STATISTICAL ANALYSIS PLAN

Study Code	D4326C00004
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A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase IIb Study to Evaluate the Safety of Zibotentan/Dapagliflozin in Combination Compared to Zibotentan Monotherapy as well as Zibotentan/Dapagliflozin and Zibotentan Monotherapy Compared to Placebo in Participants with Cirrhosis

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LIST OF ABBREVIATIONS

List abbreviations and definitions of specialized or unusual terms, measurements, or units. Examples are provided below. These can be modified at study level.

Abbreviation or Specialized Term	Definition
AE	Adverse event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of covariance
BMI	Body mass index
CI	Confidence Interval
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ICF	Informed Consent Form
IP	Investigational Product
IPD	Important Protocol Deviation
LSMD	Least Squares Mean Difference
PD	Pharmacodynamic
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System Organ Class

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	5/13/2024	Initial approved SAP	See section 2	N/A
See description	12/12/2024	Updated Changes to protocol.	See section 2	Previous changes vs CSP were implemented into CSP. The added change is due to no CCI for Japan and very few subjects in one of the CCI for rest of the world.
See description	12/12/2024	Added clarification that PKS will be analysed using assigned treatment group.	See section 2	Clarification
See description	12/12/2024	Added rules for number of decimals.	See section 2	Clarification
See description	12/12/2024	Updates to baseline definitions.	See section 2	Minor corrections to the definitions.
See description	12/12/2024	Added clarifications to imputations rules for dates. Adjusted definitions of prior and concomitant medication to align with current AZ standard.	See section 2	Align with data collection and standard definitions.
See description	12/12/2024	Added visit windowing for variables that are collected daily and that are composite endpoints.	See section 2	Due to nature of variables needed to add additional visit windowing.
See description	12/12/2024	Added Japanese specific analyses.	See section 2	Scope of TLFs was extended.
See description	12/12/2024	Added cirrhosis etiology characteristics.	See section 2	Missed in previous version.

See description	12/12/2024	Added clarification about dose interruptions for compliance.	See section 2	Clarification
See description	12/12/2024	Updated analyses method and population summary for exploratory objectives.	See section 2	Correction of previous and aligning with analyses used for key objectives.
See description	12/12/2024	Added clarification about how to handle values below lower limit of detection.	See section 2	Clarification
See description	12/12/2024	Added CCI for composite endpoints.	See section 2	Requested by FDA.
See description	12/12/2024	Added seed and information about number of imputations.	See section 2	Was missed to be specified in first version.
See description	12/12/2024	Added information about how to derive and analyse PRO.	See section 2	More detailed information added
See description	12/12/2024	Added information about additional AE outputs.	See section 2	Clarification and extended TLF scope.
See description	12/12/2024	Corrections and clarifications added to laboratory safety section. Information about additional KSI and individual graphs of laboratory data added.	See section 2	Clarification and extended TLF scope.
See description	12/12/2024	Clarifications to ECG section added.	See section 2	Clarification

1 INTRODUCTION

The purpose of this document is to give details for statistical analysis of study D4326C00004 supporting the clinical study report. The reader is referred to the CSP and the CRF for details of study conduct and data collection.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Note that this section lists deviations as from current CSP at the time of signing this SAP version. Future CSP amendments might include below listed topics and if so the SAP will no longer deviate from the CSP.

CSP states that the analysis model will include the fixed categorical effects of CCI factor but this will not be included in the models. Reason for change is that there is no CCI for Japan and very few subjects in one of the CCI for rest of the world.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

This study will have no interim analysis but there are originally two planned DMC meetings during the study to monitor safety as specified in the DMC Charter. At the time of SAP amendment it was known that the study would only have one DMC meeting before last subject last visit. The DMC works independent of the Global Study Team and will review unblinded study safety data.

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

3.2 Analysis Populations

The following analysis sets are defined for the study and detailed in Table 1:

Table 1 Populations for Analysis

Population/analysis set	Description
Screened analysis set	All participants who signed the ICF. Unless otherwise stated, the enrolled set will be used for the presentation of disposition data.

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

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

3.3 General Considerations

The FAS will be used for all analyses unless otherwise stated.

Descriptive summaries of continuous data will be done by following statistics, unless otherwise stated, n, mean, SD, minimum, median, and maximum as appropriate. Q1 and Q3 may also be shown.

Descriptive summaries of categorical data will be done as the number and percentage of subjects in each category for each treatment group. When appropriate, for study population the number of missing observations will be presented, and these will be included in the denominator when calculating percentages unless otherwise stated. For treatment emergent and shift tables number of observations will be used as denominator. For AE tables the denominator will be the number of participants within the analysis set.

In general the reported CIs will be 90% two-sided intervals.

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. Categorical data presented as percentages will be presented to one decimal place.

When coding using MedDRA the most recent version of the MedDRA that have been released for execution at AstraZeneca or designee will be used.

3.3.1 General Study Level Definitions

3.3.1.1 Baseline

For alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, alkaline phosphatase (ALP) and international normalized ratio (INR) baseline is defined as the mean of the values obtained during the screening period including unscheduled visits and the day of first dose.

For ECG and vital signs, baseline is defined as the last non-missing value prior to first administration of dose i.e. post-dose assessment on the day of first administration is not to be used.

The baseline value will for all other data be defined as the last non-missing value prior to or on the same date as administration of the first dose, 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 Loop diuretic baseline definition see section 3.3.1.5.

3.3.1.2 Analysis Periods

Planned treatment period

The planned treatment period starts on the date of first administration and ends on date of Visit 6.

Follow-up period

Starts the day after planned treatment period and ends on earliest of date of withdrawal of consent, death and last clinical assessment.

On-study analysis period

Starts on the date of first administration of study intervention and ends on the earliest of date of withdrawal of consent, death and last clinical assessment.

On-treatment period

Starts on the date of first administration and ends on the earliest of 28 days following the date of last dose of IMP or the end of the on-study analysis period.

3.3.1.3 Study Day

'Study Day' will be calculated relative to the date of first dose of study treatment i.e.:

if Assessment Date < Date of First Dose of Study Treatment, then

$$Study\ Day = Assessment\ Date - Date\ of\ First\ Dose\ of\ Study\ Treatment$$

else if Assessment Date ≥ Date of First Dose of Study Treatment, then

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

This means that Study Day 1 is the day of first dose, Study Day -1 is the day prior to the date of first dose, there is no Study Day 0.

3.3.1.4 Imputation of Incomplete dates

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 (unless below puts the date before the date of first dose of treatment, if so date of first dose will be used):

- 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 CRF, the bullets below will be applied.
- If the year is missing the year should be imputed as the year that 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 start date is completely missing, the date of first dose of treatment will be used.

Partially or completely missing medication or AE stop dates will be imputed as follows (unless below puts the date after the date of end of study, if so date of end of study will be used):

- 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 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.

The following imputed dates will only be used for analysis purpose and will remain as reported (partially or completely missing) in subject listings.

3.3.1.5 Loop diuretic equivalents

Table 2 Loop-diuretic equivalents

Drug	Global dose equivalent [a]	Japan dose equivalent
Furosemide	40	40
Bumetanide	1	N/A
Torsemide	20	8
Azosemide	N/A	60
Etacrynic/Ethacrynic acid	50	N/A

[a] Will be used for all countries except Japan.

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

3.3.1.6 eGFR, MELD score and Child-Pugh score calculations

eGFR

The participant's eGFR will be calculated based on two different equations. eGFR1 is according to the 2021 CKD-EPI equation, based on serum creatinine concentration alone (Inker et al, 2021). eGFR2 will be calculated based on both serum creatinine and serum cystatin C concentrations (Inker et al, 2021).

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

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

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

MELD score

The Model for end stage liver disease score, MELD score, is calculated for each visit according to:

MELD = 3.78 × ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57 × ln[serum creatinine (mg/dL)] + 6.43 If bilirubin, INR and/or creatinine values are less than 1.0, the value is set as 1.0.

Child-Pugh score

Child-Pugh score is calculated according to table Table 3.

Table 3 Child-Pugh Score

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

Abbreviations: INR = International Normalised Ratio.

3.3.1.7 Subgroups

Below defines the different subgroups to be analysed as stated in this document:

- CCI [redacted] patients

3.3.2 Visit Window

For the purpose of analysing visit based data, analysis visit windows will be used and are based on first dose date. All scheduled and unscheduled visits occurring the day after first dose or later (including Early Termination visit), will be mapped to an appropriate visit. Unless specified otherwise visit based analyses will follow as shown in Table 4.

Table 4 General visit windowing

Analysis visit label	Analysis visit window start day (day included)[a]	Analysis visit window end day (day included)[a]	Target Day[a]
Week 1	Day 2	Day 11	Day 8
Week 2	Day 12	Day 18	Day 15
Week 3	Day 19	Day 31	Day 22
Week 6	Day 32	Day 50	Day 43
Week 8	Day 51	Day 78	Day 57

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

For general 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.

Composite endpoints (key objective 1,2,7 and 8) will follow Table 5.

Table 5 Composite endpoints visit windowing

Analysis visit label	Analysis visit window start day (day included)[a]	Analysis visit window end day (day included)[a]
Week 1	Day 1 for component of fluid retention AEs Day 2 for other components	Day 11
Week 2	Day 12	Day 18
Week 3	Day 19	Day 25
Week 6	Day 26	Day 48
Week 8	Day 49	Each subjects EOS[b]

a Relative to the date of first dose of study treatment.
b Given that EOS occurs on or after study day 49.

Data that has been collected daily (loop-diuretic and home weight) will be summarized using visit windowing presented in Table 6.

Table 6 Home weight and Loop-diuretic visit windowing

Analysis visit label	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

Analysis visit label	Analysis visit window start day (day included)[a]	Analysis visit window end day (day included)[a]
Week 3	Day 16	Day 22
Week 4	Day 23	Day 29
Week 5	Day 30	Day 36
Week 6	Day 37	Day 43
Week 8	Day 44	Each subjects EOS[b]

a Relative to the date of first dose of study treatment.
b Given that EOS occurs on or after study day 49.

In general, for summaries of extreme data at a subject level, all observations will be included regardless of whether it is included in the by-visit data presentation, e.g. when deriving a statistic such as the maximum.

3.3.3 Handling of Unscheduled Visits

See section 3.3.2.

3.3.4 Multiplicity/Multiple Comparisons

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

3.3.5 Handling of Protocol Deviations in Study Analysis

Deviations from protocol will be assessed as “important” (IPD) or “non-important”. The final classification will be made prior to clinical data lock and all IPDs will be identified and documented by the study team prior to unblinding of the trial. Further details are described in the protocol deviation plan. IPDs will include following categories:

- Inclusion criteria
- Exclusion criteria
- Discontinuation criteria for study product met but participant not withdrawn from study treatment
- Discontinuation criteria for overall study withdrawal met but participant not withdrawn from study
- Investigational product deviation
- Excluded medication taken
- Deviations related to study procedure
- Other important protocol deviations

Protocol deviations will not be a reason for exclusion from analyses.

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 Completion Status

4.1.1.1 Definitions and Derivations

Disposition will be based on the Screened analysis set and following statuses are defined:

- Screened will be defined as a participant who signed ICF.
- Screen failure will be defined as a participant who signed ICF but are not subsequently randomised to a treatment group.
- Randomised will be defined as a participant who has been randomised to a treatment group.
- Randomised, not treated will be defined as a participant who has been randomised to a treatment group but who did not receive any dose of study intervention.
- Started treatment will be defined as a participant who has received at least one dose of study intervention.
- Completed treatment will be defined as a participant who has not permanently prematurely discontinued study intervention during the study.
- Discontinued treatment will be defined as a participant who have permanently prematurely discontinued study intervention.
- Completed planned treatment period will be defined as participant who has completed this period defined in section 3.3.1.2.
- Completed study will be defined as a participant who has completed all phases of the study including the follow-up visit.
- Withdraw from the study will be defined as a participant who did not complete the study.

4.1.1.2 Presentation

Subject disposition and completion status will be described by treatment group and for the total number of participants. Number of participants in each disposition status category will be presented, when applicable, percentages will also be presented. The reason for screen failed, discontinued treatment and withdrawn from study will also be presented based on reasons captured in CRF.

Listings for individual disposition statuses will be provided.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

For definitions of the analysis sets see section 3.2.

4.1.2.2 Presentation

The number of participants included FAS and PKS, as well as the number of randomised participants excluded from them will be presented in a summary table overall and by treatment group.

Listing presenting subjects excluded from analyses sets will be provided.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Only IPDs will be presented. The IPD categories to be presented are defined in section 3.3.5.

4.1.3.2 Presentation

The number and percentage of participants 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.

All the important protocol deviations will be listed by participant.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographics variables include:

- Age (years)
- Age group (years) with categories: <30, >=30 - <50, >=50 - <65, >=65
- Sex with categories: Male, Female
- Race with categories: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Multiple (if multiple races have been reported), Not reported.
- Ethnicity with categories: Hispanic or Latino, Not Hispanic or Latino, Not reported

4.1.4.2 Presentation

Demographics will be presented by treatment group and total. 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. Demographics will also be presented for Japanese sub-population.

Per participant listing including demographics will be provided.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics include:

- Height (cm)
- Body weight (kg)
- Body weight group (kg) with categories: <50, >=50 - <75, >=75 - <90, >=90 - <120, >=120
- BMI (kg/m2)
- BMI group (kg/m2) with categories: Underweight (<18.5), Normal weight (>=18.5 - <25), Overweight (>=25 - <30), Obese (>=30)

4.1.5.2 Presentation

Baseline patient characteristics will be presented descriptively by treatment group and overall. Baseline patient characteristics will also be presented for Japanese sub-population.

Per participant listing including certain baseline characteristics will be provided.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

The following disease characteristics for cirrhosis will be presented at baseline:

- MELD score (see section 3.3.1.6)
- Child-Pugh score (see section 3.3.1.6)
- Ascites with categories: Grade 1, Grade 2, Grade 3, Unknown, Diuretic resistant ascites
- Alcohol usage with categories: Current, Former, Never
- AUDIT score
- Nicotine usage with categories: Current, Former, Never

- eGFR (mL/min/1.73m2), based on eGFR1 (see section 3.3.1.6).
- eGFR group (mL/min/1.73m2), based on eGFR1 (see section 3.3.1.6) with categories: <60, >=60 - <90, >=90
- CCI [redacted]
- CCI [redacted]
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Total body fat (kg)
- Total body water volume (L)
- Total extracellular water volume (L)
- Total intracellular water volume (L)
- Loop-diuretic usage with categories: Yes, No
- CCI [redacted]
- Type 2 diabetes with categories: Yes, No
- HbA1c (%)
- HbA1c for subjects with Type 2 diabetes (%)
- HbA1c for subjects without Type 2 diabetes (%)
- Non-selective beta blockers usage with categories: Yes, No
- Alcohol consumption (units)

The following cirrhosis etiology characteristics will be presented at baseline with categories Yes, No:

- Alcohol
- Hepatitis B

- Hepatitis C
- NASH
- Hemochromatosis
- Autoimmune hepatitis
- Wilson´s Disease
- A1AD
- Sarcoid
- Unknown/idiopathic
- Other cause of cirrhosis

4.1.6.2 Presentation

Baseline disease characteristics will be presented descriptively by randomised treatment group and overall. Variables in section 4.1.6.1 not specified as categorical are continuous. The presentation will be descriptive and follow the rules defined in section 3.3. Baseline disease characteristics for certain characteristics will also be presented for Japanese sub-population.

A separate table of cirrhosis etiology will be presented descriptively by randomised treatment group and overall. This information will also be listed.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

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

4.1.7.2 Presentation

Medical and surgical history will be presented descriptively by treatment group and total. Percentages will be calculated with number of subjects in the analysis set 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 sorted by international order of SOC and alphabetically by PT.

4.1.8 Prior and Concomitant Medications

4.1.8.1 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 prior to study start in the CRF the medication will be prior medication.

A medication will be 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 concomitant.

Disallowed concomitant medication are defined in Section 6.9.1, 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).

4.1.8.2 Presentation

Prior, allowed concomitant and disallowed medications will be presented descriptively by treatment group and total. Percentages will be calculated with the number of subjects in the analysis set as denominator. Subjects are only counted once per ATC classification and generic drug name regardless of the number of medications 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.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

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

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

The percentage of treatment compliance for dapagliflozin/placebo for dapagliflozin 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:

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

The number of capsules and/or tablets expected to be taken is one capsule and one tablet per day starting at the date of first dose to the earliest date of end of treatment, lost to follow up or death, 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.

4.1.9.2 Presentation

Compliance will be presented by treatment group and total. Compliance will be presented for zibotentan/placebo for zibotentan, as well as for dapagliflozin/placebo for dapagliflozin and also overall. This will be done as a continuous variable with descriptive statistics and categorically by compliance group.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as key and exploratory endpoints including sensitivity analyses.

The estimand attributes Population, Treatment and Intercurrent event strategy are the same for all estimands and defined below. Attributes Endpoint and Population level summary are defined for each objective in Table 7.

Population: Patients with cirrhosis with or without a history of decompensation, and who meet eligibility criteria as defined by the inclusion and exclusion criteria. See CSP for details.

Treatment: Fixed daily dose of zibotentan and dapagliflozin in combination, zibotentan monotherapy or placebo, in addition to their standard of care (SoC). See CSP for details.

Intercurrent event strategy: In general the treatment policy strategy will be used e.g. for premature treatment discontinuation due to any reason or prohibited medication. Measurements for the variables of interest will be collected and analysed regardless of intercurrent events. For terminal events (i.e. death) a while-alive strategy will be applied. Terminal events are expected to be few without substantial impact on the key and exploratory analyses.

Table 7 Key and Exploratory objectives

Statistical / Estimand category	Endpoint	Population/Analysis set	Intercurrent event strategy	Population level summary (analysis)	Details in section
Key objective 1: To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on a composite endpoint of fluid retention.					
Primary analysis	Occurrence of any of the following components of this composite endpoint from baseline to Week 6: • > 2 kg increase from baseline in body weight (office-based) • > 2 L increase from baseline in total body water • Increase from baseline in 2 or more loop-diuretic equivalents (see section 3.3.1.5 for details) • Fluid retention AEs	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Risk difference	4.2.1
Key objective 2: To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on a composite endpoint of fluid retention.					

Statistical / Estimand category	Endpoint	Population/Analysis set	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary analysis	Occurrence of any of the following components of this composite endpoint from baseline to Week 6: • > 2 kg increase from baseline in body weight (office-based) • > 2 L increase from baseline in total body water • Increase from baseline in 2 or more loop-diuretic equivalents [a] • Fluid retention AEs	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Risk difference	4.2.1
Key objective 3: To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on body weight, body water volumes, and body fat mass.					
Primary analysis	Change in body weight (kg) over time course of study (home-based monitoring). Change from baseline in body weight, total body water, extracellular and intracellular water volumes, body fat mass at Week 6 (office-based monitoring).	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Least square mean difference in change from baseline	4.2.2
Key objective 4: To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on body weight, body water volumes, and body fat mass.					

Statistical / Estimand category	Endpoint	Population/Analysis set	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary analysis	Change in body weight (kg) over time course of study (home-based monitoring). Change from baseline in body weight, total body water, extracellular and intracellular water volumes, body fat mass at Week 6 (office-based monitoring).	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Least square mean difference in change from baseline	4.2.2
Key objective 5: To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on total loop-diuretic equivalents use. [a]					
Primary analysis	Change in total dosage of loop-diuretic equivalents use from baseline to Week 6 [a].	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Least square mean difference in change from baseline	4.2.3
Key objective 6: To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on total loop-diuretic equivalents use. [a]					
Primary analysis	Change in total dosage of loop-diuretic equivalents use from baseline to Week 6 [a].	Estimand population: See above for respective arms. Analysis set: FAS.	Treatment policy strategy	Least square mean difference in change from baseline	4.2.3
Key objective 7: To evaluate the effects of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on the composite of total body water and total dosage of loop-diuretic equivalents. [a]					
Primary analysis	Occurrence of either of the two components of this composite: ● > 3 L increase from baseline in total body water volume	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Risk difference	4.2.4

Statistical / Estimand category	Endpoint	Population/Analysis set	Intercurrent event strategy	Population level summary (analysis)	Details in section
	from baseline to Week 6. • Increase from baseline in 3 or more loop-diuretics equivalents use from baseline to Week 6 [a].				
Key objective 8: To evaluate the effects of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on the composite of total body water and total dosage of loop-diuretic equivalents. [a]					
Primary analysis	Occurrence of either of the two components of this composite: • > 3 L increase from baseline in total body water volume from baseline to Week 6. • Increase from baseline in 3 or more loop-diuretics equivalents use from baseline to Week 6 [a].	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Risk difference	4.2.4
Key objective 9: To evaluate the effect of zibotentan/dapagliflozin versus corresponding zibotentan monotherapy on office-based systolic and diastolic blood pressure.					
Primary analysis	Absolute change in systolic and diastolic blood pressure from baseline to Week 6.	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Least square mean difference in change from baseline	4.2.5
Key objective 10: To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on office-based systolic and diastolic blood pressure.					

Statistical / Estimand category	Endpoint	Population/Analysis set	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary analysis	Absolute change in systolic and diastolic blood pressure from baseline to Week 6.	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Least square mean difference in change from baseline	4.2.5
Exploratory objective 1: To characterise the plasma exposure to zibotentan and dapagliflozin.					
Primary analysis	Plasma concentrations of zibotentan and dapagliflozin.	Estimand population: See above for respective arms. Analysis set: PKS	Treatment policy strategy	Descriptive statistics	4.2.6
Exploratory objective 2: To evaluate the effect of zibotentan/dapagliflozin in combination and zibotentan monotherapy versus placebo on CCI and/or CCI.					
Primary analysis	Percentage and absolute change in CCI and CCI from baseline to Week 6.	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Mean difference between treatment groups	4.2.7
Exploratory objective 3: To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on liver health and portal hypertension biomarkers.					
Primary analysis	• Percentage and absolute change in AST and ALT from baseline to Week 6. • Absolute change in MELD score from baseline to Week 6.	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Mean difference between treatment groups	4.2.8
Exploratory objective 4: To assess the effect of zibotentan/dapagliflozin in combination and zibotentan monotherapy versus placebo on plasma/serum levels of CCI.					
Primary analysis	Changes in blood and urine biomarkers across time from baseline to Week 6.	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Mean difference between treatment groups	4.2.9

Statistical / Estimand category	Endpoint	Population/Analysis set	Intercurrent event strategy	Population level summary (analysis)	Details in section
Exploratory objective 5: To evaluate the effect of zibotentan/dapagliflozin versus zibotentan monotherapy and placebo on eGFR.					
Primary analysis	Change in eGFR from baseline to Week 6.	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Mean difference between treatment groups	4.2.10
Exploratory objective 6: To evaluate the effect of zibotentan/dapagliflozin and zibotentan monotherapy versus placebo on fatigue, abdominal symptoms, physical functioning and health-related quality of life					
Primary analysis	Change from baseline to Week 6 in CLDQ Fatigue and Abdominal Symptoms scores, SF-36v2 Physical Functioning score, Total CLDQ score, SF-36v2 Physical Component Summary score, SF-36v2 Mental Component Summary score, Patient Global Impression of Severity - Liver Disease	Estimand population: See above for respective arms. Analysis set: FAS	Treatment policy strategy	Descriptive statistics	4.2.11
Exploratory objective 7: To collect and store plasma, serum and urine samples for exploratory research aimed at exploring biomarkers involved in PK, PD, safety and tolerability related to zibotentan and dapagliflozin in combination versus placebo or CCI This objective will not be reported in the CSR.					
-	Evaluation of changes in blood and urine biomarkers	-	-	-	-

a See section 3.3.1.5 for details.

For timing of data collection for above endpoints please see SoA in CSP.

Unless otherwise stated the analyses within each section below will be applied for the treatment groups as indicated in the objectives. In general for comparisons of key objectives the following comparisons will be made: zibotentan/dapagliflozin versus zibotentan monotherapy, zibotentan/dapagliflozin versus placebo and zibotentan monotherapy versus placebo.

In case of convergence issues for the analysis model the CCI , defined as CCI , will be adjusted appropriately to accommodate convergence for the model.

Assessed values of the form '<x' (below the lower limit of quantification) will be imputed as 'x' in calculations for key and exploratory objectives.

Subgroup analyses defined in sections below will be done if adequate numbers of observations are available.

4.2.1 Key Objective 1 and 2, Composite fluid retention

4.2.1.1 Definition

The estimand is defined in section 4.2.

4.2.1.2 Derivations

The endpoint will be assessed throughout the time period by looking at each observation compared to baseline. For loop-diuretic equivalent derivation see section 3.3.1.5. The composite variable will be yes if any event has occurred on or prior to analyses date.

4.2.1.3 Handling of Dropouts and Missing Data

No imputation will be done.

4.2.1.4 Primary Analysis of key objective

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

4.2.1.5 Sensitivity Analyses of the key objective

Following analysis for evaluating impact of missing data will be done:

- A conservative imputation approach will be conducted and missing data will be imputed for each component separately except for component of fluid retention AEs and loop-diuretics. For the placebo group, missing data will be imputed as "No event". For the zibotentan/dapagliflozin and zibotentan monotherapy treatment

groups the missing data will be imputed based on the overall probability for "Event" at a given visit in the combined zibotentan/dapagliflozin and zibotentan monotherapy treatment groups. This probability will be estimated using the observed probability. Seed 3456 will be used. For component of fluid retention AEs, no imputation will be done. For component of loop-diuretics, having no reported loop-diuretics is not considered as missing data. The analyses method will follow section 4.2.1.4.

4.2.1.6 Supplementary Analyses of the key objective

Not applicable.

4.2.1.7 Subgroup Analyses

The primary analysis of this endpoint will be performed for the subgroups defined in section 3.3.1.7 if appropriate.

4.2.2 Key Objective 3 and 4, Change from baseline in body weight (based on values obtained both at home, and at the site), water volumes and body fat mass

4.2.2.1 Definition

Estimand is defined in section 4.2.

4.2.2.2 Derivations

Home body weight which is measured daily will be represented weekly by taking the average of the daily measurement each week and use that for the analyses.

4.2.2.3 Handling of Dropouts and Missing Data

Missing data is assumed to be MAR and no imputation will be done.

4.2.2.4 Primary Analysis of key objective

Will be analysed using MMRM methodology. The analytic model will include CCI CCI of CCI and CCI and CCI CCI. An CCI will be used for CCI.

4.2.2.5 Sensitivity Analyses of the key objective

Following analysis for evaluating impact of analyses method and missing data will be done:

- To analyse the method choice of MMRM the analyses will be performed using ANCOVA after missing data has been imputed under MAR assumption using multiple imputation. A total of 1000 imputations will be performed using a seed of 4567.

4.2.2.6 Supplementary Analyses of the key objective

Not applicable.

4.2.2.7 Subgroup Analyses

The primary analysis of this endpoint will be performed for the subgroups defined in section 3.3.1.7 if appropriate.

4.2.3 Key Objective 5 and 6, Change from baseline in Loop-diuretic usage

4.2.3.1 Definition

Estimand is defined in section 4.2.

4.2.3.2 Derivations

See section 3.3.1.5.

4.2.3.3 Handling of Dropouts and Missing Data

For missing partial dates for loop-diuretics see section 3.3.1.4. Other missing data is assumed to be MAR and no imputation will be done.

4.2.3.4 Primary Analysis of key objective

Will be analysed using MMRM methodology. The analytic model will include CCI CCI of CCI , and CCI , and CCI CCI . An CCI will be used for CCI .

4.2.3.5 Sensitivity Analyses of the key objective

Following analysis for evaluating impact of analyses method and missing data will be done:

- To analyse the method choice of MMRM the analyses will be performed using ANCOVA.

4.2.3.6 Supplementary Analyses of the key objective

Not applicable.

4.2.3.7 Subgroup Analyses

The primary analysis of this endpoint will be performed for the subgroups defined in section 3.3.1.7 if appropriate.

4.2.4 Key Objective 7 and 8, Composite endpoint of water and loop-diuretic

4.2.4.1 Definition

Estimand is defined in section 4.2.

4.2.4.2 Derivations

The endpoint will be assessed throughout the time period, looking at each observation compared to baseline. For loop-diuretic derivation see section 3.3.1.5. The composite variable will be yes if any event has occurred on or prior to analyses date.

4.2.4.3 Handling of Dropouts and Missing Data

No imputation of missing will be performed.

4.2.4.4 Primary Analysis of key objective

Exact 90% (two-sided) CIs for proportions of participants with the composite of fluid retention in treatment groups will be calculated using the Clopper-Pearson method. The exact unconditional 90% (two-sided) CIs for pairwise difference in proportions between 2 treatment groups compared, as specified in objectives, will be computed based on score statistic (Chan and Zhang, 1999). CCI will also be presented.

4.2.4.5 Sensitivity Analyses of the key objective

Following analysis for evaluating impact of missing data will be done:

- A conservative imputation approach will be conducted and missing data will be imputed for each component separately except for component of fluid retention AEs. The placebo group will have missing data imputed as "No event". For the zibotentan/dapagliflozin and zibotentan monotherapy treatment groups the missing data will be imputed based on the overall probability for "Event" at a given visit in the combined zibotentan/dapagliflozin and zibotentan monotherapy treatment groups. This probability will be estimated using the observed probability. For component of fluid retention AEs, no imputation will be done. The analyses method will follow section 4.2.4.4.

4.2.4.6 Supplementary Analyses of the key objective

Not applicable.

4.2.4.7 Subgroup Analyses

The primary analysis of this endpoint will be performed for the subgroups defined in section 3.3.1.7 if appropriate.

4.2.5 Key Objective 9 and 10, Change from baseline in Systolic and diastolic blood pressure

4.2.5.1 Definition

Estimand is defined in section 4.2. Supine blood pressure will be analysed.

4.2.5.2 Derivations

Not applicable.

4.2.5.3 Handling of Dropouts and Missing Data

Missing data is assumed to be MAR and no imputation will be done.

4.2.5.4 Primary Analysis of key objective

Will be analysed using MMRM methodology. The analytic model will include the CCI CCI of CCI , and CCI , and CCI CCI . An CCI will be used for the CCI .

4.2.5.5 Sensitivity Analyses of the key objective

Following analysis for evaluating impact of analyses method and missing data will be done:

- To analyse the method choice of MMRM the analyses will be performed using ANCOVA after missing data has been imputed under MAR assumption using multiple imputation. A total of 1000 imputations will be performed using a seed of 4567.

4.2.5.6 Supplementary Analyses of the key objective

Not applicable.

4.2.5.7 Subgroup Analyses

The primary analysis of this endpoint will be performed for the subgroups defined in section 3.3.1.7 if appropriate.

4.2.6 Exploratory Objective 1, PK-analyses

4.2.6.1 Definition

PKS analysis set will be used. Estimand is defined in section 4.2.

4.2.6.2 Derivations

Not applicable.

4.2.6.3 Handling of Dropouts and Missing Data

Missing data is assumed to be MAR and no imputation will be done.

4.2.6.4 Primary Analysis of exploratory objective

The data will be descriptively summarised by treatment group, visit, and time-point. Geometric mean and CV will be presented in addition to arithmetic mean and SD. PK assessments that should only be collected once according to schedule of activities in CSP will be summarised using the assessment closest to target date even if outside of visit windowing.

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

4.2.6.5 Additional Analyses of the exploratory objective

Not applicable.

4.2.6.6 Subgroup Analyses

Not applicable. Certain analyses will be divided into Japanese vs non-Japanese based on the collection specified in CSP.

4.2.7 Exploratory Objective 2, Change from baseline in CCI and CCI

This exploratory endpoint might not be collected for all subjects and is collected at screening and Visit 6, see CSP for details on data collection.

4.2.7.1 Definition

Estimand is defined in section 4.2.

4.2.7.2 Derivations

Not applicable.

4.2.7.3 Handling of Dropouts and Missing Data

Missing data is assumed to be MAR and no imputation will be done.

4.2.7.4 Primary Analysis of exploratory objective

The analysis is performed using ANCOVA for both absolute and percentage change from baseline. The data will be descriptively summarised by treatment group and presenting absolute and percentage change from baseline.

4.2.7.5 Additional Analyses of the exploratory objective

Not applicable.

4.2.7.6 Subgroup Analyses

Not applicable.

4.2.8 Exploratory Objective 3, Change from baseline in AST, ALT and MELD- score

4.2.8.1 Definition

Estimand is defined in section 4.2.

4.2.8.2 Derivations

Data for AST, ALT taken from safety data. MELD score is derived as defined in section 3.3.1.6.

4.2.8.3 Handling of Dropouts and Missing Data

Missing data is assumed to be MAR and no imputation will be done.

4.2.8.4 Primary Analysis of Exploratory objective

The analysis is performed using MMRM, similar to key objective, for both absolute and percentage change from baseline for AST and ALT and for absolute change for MELD score. The data will be descriptively summarised by treatment group and visit. For AST and ALT absolute and percentage change from baseline will be presented. For MELD score absolute change from baseline will be presented.

4.2.8.5 Additional Analyses of the Exploratory objective

Not applicable.

4.2.8.6 Subgroup Analyses

Not applicable.

4.2.9 Exploratory Objective 4, Change from baseline in Blood biomarkers

4.2.9.1 Definition

The variables to be analysed are: Plasma/serum CCI [redacted]

Estimand is defined in section 4.2.

4.2.9.2 Derivations

Not applicable.

4.2.9.3 Handling of Dropouts and Missing Data

No imputation will be done.

4.2.9.4 Primary Analysis of Exploratory objective

The analysis is performed using MMRM, similar to key objectives, for absolute change from baseline. Data will be summarised descriptively by treatment group and visit.

4.2.9.5 Additional Analyses of the Exploratory objective

Not applicable.

4.2.9.6 Subgroup Analyses

Not applicable.

4.2.10 Exploratory Objective 5, Change from baseline in eGFR

4.2.10.1 Definition

Estimand is defined in section 4.2.

4.2.10.2 Derivations

See section 3.3.1.6. Data for calculation of eGFR1 should be collected for all post-randomization visits while data for calculation of eGFR2 will be collected at certain visits post-randomization, see CSP SoA for details.

4.2.10.3 Handling of Dropouts and Missing Data

No imputation will be done.

4.2.10.4 Primary Analysis of Exploratory objective

The analysis is performed using MMRM, similar to key objectives, for absolute change from baseline. Data will be summarised descriptively by treatment group and visit.

4.2.10.5 Additional Analyses of the Exploratory objective

Not applicable.

4.2.10.6 Subgroup Analyses

Not applicable.

4.2.11 Exploratory Objective 6, Change in PROs

4.2.11.1 Definition

Following data will be analysed:

CLDQ

- CLDQ Fatigue Symptoms score
- CLDQ Abdominal Symptoms score
- CLDQ Systemic Symptoms score
- CLDQ Activity Symptoms score
- CLDQ Emotion Symptoms score
- CLDQ Worry Symptoms score
- Total CLDQ score

SF-36v2 domain scores

- SF-36v2 Physical functioning score
- SF-36v2 Mental health score
- SF-36v2 Bodily pain score

- SF-36v2 General health score
- SF-36v2 Vitality score
- SF-36v2 Social Functioning score
- SF-36v2 Role limitations due to emotional problems score
- SF-36v2 Role limitations due to physical health score

SF-36v2 component scores

- SF-36v2 Physical Component Summary score
- SF-36v2 Mental Component Summary score

PGIS

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

Estimand is defined in section 4.2.

4.2.11.2 Derivations

SF-36v2

SF-36v2 will be scored by Quality Metric using norm-based scoring.

CLDQ

The CLDQ is comprised of six domains. The domains are listed below with the corresponding question numbers. First, the sum of the corresponding questions is taken. This is then divided by the number of items in the domain to get the domain score. To get the overall CLDQ score, the sum of the domains are taken and then divided by the total number of domains.

If items are missing the denominator below will need to be adjusted to match the number of items. If half or more of the items are missing it will not be calculated.

Abdominal (AB) = Sum of N1 + N5 + N17
Fatigue (FA) = Sum of N2 + N4 + N8 + N11+ N13
Systemic (SY) = Sum of N3 + N6 + N21 + N23 + N27
Activity (AC) = Sum of N7 + N9 + N14
Emotion (EM) = Sum of N10 + N12 + N15 + N16 + N19 + N20 + N24 + N26
Worry (WO) = Sum of N18 + N22 + N25 + N28 + N29

Each CLDQ domain symptoms score is calculated as:
ABM = AB/3
FAM = FA/5
SYM = SY/5
ACM = AC/3

EMM = EM/8
WOM= WO/5
CLDQM = SUM (OF ABM FAM SYM ACM EMM WOM)/6

4.2.11.3 Handling of Dropouts and Missing Data

No imputation will be done.

4.2.11.4 Primary Analysis of Exploratory objective

Data will be descriptive summarized for each treatment group. PGIS will be presented with number and percentage per response category and timepoint, as well as shift from baseline. For the CLDQ and SF-36v2 actual score and change from baseline will be summarised for the different components.

4.2.11.5 Additional Analyses of the Exploratory objective

Additional analyses may be conducted as appropriate.

4.2.11.6 Subgroup Analyses

Not applicable.

4.2.12 Exploratory Objective 7, Exploratory research

This will not be reported in the CSR.

4.3 Pharmacodynamic Endpoints

Details for these endpoints are described in Section 4.2.

4.4 Pharmacokinetics

Details are provided in Section 4.2.6.

4.5 Immunogenicity

Not applicable.

4.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG.

The estimand attributes Population and Treatment are the same as for key and exploratory objectives, see definition in section 4.2. The main Intercurrent event strategy is Treatment policy. Attributes Endpoint is defined in Table 8

Intercurrent event strategies:

Treatment policy strategy
In general the treatment policy strategy will be used e.g. for premature treatment discontinuation due to any reason or prohibited medication. Then measurements for the variables of interest will be collected and analysed regardless of intercurrent events. For terminal events (i.e. death) a while-alive strategy will be applied unless death is one of the events being analysed e.g. for AEs then it will be included.

Population summary:
Descriptive statistics presenting distribution of endpoints by treatment group. For continuous variables the mean will be used and for categorical n and % will be used.

Table 8 Safety objectives

Statistical / Estimand category	Endpoint	Population/Analysis set	Intercurrent event strategy	Population level summary (analysis)	Details in section
Safety objective: To assess the safety and tolerability of zibotentan/dapagliflozin and zibotentan versus placebo.					
Primary analysis	• AEs, SAEs, and DAEs • AESIs CCI [redacted] • Vital signs • Safety laboratory tests • ECG assessments	Estimand population: See above for respective arms. Analysis set: FAS	*Treatment policy strategy*	See above.	4.6

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

The duration of exposure (days) will be calculated as: date of last dose – date of first dose +1.

4.6.1.2 Presentation

Duration of exposure will be summarised by treatment group and total number of subjects and will be presented as a continuous variable with descriptive statistics.

Listing presenting individual exposure will be provided.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

For Adverse events of special interest see section 4.6.8.

The definitions and information on collection of AEs and SAEs can be found in CSP. All AEs will be classified by SOC and PT according to a MedDRA. Only AEs occurring with an onset date, or worsening, on or after first dose of study intervention, throughout the treatment period and including the follow-up period will be presented in summary tables

The following definitions and principles are to be followed:

AE
AE reported with an onset date within the defined analysis period.

SAE
SAE where the onset date of the premediating AE 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 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, permanent discontinuations is not included.

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". If a subject has multiple AEs within the same category of different intensities, the more severe intensity will be considered in the presentations.

4.6.2.2 Presentation

The number and percentage of subjects with AEs will be tabulated by treatment group. For subject count presentations, subjects will only be counted once per category, regardless of the number of AEs satisfying the condition.

The following summaries will be presented:

Overall summary of AEs

Number of subjects with any AE, any SAE, any AE with outcome of death, any AE leading to discontinuation of IP, any AE leading to interruption of IP, any AE possible related to IP and any AESIs (see section 4.6.8) will be presented. This will also be presented for Japanese sub-population.

By SOC and PT

Separate AE tables by SOC and PT will be provided for: Any AE, any SAE, any AE 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. AE table by SOC and PT for any AE will also be presented for Japanese sub-population. Event count table will be presented for AEs and SAEs by SOC and PT.

By PT

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

Maximum intensity

AEs will be presented by their maximum intensity for all AE and by PT.

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.

Assessment of potential proarrhythmic effect

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).

Key subject information

Key subject information for subjects with SAEs, AEs with outcome death and AEs leading to discontinuation of IP will be provided.

Key subject information will also be presented for subjects with modified Hy's law during the study, if appropriate a summary table will be produced.

Listings and narratives

An AE listing including individuals in FAS covering details for each individual AE will be produced. An AE listing for participants who were randomized but not exposed to study intervention is presented separately. SAEs occurring prior to start of study intervention will be included in data listings. Narratives may also be produced.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Blood samples for determination of clinical laboratory assessments are collected according to the CSP. Clinical laboratory assessments of blood samples, including electrolytes, will be categorised into haematology, chemistry and coagulation parameters as defined below in Table 9.

Table 9 Clinical blood laboratory parameters

Haematology	
White blood cell count	Lymphocytes absolute count
Red blood cell count	Monocytes absolute count
Haemoglobin	Eosinophils absolute count
Haematocrit	Basophils absolute count
Neutrophils absolute count	Platelet absolute count
Chemistry	
BUN	Alanine aminotransferase
Creatinine and calculated eGFR (CKD-EPI) and eGFR2	Aspartate aminotransferase
Total bilirubin and direct bilirubin	Alkaline phosphatase
Albumin	Creatine kinase
Calcium	Serum glucose
Phosphate	Gamma-glutamyl transferase
Serum Osmolality	NT-pro BNP
Bicarbonate (HCO_3-)	Sodium
Chloride (Cl-)	Potassium
Magnesium (Mg^+)	
Coagulation	
International normalised ratio	Prothrombin time
Partial thromboplastin time	

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.

Treatment emergent

A treatment emergent abnormality is defined as either of below:

- A switch in parameter from normal at baseline 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.

When the predefined criteria for a parameter abnormality is referring to ULN then this is based on reference ranges from the central laboratory. For some parameters there are different criteria for the same parameter that can be separately fulfilled and will be presented separately.

Predefined criteria for Haematology
Platelet absolute count (10^9/L): <50, <75

Predefined criteria for Chemistry
NT-pro BNP (pg/mL): >1 x 125, >2 x 125, >5 x 125
Alanine aminotransferase (U/L), Alkaline phosphatase (U/L), Aspartate aminotransferase (U/L): >1 x ULN, >3x ULN, >5 x ULN
Direct bilirubin (mg/dL): >1 x ULN, >2x ULN, >3x ULN
Total bilirubin (mg/dL): >1 x ULN, >2x ULN, >5 x ULN
Alkaline phosphatase (U/L): >= 2 x baseline
Alanine aminotransferase (U/L), Aspartate aminotransferase (U/L): >= 2 x baseline and > 1 x ULN
Direct bilirubin (mg/dL): >= 1 mg/dL over baseline
Total bilirubin (mg/dL): >= 2 x baseline and > 2 x ULN
Combination criteria: Aspartate aminotransferase (U/L) or Alanine aminotransferase (U/L) >= 3 x ULN and Total bilirubin (mg/dL) > 2 x ULN

Predefined criteria for Coagulation
INR: > 0.2 + Baseline, > 0.4 + Baseline, > 0.6 + Baseline

Shift table definitions

Below parameters will be categorised according to below categories for the shift tables.

Haematology, shift from baseline to minimum value
Platelets (10^9/L) with categories: <50, >=50 - <75, >=75 - <150, >=150 - <400, >=400

Chemistry, shift from baseline to maximum value
Alanine aminotransferase (U/L), Alkaline phosphatase (U/L), Aspartate aminotransferase (U/L), Direct bilirubin (mg/dL), Total bilirubin (mg/dL) with categories: Normal(<= ULN), High (> 1 x ULN and <= 2 x ULN), Higher (>2 x ULN and <= 5 x ULN), Highest (> 5 x ULN). N-Terminal proB-type natriuretic peptide (pg/mL) with categories: Normal(<= 1 x 125), High (> 1 x 125 and <= 2 x 125), Higher (>2 x ULN and <= 5 x 125), Highest (> 5 x 125).

4.6.3.2 Presentations

All laboratory data will be presented in SI or conventional units.

The haematology, chemistry and coagulation parameters defined in Table 9 will be presented as continuous variables using descriptive statistics as specified in section 3.3 and will be presented by treatment group and by scheduled post-baseline visits for observed values and change from baseline.

The number of subjects with treatment-emergent laboratory parameter abnormalities will be presented categorically by treatment group. Only the most extreme value per subject will be accounted for.

Shift tables from baseline to maximum or minimum value will also be presented by treatment group. For INR summary table for maximum on study value as compared to baseline will be presented.

Scatter plot of maximum ALT or AST versus maximum total bilirubin and corresponding tabulation will be presented as well.

Key subject information will be presented for subjects with treatment emergent abnormalities for haematology, chemistry or coagulation abnormalities.

Additional key subject information and graphs of individual data will be presented including laboratory parameters which are associated with liver safety. This will be done for e.g. subjects with investigational product interruptions and discontinuations, subjects with DILI/modified Hy’s Law.

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

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

Safety urinalysis to be presented is the urine culture collected in the event of symptoms of urinary tract infection.

4.6.4.2 Presentations

A summary table of number and percentage of subjects with urine culture preformed and number and percentage of subjects with positive or negative urine cultures will be presented by treatment group. 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.

4.6.5 Other Laboratory Evaluations

Not applicable.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Following Vital signs will be presented:

- Body Temperature (C)
- Body Weight (kg)
- Pulse (beats/min)
- Standing Diastolic Blood Pressure (mmHg)
- Supine Diastolic Blood Pressure (mmHg)
- Standing Systolic Blood Pressure (mmHg)
- Supine Systolic Blood Pressure (mmHg)

Treatment emergent

A treatment emergent abnormality is defined as either of below:

- A switch in parameter from normal at baseline 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.

Predefined criteria used for shift tables and treatment emergent reporting

The following definitions of vital sign abnormalities will be used for specified 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

4.6.6.2 Presentations

Vital sign parameters will be presented for each treatment group. Vital signs for scheduled post-baseline visits will be presented descriptively for observed values and change from baseline.

Vital sign shift from baseline to maximum will be presented by treatment group.

Treatment emergent vital signs will be presented by treatment group.

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

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

Digital ECGs will be recorded in triplicate and the average of available observations will be used for analyses.

Following ECG parameters will be presented:

- ECG Mean Heart Rate (beats/min)
- PR Interval, Aggregate (msec)
- RR Interval, Aggregate (msec)
- QRS Duration, Aggregate (msec)
- QT Interval, Aggregate (msec)
- QTcF Interval, Aggregate (msec)

The Central ECG reading will make an assessment per ECG reading whether the ECG finding is normal or abnormal. For analyses, if multiple readings at the same visit the overall assessment will be classified as abnormal if at least one reading is abnormal. The investigator will make an overall assessment of the ECG whether the ECG finding is normal or abnormal and if abnormal, clinically significant or not. The central ECG reading will be used for summary outputs. Both central and investigator assessments will be listed.

Ranges and criteria to be used for each parameter is defined in Table 10.

Table 10 Ranges and criteria for ECG presentation

Variable	Unit	Outside lower limit if	Outside upper limit if	AZ extended reference range - low	AZ extended reference range - high	Treatment emergent increase if	Extended treatment emergent increase if
Heart rate	bpm	<50	>100	<45	>120	NA	NA
				<30	>150		
RR interval	ms	<600	>1200	<500	>1333	NA	NA
				<400	>2000		
PR interval	ms	<110	>220	<100	>240	>40	>60
QRS	ms	<75	>115	<70	>120	>15	>30
QT	ms	<320	>450	<300	>480	>30	>60
					>500		
QTcF	ms	<320	>450	<300	>480	>30	>60
					>500		

ms = milliseconds, bpm = beats per minute, NA= not applicable.

Note that for treatment emergent ECGs only the increase is considered, no classification of normal/abnormal of the absolute level.

4.6.7.2 Presentations

ECG parameters will be summarised descriptively as continuous variables presented by treatment group and scheduled post-baseline visits. Observed values and change from baseline will be presented.

Overall electrocardiogram assessment (normal/abnormal) will be presented with number and percentages, by treatment group for baseline versus last observation. Overall electrocardiogram assessment (normal/abnormal) will also be presented with number and percentages, by treatment group for each scheduled timepoint.

Summary tables and key subject information presenting subjects reaching the criteria defined in Table 10 for extended reference range, treatment emergent and extended treatment emergent will also be presented.

Electrocardiogram data will be listed for each participant and will include the ECG parameters (where applicable) and changes from baseline and be flagged based on lower and upper limit in Table 10. Assessment by the investigator (normal/abnormal not clinically significant/abnormal clinically significant) and details of any abnormalities will be listed.

Assessment by the central reading (normal/abnormal) will also be listed together with central reading ECG findings.

4.6.8 Other Safety Assessments - AESI

4.6.8.1 Definitions and Derivations

For specification of MedDRA version and collection of AEs see section 4.6.2.

AESI categories will be classified using PT list for the following safety topics:

- New diagnosis of CCI or CCI of the existing CCI condition
- CCI or worsening of CCI
- CCI
- CCI
- CCI
- CCI

Objective measurement for CCI
Objective measurement of CCI is defined as a CCI of CCI in CCI or a CCI of CCI in CCI within CCI CCI, i.e. this will not be classified using SOC or PT.

4.6.8.2 Presentations

AEs of special interest
Number of subjects with an AESI will be presented by event category and by PT within the event category. Event count table will also be presented. Key subject information for subjects with AESI will be presented.

Objective measurement for CCI
Number and percentage of subjects who met objective measurement for CCI CCI will be presented by treatment group.

4.6.9 Other Safety Assessments - To assess liver safety

4.6.9.1 Definitions and Derivations

Modified Hy's Law
AEs that are cases of modified Hy's law will be identified based on preferred term.

4.6.9.2 Presentations

The number and percentage of subjects with event will be tabulated by treatment group

5 INTERIM ANALYSIS

No interim analysis is planned. For information about the DMC safety monitoring during the study see DMC Charter.

6 REFERENCES

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7 APPENDIX

Not applicable.