.2.4
Objective 5:					
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.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.2.4
Objective 6:					
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.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.2.4

Table 8 Part B Efficacy and PK Objectives Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 7:					
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.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.2.4
Exploratory Efficacy Objectives:					
Objective 8:					
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.	FAS	Treatment policy	Risk difference	4.2.3.2
Objective 9:					
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.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, ANCOVA)	4.2.3.3

Table 8 Part B Efficacy and PK Objectives Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 10:					
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.	Percentage and absolute change in liver and/or spleen stiffness from baseline to Week 6.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, ANCOVA)	4.2.3.4
Objective 11:					
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on liver health and portal hypertension biomarkers.	• Percentage and absolute change from baseline in AST and ALT from baseline to Week 6 and Week 16. • Absolute change from baseline in AST:ALT ratio, AST:platelet ratio, 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.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.3.5

Table 8 Part B Efficacy and PK Objectives Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 12:					
To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on proportion of participants experiencing a decompensation event defined as any of the following: variceal haemorrhage, clinically apparent ascites (grade 2 or 3), spontaneous bacterial peritonitis, hepatic encephalopathy, acute kidney injury or MELD score ≥ 15 on two consecutive occasions (visits) or death.	Composite of time to first event of: • Variceal haemorrhage. • Ascites (clinical grade 2 or 3). • Spontaneous bacterial peritonitis. • Overt hepatic encephalopathy (West Haven grading 2 or higher). • Acute kidney injury. • MELD score ≥15 on two consecutive occasions (visits). • Death.	FAS	Treatment policy	Hazard ratio (Cox-proportional hazards model)	4.2.3.6
Objective 13:					
To determine the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on CCI	Change in CCI from baseline to Week 6 and Week 16.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.3.7

Table 8 Part B Efficacy and PK Objectives Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 14:					
To assess the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on plasma/serum [redacted]	Evaluation of changes in blood and urine biomarkers across time course of the study.	FAS	Treatment policy	Mean difference between treatment groups (LSMD from change from baseline, ANCOVA or MMRM)	4.2.3.8
Exploratory PK Objectives:					
Objective 15:					
To assess the plasma exposure of zibotentan and dapagliflozin in the participant population.	Plasma concentrations of zibotentan and dapagliflozin per treatment, visit and timepoint.	PKS	While-on-treatment	Descriptive statistics	4.2.3.9

Table 8 Part B Efficacy and PK Objectives Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Exploratory Biomarkers and Genetics Objectives:					
Objective 16:					
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. Will be reported outside this study's CSR.	NA	NA	NA	NA
Objective 17:					
(Optional) Collect and store blood samples for genetic research (according to each country's local and ethical procedures).	Exploratory research into genes/genetic variation that may influence response to treatment. Will be reported outside this study's CSR.	NA	NA	NA	NA

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

4.2.1 Primary Endpoint

4.2.1.1 Definition

For Part A the primary efficacy endpoint is the absolute change in HVPG from baseline to Week 6. No formal hypothesis testing will be carried for Part A.

For Part B the primary efficacy endpoint is the absolute change in HVPG at Week 6. The primary hypothesis is that the combination of zibotentan and dapagliflozin will reduce HVPG at Week 6 compared to placebo.

4.2.1.2 Handling of Dropouts and Missing Data

Since baseline HVPG is an inclusion criterion for both Part A and Part B of the study, no imputation will be done for the baseline HVPG value. For post-baseline missing HVPG values a monotone missing data pattern will be used. Monotone missing data are defined as missing data which constitute the end of a subject follow-up, in this case their HVPG reading at Visit [redacted] For both Part A and Part B missing at random is assumed.

Missing HVPG data due to terminal events will not be imputed (i.e., subjects will be excluded).

Part A and Part B

The PROC MI regression will be used to impute missing data for HVPG at Visit [redacted] for Part A and Part B. The imputation model will include treatment group, baseline HVPG and HVPG at Visit [redacted] in this order. Following steps will be taken:

- Step 1: Missing HVPG values in each arm will be imputed with non-missing HVPG values in the same treatment group using PROC MI with the MONOTONE statement set to the REGRESSION option, treatment group and baseline HVPG as covariates.
- Step 2: Impute 1000 datasets using seed 4407 (Part A). Impute 1000 datasets using seed 9308 (Part B).
- Step 3: Fit the pre-specified analysis of covariance (ANCOVA) model to each imputed dataset using PROC MIXED and store the 1000 resulting least square mean estimates for each treatment group and the difference between treatment groups, and corresponding standard errors for each model.
- Step 4: Pool results using Rubin's rule in PROC MIANALYZE to provide the final least square mean estimates, two-sided 90% CIs, and one-sided p-value for the difference between treatment groups.

4.2.1.3 Primary Analysis of Primary Endpoint

For Part A and Part B the absolute change in HVPG from baseline to Week 6 will be analysed with an ANCOVA model, including all subjects in the FAS. In Part A and Part B the model will include treatment group as fixed categorical factor and HVPG baseline value as a continuous covariate. In the models the dependent variable will be the absolute change in HVPG from baseline to Week 6.

Least square mean estimates for each treatment group and the difference between treatment groups (compared to placebo), two-sided 90% CIs and one-sided p-value will be presented.

In addition, descriptive statistics will be presented.

By-subject listings of the HVPG data will be provided for both Part A and Part B.

4.2.1.4 Sensitivity Analyses of the Primary Endpoint

The following sensitivity analysis will be conducted:

- The same approach as in Section 4.2.1.3 for the primary analysis for the FAS but using control-based pattern instead under the missing not at random assumption. Control based imputation will ultilize only placebo to inform missing data.

4.2.1.5 Supplementary Analysis of the Primary Endpoint

The following supplementary analysis will be conducted:

- The same approach as in Section 4.2.1.3 for the primary analysis but for the PPS instead but without imputing missing HVPG data at Week 6, (i.e., subjects with missing data will be excluded).
- The same approach as in Section 4.2.1.3 for the primary analysis for the FAS but without imputing missing HVPG data at Week 6, (i.e., subjects with missing data will be excluded).
- The same approach as in Section 4.2.1.3 for the primary analysis for the FAS but using a composite strategy for handling of terminal events. Missing HVPG data at Week 6 due to terminal eventswill be imputed with their baseline value + uniform(0, 10) using RANUNI with seed 8275 (Part B only).

4.2.1.6 Subgroup Analysis of the Primary Endpoint

The following baseline and demographic variables are defined for the purpose of efficacy subgroup analysis to assess consistency of effect for Part A and Part B unless otherwise stated:

- Baseline HVPG (< 10 mmHg, ≥ 10 mmHg) (Part A only).
- Baseline HVPG (< 12 mmHg, ≥ 12 mmHg).
- Baseline HVPG (< 16 mmHg, ≥ 16 mmHg) (Part B only).
- Use of non-selective beta-blockers (NSBB) at baseline (Yes/No).
- History of Type 2 diabetes (Yes/No).
- Sex (Male/Female).
- Baseline mean arterial pressure (≤ 100 mmHg, >100 mmHg).
- Baseline etiology (NASH/Other etiologies excluding NASH) (Part B only).
- Baseline etiology (ASH/Other etiologies excluding ASH) (Part B only).
- Baseline cirrhosis (Compensated/Decompensated) (Part B only).
- Baseline Child-Pugh class(Child-Pugh A/ Child-Pugh B) (Part B only).

Mean arterial pressure is defined as:

$$Mean\ arterial\ pressure\ (mmHg) = diastolic\ blood\ pressure + \frac{systolic\ blood\ pressure - diastolic\ blood\ pressure}{3}$$

For Part A and Part B, descriptive statistics of HVPG will be presented for each subgroup.

Besides, model based analysis will be performed as follows for Part B. Given the number of patients expected in each subgroup and the exploratory nature of these subgroup analyses, the same ANCOVA model for the primary analysis described in Section 4.2.1.3 will be performed separately in each subgroup population. Thus no p-value of subgroup-by-treatment interaction will be presented.~~.~~

Participants with missing values in a subgroup variable will be excluded from the corresponding subgroup analysis.

The estimates within each subgroup, including least square mean estimates for each treatment and the difference between treatment, and 90% CIs, will be obtained in a similar way as for the primary analysis.

Results of the subgroup analyses will be presented in tables ~~and a forest plot~~.

4.2.2 Secondary Endpoint

4.2.2.1 Handling of Dropouts and Missing Data

In general, other than specified in the particular analysis, missing data will not be imputed and will be treated as missing.

4.2.2.2 Percentage change in HVPG

For Part A and Part B the percentage change in HVPG from baseline to Week 6 will be analysed with an ANCOVA model, including all subjects in the FAS. In Part A and Part B the model will include treatment group as fixed categorical factor and baseline value as a continuous covariate. In the models the dependent variable will be the percentage change from baseline to Week 6.

Missing HVPG data at Week 6 will be imputed according to the principles outlined in Section 4.2.1.2, except for missing due to terminal events. Patients with missing HVPG due to terminal events will not be imputed (i.e., subjects will be excluded).

In addition, descriptive statistics will be presented.

Least square mean estimates for each treatment group and the difference between treatment groups (compared to placebo), two-sided 90% CIs and one-sided p-value will be presented.

4.2.2.3 HVPG response

For Part A and Part B the HVPG response difference at Week 6 will be analysed via risk difference. The risk difference between the treatments will be calculated using PROC FREQ procedure with the RISKDIFF option in the table statement.

A HVPG responder in Part A is defined as a subject having < 10 mmHg at Week 6 if baseline HVPG ≥ 10 or a reduction of ≥ 1.5 mmHg from baseline to Week 6.

A HVPG responder in Part B is defined as a subject having at least 20% decrease or a reduction to or below 12 mmHg if baseline HVPG > 12 mmHG from baseline to Week 6.

Exact 90% (two-sided) CIs for response in each treatment group will be calculated using the Clopper-Pearson method. The exact unconditional 90% (two-sided) CI's for difference in response between the treatments will be computed based on score statistics [Chan and Zhang, 1999].

The number of HVPG responder per treatment group will be presented and the estimated response difference, with two-sided exact unconditional 90% CI's and a one-sided p-value calculated from the fishers exact test, will be reported for the comparisons for zibotentan and dapagliflozin in combination versus placebo. If the risk difference of response for an active treatment relative to placebo is > 0, it indicates the result is in favour of the active treatment.

Missing HVPG data at Week 6 will not be imputed (i.e., subjects with missing data will be excluded).

4.2.2.4 Change in body weight, total body water, extracellular water, intracellular water volumes, body fat mass, total dosage of loop-diuretic equivalents, systolic blood pressure, diastolic blood pressure

For Part A and Part B the secondary endpoint of percentage and absolute change from baseline in body weight, body water volumes, body fat mass, and absolute change from baseline in total dosage of loop-diuretic equivalents and blood pressure, at Week 6 and Week 16 (for Part B), a mixed model for repeated measures (MMRM) will be used. The percentage change from baseline or absolute change from baseline at each scheduled post baseline assessment is the dependent variable.

Same analysis will be applied to the subgroup of compensated and decompensated cirrhosis for these variables in Part B.

Loop-diuretic equivalents are defined as in Table 9 Loop-diuretic equivalents.

Table 9 Loop-diuretic equivalents

Drug	Global dose equivalent
Furosemide	40
Bumetanide	1
Torsemide	20
Etacrynic/Ethacrynic acid	50

For analyses of loop-diuretic equivalents, the cumulative actual loop equivalents taken will be compared to what the subject would have taken if continued to take equivalents as he/she did at baseline.

The model will include the continuous covariate of the baseline measurements as the fixed effect covariate, and the fixed categorical effects of treatment group, visit, and treatment-by-visit interaction.

The covariance structure used is unstructured. If the model does not converge with the unstructured covariance structure then Toeplitz, first-order autoregressive or compound symmetric covariance structure will be tried and the covariance structure will be decided based on model convergence status.

MMRM model assumes missing at random for subjects with missing data, missing data for subjects who have discontinued IP are treated the same way as the observed measurement from subjects who have not discontinued IP in the same treatment group.

Least square mean estimates for each treatment group, the difference between treatment groups, and two-sided 90% CIs along with a one-sided p-value will be presented. Figures (based on MMRM) showing absolute change and percentage respectively, from baseline to each scheduled assessment will be presented for all variables.

Besides MMRM, descriptive statistics of observed values as well as change from baseline for body weight, body water volumes, body fat mass, blood pressure will be presented from baseline to each scheduled post baseline assessment up to Week 18 for Part B. CCI [redacted] CCI [redacted] CCI [redacted] Observed values and absolute change from baseline by treatment group will be presented. No formal hypothesis testing will be carried out.

4.2.3 Exploratory Endpoint

4.2.3.1 Handling of Dropouts and Missing Data

In general, other than specified in the particular analysis, missing data will not be imputed and will be treated as missing.

4.2.3.2 Different HVPG response

For Part B the exploratory endpoint of HVPG response at Week 6, where a responder is defined as a subject exhibit 10%, 20%, and 30% decrease in HVPG from baseline to Week 6 will be analysed with risk difference for the FAS.

Tables for 10%, 20%, and 30% definition of a HVPG responder will be produced as described in Part B in Section 4.2.2.3.

Only subjects with non-missing HVPG values are included in the analysis.

4.2.3.3 Absolute change in HVPG compared to dapagliflozin monotherapy

For Part B the exploratory endpoint of absolute change from baseline in HVPG to Week 6 will be analysed with an ANCOVA model, including all subjects in the FAS. The model will include treatment group as fixed categorical factor and baseline value as a continuous covariate. In the model the dependent variable will be the absolute change from baseline to Week 6.

Missing HVPG data at Week 6 will be imputed according to the principles outlined in Section 4.2.1.2.

Least square mean estimates for each treatment group and the difference between treatment groups (compared to dapagliflozin monotherapy), two-sided 90% CIs and one-sided p-value, will be reported for the comparisons for zibotentan and dapagliflozin in combination versus dapagliflozin monotherapy.

4.2.3.4 Percentage and absolute change in liver and/or spleen stiffness

For Part A the exploratory endpoint of percentage and absolute change in spleen stiffness and for Part B, percentage and absolute change in liver stiffness and/or spleen stiffness from baseline to Week 6 will be analysed with an ANCOVA model, including all subjects in the FAS. The same model approach as in Section 4.2.2.2 will be used except missing data will not be imputed in this analysis.

4.2.3.5 Liver health and portal hypertension biomarkers

For Part B the exploratory endpoint of percentage and absolute change from baseline in AST and ALT to Week 6 and Week 16 will be analysed with an MMRM model for the FAS. The same model approach as in Part B in Section 4.2.2.4 will be used.

For Part B the exploratory endpoint of absolute change from baseline in AST:ALT ratio, AST:platelet ratio, and CCI to Week 6 and Week 16 will be analysed with an MMRM model for the FAS. CCI is calculated using the following formula:

CCI

The same model approach as in Part B in Section 4.2.2.4 will be used.

For Part B the exploratory endpoint of absolute change from baseline in MELD score to Week 6 and Week 16 will be analysed with an MMRM model for the FAS, same model approach as in Section 4.2.2.4 will be used.

4.2.3.6 Decompensation event

For Part B the exploratory endpoint of evaluating the proportion of subjects experiencing a decompensation event will be analysed with a Cox-proportional hazards model for the FAS.

Time to a decompensation event is defined as the composite of first event of:

- Variceal haemorrhage.
- Ascites (clinical grade 2 or 3).
- Spontaneous bacterial peritonitis.
- Overt hepatic encephalopathy (West Haven grading 2 or higher).
- Acute kidney injury.
- MELD score ≥15 on two consecutive occasions (visits).
- Death.

The number of subjects with events in the decompensation composite will be presented by treatment group. If there are at least one or more decompensation composite events, the time to first event will also be analysed using survival analysis.

For subjects with an event, the time at risk will be derived as:

- $Event\ onset\ date - date\ of\ randomisation + 1$ for the FAS.

All subjects who are event free for the given endpoint will be censored at the earliest of the date of withdrawal of consent or the date of the last study visit. Events are included regardless of discontinuation of study medication.

Cox-proportional hazards model will be used to analyse the composite endpoint and the components with a factor for treatment group using the Efron method for ties. Two-sided 90% CI for the hazard ratio (HR) will be based on the Wald statistic. The Kaplan-Meier with two-sided 90% CI, HR, and two-sided 90% CI of the HR will be reported. Kaplan-Meier estimate of the cumulative proportion of subjects with the composite endpoint will be plotted and the estimate at Week 6 and Week 16 will be presented in tables. In the summary table of this analysis in addition to HR with two-sided 90% CI and Kaplan-Meier estimate, presentation will include the number and percentage of subjects with events for the composite and components per treatment group.

The number of subjects with events for each component of the composite will be presented. If there are at least one or more events reported for the composite or the individual component of the composite, HR with two-sided 90% CI and Kaplan-Meier estimate at

Week 6 and Week 16 with two-sided 90% CI will be presented, otherwise only the number and percentage of subjects with event will be presented.



4.2.3.8 Change in blood and urine biomarkers

For Part A and Part B the exploratory endpoint of percentage and absolute change in blood and urine biomarkers for plasma/serum CCI , CCI CCI , CCI from baseline to Week 6 and from baseline to Week 16 (for Part B) will be analysed with an MMRM model for the FAS, same approach as in Section 4.2.2.4 will be used for respective part. No formal hypothesis testing will be carried out.

For Part A and Part B the exploratory endpoint of percentage and absolute change in blood and urine biomarkers for CCI from baseline to Week 6 (Part A) and Week 16 (Part B) will be analysed with an ANCOVA model, including all subjects in the FAS. The same model approach as in Section 4.2.2.2 will be used except missing data will not be imputed in this analysis. No formal hypothesis testing will be carried out.

The following variables are not part of the analysis above and are outside of the scope of the CSR and will be reported separately, if data permits:

- CCI
-
-
-

4.2.3.9 Plasma concentration

For Part A and Part B, for plasma concentrations of both zibotentan and dapagliflozin, descriptive statistics will be presented for observed values at each visit and timepoint by treatment group for the PKS.

Pharmacokinetic profile collected at Week 3 of both zibotentan and dapagliflozin will also be presented over the following sampling times: pre-dose, 0.5 to 1.0, 1.5 to 2.0, 2.5 to 3.0, 3.5 to 4.0, 4.5 to 5.5 hours post-dose, by treatment group for the PKS.

4.2.3.10 HVPG further understanding

For Part A and Part B descriptive statistics for wedge hepatic venous pressure (WHVP), free hepatic venous pressure (FHVP) and right atrial pressure will be presented for observed values and absolute change from baseline by treatment group for the FAS.

4.3 Pharmacodynamic Endpoint(s)

Details for these endpoints are described in Section 4.2.

4.4 Pharmacokinetics

Details are provided in Section 4.2.3.9.

4.5 Immunogenicity

Not applicable.

4.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs and ECG for Part A and for Part B.

Safety endpoints will be assessed through the estimand defined by the following attributes:

- Population: Patients with cirrhosis with signs of clinically significant portal hypertension due to any etiology except from chronic cholestatic liver disease. Details of the study population are defined by the inclusion and exclusion criteria in

the CSP Section 5 and will be implemented through the use of the SAS for Part A and the FAS for Part B (see Section 4.1.2).

- Treatment: Zibotentan and dapagliflozin in combination, dapagliflozin monotherapy (Part B) or placebo, in addition to their SoC.
- Intercurrent events: All analysis will be provided using the two complementary approaches:
  - Hypothetical, censoring patients beyond premature discontinuation of study treatment, implemented by using the on-treatment analysis period defined in Section 4.6.2.1.
  - Treatment policy, ignoring study treatment discontinuation, implemented by including all avaible data, using on + off treatment period defined in Section 4.6.2.1.
- Variables : Table 10.
- Population level summary: Distribution of endpoints by treatment group.

Table 10 Part A and Part B Safety Objectives and Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary Safety Objectives					
Objective 1:					
To asses the safety and tolerability of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy (applicable for Part B) versus placebo.	• AEs, SAEs and DAEs. • AESIs CCI CCI CCI CCI CCI CCI •	SAS (Part A) /FAS (Part B)	Hypothetical and treatment policy	Descriptive statistics	4.6.2
	• Clinical laboratory tests. • Vital signs. • ECG asssessments.	SAS (Part A) /FAS (Part B)	Treatment policy	Descriptive statistics	4.6.3, 4.6.4

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

The duration of exposure (days) will be calculated as:

$$Duration\ of\ Exposure\ (Days) = Date\ of\ Last\ Dose - Date\ of\ First\ Dose + 1.$$

Date of last dose will be extracted from DOSDISC form, while the first dose date is derived from the earliest administrated dose collected on the EX form.

4.6.1.2 Presentation

Duration of exposure will be calculated for all subjects in the SAS for Part A and the FAS for Part B by treatment group and total number of subjects. Duration of exposure will be presented as a continuous variable with descriptive statistics.

4.6.2 Adverse Event

Safety analyses will be performed using all subjects included in the SAS for Part A and the FAS for Part B. Safety data will be presented using descriptive statistics unless otherwise specified.

4.6.2.1 Definitions and Derivations

All AEs will be collected after the subject has received the first dose of the study intervention and SAEs will be recorded from the time of signing the ICF. All AEs will be collected until the end of subjects follow-up period.

All AEs will be listed and assigned to on/on + off treatment period, see Section 3.2.1.2:

- Prior treatment
- On + off treatment
- On treatment
- Off treatment

For on + off treatment period the assumption is that the risk for an event is independent of continued exposure to study drug, while the on-treatment the assumption is that the intercurrent events are non-informative. On + off treatment and on-treatment approaches are complementary estimands.

All AEs will be classified by SOC and PT according to a MedDRA version not more than one older than the latest version available at the time of database lock.

The following definitions and principles are to be followed:

Any AE

Defined as subjects with at least one reported AE with an onset date within the defined period.

AEs leading to discontinuation of IP

Defined as an AE with action taken study intervention reported as drug permanently discontinued. The onset date of the AE determines the analysis period, irrespectively of date of discontinuation of study intervention.

AEs leading to interruption of IP

Defined as an AE with action taken study intervention reported as drug interrupted.

SAEs

Defined as an AE reported as serious, irrespective of outcome. Any AEs caused by the HVPG procedure will be reported if it meets the SAE criteria in the SERAE form as "SAE Caused by Study Procedures(s)". The onset date of the premediating AE determines whether the SAE belongs to the analysis period, irrespectively of the date the AE becomes serious.

SAEs with outcome of death

Defined as SAE with reported outcome as "fatal", there may be more than one AE with outcome death for a subject. The onset date of the AE determines the analysis period, irrespective of date of death.

AEs possibly related to IP

Defined as an AE that is reported by the investigator as "reasonable possibility AE caused by IP". If this causality evaluation is missing, it will be counted as an AE possible related to study intervention.

AEs by maximum intensity

AEs will be classified by the reported maximum intensity (mild, moderate, and severe). If the maximum intensity evaluation is missing, it will be counted as "Severe".

AEs related to specific study procedures.

Any AE caused by the HVPG procedure should be reported only if it meets the SAE

Adverse events of special interest

CCI

- CCI
- [redacted]
- [redacted]

In addition, PTs will be used in order to categories. AESIs as reported by the investigator could be used as a complementary approach, if applicable.

CCI /modified Hy's law

AEs that are cases of CCI /modified Hy's law will be identified based on preferred term. Hy's law criteria as described in the Appendix E 3 of the CSP.

4.6.2.2 Presentation

The number and percentage of subjects with AEs will be tabulated. Unless otherwise specified summaries of AEs will be presented for the SAS, by actual treatment group, for both the on-treatment period and on + off treatment period for Part A and for the FAS, by planned treatment group, for both the on-treatment period and on + off treatment period for Part B. Percentages will be calculated with number of subjects in the analysis set as denominator, and subjects will only be counted once per category, regardless of the number of AEs satisfying the condition. Tables where AEs are presented by SOC and PT, will be sorted by international order for SOC and alphabetically order for PT. Tables where only PT is presented will be sorted by decreasing frequency of PT based on the highest dose combination of zibotentan and dapagliflozin.

All AE summary tables will be presented for on treatment AEs and for on + off treatment AEs. Prior treatment SAEs will be listed but not summarised.

The following summaries will be presented:

Overall summary of AEs

Number of subjects with any AE, any SAE, any SAE with outcome of death, any AE leading to discontinuation of IP, any AE leading to interruption of IP, AESIs, and any AE possible related to IP will be presented.

Number and percentage of subjects by treatment group will be presented.

By SOC and PT

Separate AE tables by SOC and PT will be provided for: Any AE, any SAE, any SAE with outcome of death, any AE leading to discontinuation of IP, any AE leading to interruption of IP, and any AE possible related to IP.

Number and percentage of subjects by treatment group will be presented.

Number of events by treatment group will be presented, if applicable.

By PT

Separate AE table sorted by decreasing frequency on PT level will be presented.

Number and percentage of subjects by treatment group will be presented.

Number of events by treatment group will be presented, if applicable.

Maximum intensity

AEs will be presented by their maximum intensity for all AE and by SOC and PT. Subjects are counted once for the maximum intensity per SOC and PT.

Number and percentage of subjects by their maximum intensity by treatment group will be presented.

Most common non-serious AEs

A table of non-serious AEs occurring in more than 5% of subjects in any treatment group will be presented by SOC and PT.

Number and percentage of subjects by treatment group will be presented.

Assessment of potential proarrhythmic effect

For Part B, a table with number and percentage of subjects with PTs relevant for assessment of potential proarrhythmic effect will be presented. PTs are based on the SMQ Torsade de pointes/QT prolongation (narrow and broad scope).

AEs of special interest

Number and percentage of subjects with an AESI will be presented by event category and by PT within the event category, by treatment group. Event count table will also be presented, by treatment group.

CCI /modified Hy's law

Number and percentages of subjects with event will be tabulated by treatment group.

Key subject information

Key subject information will be presented for subjects with SAEs, SAEs with outcome of death, AESIs, CCI /modified Hy's law, and AEs leading to discontinuation of IP.

Listings

An AE listing will cover details for each individual AE, a separate listing for subjects who were randomised but not exposed to IP will be presented.

SAEs that occurred during prior treatment period will be presented in a listing.

Narratives

Narratives will be produced for all deaths, SAEs, AE leading to discontinuation of IP and AESIs. Patients with drug interruptions and discontinuations due to CCI, liver safety and cardiac safety may also be presented as narratives.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Blood samples for determination of clinical chemistry, haemotology and coagulation will be collected according to the schedule of activities (SoA) according to Section 1.2 of the CSP. Clinical Safety Laboratory Assessments are listed in Appendix 7.1 of the SAP.

A laboratory value will be considered treatment emergent abnormality if it meets the predefined criteria for the abnormality, except where the baseline value met the criteria for the abnormality and the post-baseline value is less extreme (closer to the limit) or the same as the baseline value.

Subjects with clinical chemistry, haemotology and coagulation parameters abnormalities will be defined according to non-mutually exclusive thresholds based on reference ranges from the central lab, where applicable. In addition, the following definitions of laboratory abnormalities will be used for specific parameters:

- ALT: > 1 x ULN, > 3 x ULN, > 5 x ULN.
- AST: > 1 x ULN, > 3 x ULN, > 5 x ULN.
- AST or ALT ≥ 3 x ULN and Total Bilirubin > 2 x ULN.
- ALP: > 1 x ULN, > 3 x ULN, > 5 x ULN.
- Total Bilirubin: > 1 x ULN, > 2 x ULN, > 5 x ULN.
- Direct Bilirubin: > 1 x ULN, > 2 x ULN, > 3 x ULN.
- Platelet count: < 50 x 10^9/L, < 75 x 10^9/L.
- CCI
- CCI

In additional, the following laboratory abnormalities based on the subjects baseline will also be used for specific parameters:

- ALT: ≥ 2 x baseline and > 1 x ULN.
- AST: ≥ 2 x baseline and > 1 x ULN.
- ALP: ≥ 2 x baseline.
- Total Bilirubin: ≥ 2 x baseline and > 2 x ULN.
- Direct Bilirubin: ≥ 1 mg/dl + baseline.
- INR: > 0.2 + baseline, > 0.4 + baseline, > 0.6 + baseline.

Assessed values of the form '<x' (below the lower limit of quantification) or '>x' (above the upper limit of quantification) will be imputed as 'x' in calculation of summary statistics but displayed as '<x' or '>x' in listings.

CCI

CCI /modified Hy's law is defined in the Appendix E 3 of the CSP.

In shift tables, all parameters will be categorized according to the following mutually exclusive categories (when applicable): Normal(≤ upper limit normal (ULN)), High (> 1x ULN and ≤ 2 x ULN), Higher (> 2 x ULN and ≤ 5 x ULN), Highest (> 5 x ULN). In addition, platelet count, CCI and INR will be categorised according to the categories:

- Platelet count: < 50, ≥ 50 and < 75, ≥ 75 and < 150, ≥ 150 and < 400, ≥ 400 x 10^9/L.
- CCI
  CCI
- INR: ≤ 0.2 + baseline, > 0.2 + baseline and ≤ 0.4 + baseline, > 0.4 + baseline and ≤ 0.6 + baseline, > 0.6 + baseline.

4.6.3.2 Presentation

All laboratory data will be presented for the SAS in Part A and for the FAS in Part B and in SI or conventional units, if applicable.

Clinical laboratory parameters will be presented by treatment group and scheduled visit, separately for haematology, chemistry and coagulation parameters. All parameters will be presented as continuous variables with descriptive statistics for all visits at which an

assessment is scheduled. Observed value and absolute change from baseline will be presented using descriptive statistics for all scheduled assessments after baseline.

The number of subjects with treatment-emergent laboratory parameter abnormalities will be presented categorically by treatment group for the SAS in Part A and for the FAS in Part B according to the categories defined in Section 4.6.3.1.

Shift tables from baseline to maximum or minimum value during the on + off-treatment period will also be presented, by treatment group. For INR it will be based upon maximum on + off-treatment value as compared to baseline. The mutually exclusive categories are defined in Section 4.6.3.1.

For Part B, Scatter plot of maximum ALT or AST versus maximum total bilirubin and corresponding tabulation.

Key subject information will be presented for subjects with haematology abnormalities, chemistry abnormalities, coagulation abnormalities, in separate tables.

CCI

CCI

For Part B, additional key subject information and graphs of individual data will be presented including laboratory parameters which are associated with liver safety.

CCI

CCI

By-participant listings of all laboratory data will be provided.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

The following safety urinalysis are collected according to the schedule of activities (SoA) according to Section 1.2 of the CSP, pregnancy test urine and urine for screen of drug abuse. CCI .
Clinical Safety Laboratory Assessments are listed in Appendix 7.1 of the SAP.

4.6.4.2 Presentation

A summary table of number and percentage subjects with urine culture preformed and number and percentage of subjects with positive or negative urine cultures will be presented by actual treatment group for the SAS in Part A and by planned treatment group for the FAS in Part B. Percentages will be calculated with number of subjects in the analysis set as the denominator, and subjects will only be counted once per category, regardless of how many urine culture performed.

By-participant listings for urinalysis may be presented.

4.6.5 Vital Signs

4.6.5.1 Definitions and Derivations

Vital signs (body weight, pulse, body temperature, supine and standing blood pressure.) will be performed at each time points specified in the SoA of the CSP.

A treatment emergent abnormality for vital signs is defined as either of the below:

- A switch in parameter from normal to abnormal at post-baseline accordingly to predefined criteria, see below for predefined criteria.
- A baseline value that met the criteria for abnormality and the post-baseline value is more extreme (further from the limit), see below for predefined criteria.

The following predefined criterias of vital sign abnormalities will be used for specific parameters:

- Body weight (kg): Low < 50, Normal ≥ 50 and ≤130, High > 130
- Body temperature (C): Low < 35, Normal ≥ 35 and ≤ 37.5, High > 37.5
- Supine systolic blood pressure (mmHg): Low < 95, Normal ≥ 95 and ≤140, High > 140
- Supine diastolic blood pressure (mmHg): Low < 60, Normal ≥ 60 and ≤ 100, High > 100

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted].

4.6.5.2 Presentation

For each scheduled post-baseline visit, descriptive statistics for vital sign parameters (including CCI [redacted]) will be presented for observed values and absolute change from baseline by treatment group for the SAS in Part A and for the FAS in Part B.

A summary table of subjects experiencing significant changes from baseline outside predefined criteria, by vital sign parameter and treatment group for the SAS in Part A and for the FAS in Part B will be presented according to the categories defined in Section 4.6.5.1.

Shift tables from baseline to maximum on + off-treatment category will also be presented, by treatment group, according to the categories defined in Section 4.6.5.1.

Number and percentage of subjects who met CCI CCI will be presented by treatment group for both on-treatment and on + off treatment periods.

By-subject vital sign listings covering observed values and changes from baseline as well as abnormalities will be provided.

4.6.6 Electrocardiogram

4.6.6.1 Definitions and Derivations

The baseline for the safety electrocardiogram parameters will be the results obtained pre-dose on Day 1.

The (uncorrected) QT interval will be corrected according to the Fridericia's formula (QTcF). The following definitions of abnormalities will be used for specific parameter of QTcF:

- QTcF (ms); > 470 and > 500.

Borderline assessment contains both borderline not clinically significant and borderline clinically significant as collected in the eCRF.

4.6.6.2 Presentation

For Part A and Part B, no quantitative data will be collected for electrocardiogram parameters.

Shift tables for electrocardiogram assessment (normal/borderline/abnormal not clinically significant/abnormal clinically significant) for the SAS in Part A and for the FAS in Part B will be presented with number and percentages, by treatment group for baseline versus last observation on + off-treatment.

By-subject listings of electrocardiogram results and findings will be provide.

5 INTERIM ANALYSIS

There will be one administrative interim analysis being conducted by an internal AZ unblinded team for Part B, but there are no interim analysis planned for Part A. Part A will have a clinical data lock and pause enrollment, unblind the data to conduct preplanned analysis as described in the SAP and communicate with authorities before Part B of the study can start.

An administrative interim analysis for Part B is planned after all randomised participants have completed at least 6 weeks of treatment or passed the planned Week 6 visit (ie, Visit CCI. The objective of the administrative interim analysis in Part B is to facilitate the program development planning for zibotentan and dapagliflozin in combination based on the evaluation of efficacy and safety interim results.

It is worth to note that Week 6 HVPG measurements will be available for all participants by the time of data cut for the administrative interim analysis. Therefore, in the administrative interim analyses, the analysis results for all HVPG related efficacy endpoints (including primary efficacy endpoint of the absolute change in HVPG from baseline to Week 6) will be considered as final results, unless data issues are discovered after the interim analysis clinical data lock and before the final clinical data lock. Other non-HVPG related efficacy endpoints and safety endpoints will be analyzed based on available data up to data cut-off date. All the planned analysis as described in this SAP will be performed at the administrative interim and the analyses for efficacy and safety endpoints will be performed according to the methods described in Section 4.2 and Section 4.6 respectively.

The administrative interim analysis in Part B will be performed using data that is clean to the required level such that the data (up to cut-off date) for all participants will be cleaned and fully coded, where appropriate.

An internal AZ unblinded team will conduct the administrative interim analysis for Part B while a blinded study team will continue to run the study till clinical data lock for Part B. For more information regarding the blinding maintenance during the trial conduct, please refer to the Study Integrity Plan

For more information regarding the study integrity related to the interm analysis, please refer to the study integrity plan.

6 REFERENCES

[Chan and Zhang, 1999] Chan, I. S. F., and Zhang, Z. (1999). “Test-Based Exact Confidence Intervals for the Difference of Two Binomial Proportions.” *Biometrics* 55:1202–1209.

7 APPENDIX

7.1 Laboratory Safety Variables

Laboratory measurements according to Section 8 of the CSP.

Table 11 Laboratory Safety Variables

CCI

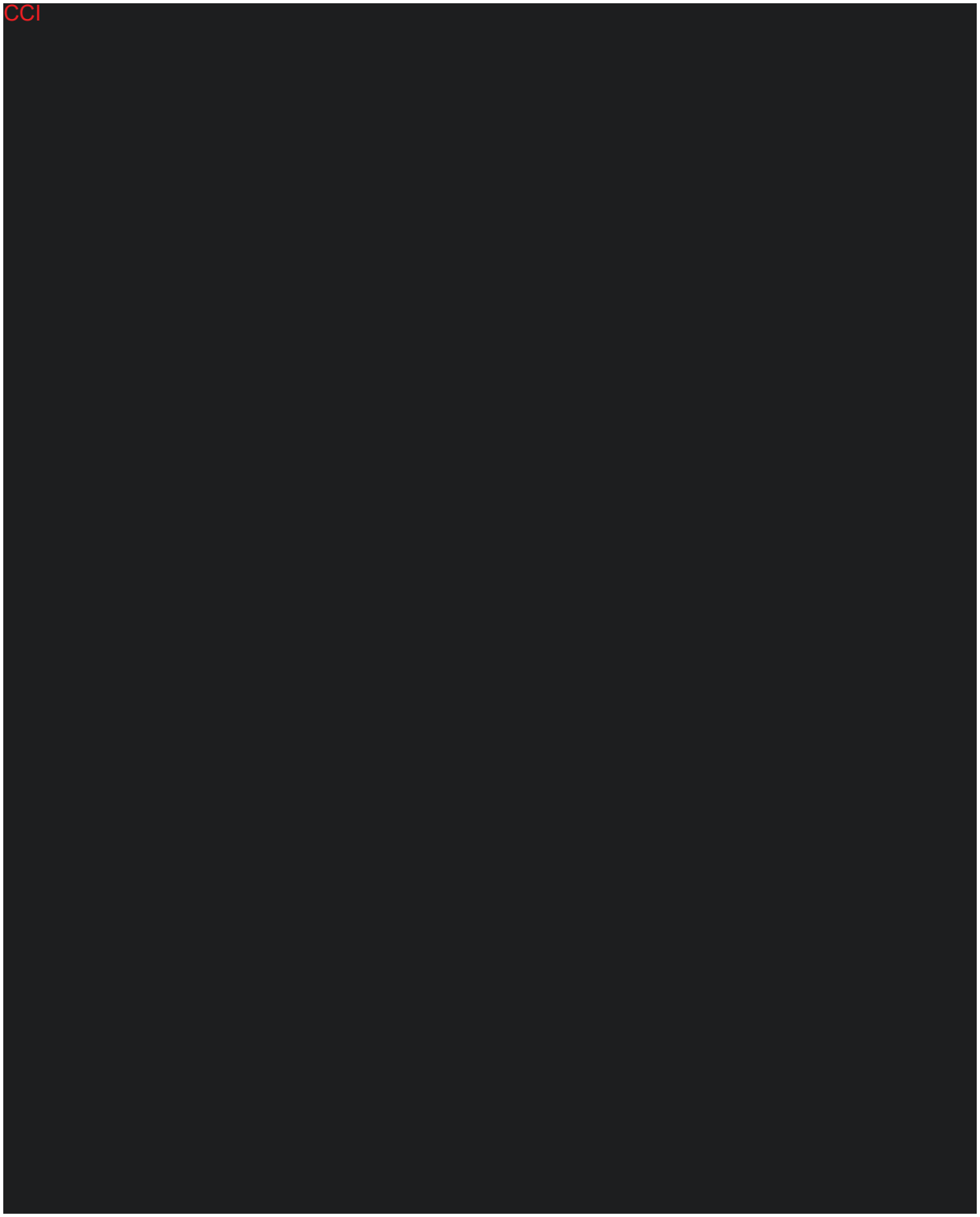


Table 11 Laboratory Safety Variables

CCI