Parexel International

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A Phase 2b Multicentre, Randomised, Double-Blind, Active-Controlled, Parallel Group Dose-Ranging Study to Assess the Efficacy, Safety and Tolerability of Zibotentan and Dapagliflozin in Patients with Chronic Kidney Disease with Estimated Glomerular Filtration Rate (eGFR) ≥ 20 mL/min/1.73 m^2

Statistical Analysis Plan

Version: 3.0

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	22 Jan 21	New document
1.1	25 May 22	Updates for alignment with Protocol Amendment 2 Updates to Appendix B to ensure alignment with the November 2021 version of the URC charter
1.2	15 Jul 22	Updates throughout document to ensure alignment with Protocol Amendment 2 Addition of multiple imputation, tipping point and supplementary analyses Updates to Appendix B to clarify CCI [redacted]
1.3	15 Aug 22	Updates to the Data Presentation and Analysis Sets sections Updates to Appendix B to clarify the interim analysis sets
1.4	04 Oct 22	Updates to the Data Presentation and Analysis Sets sections Updates to the Efficacy Evaluation section Updates to Appendix B to clarify the interim analysis plan
1.5	14 Nov 22	Updates to the Data Presentation section Updates to the sensitivity analyses part of the Primary Analysis of Primary Objective section and related sections added within the Analyses of UACR Objectives section Updates to the eGFR part of the Analysis of Secondary Objectives Other Than UACR section Updates to the Fluid-Related Measures section Updates to the Interim Analysis section Updates to Appendix B to clarify the interim analysis plan

Version No.	Effective Date	Summary of Change(s)
1.6	27 Nov 22	Updates throughout SAP to make clear results for ELDP and CT-proET-1 will not be reported in the CSR Updates to the eGFR part of the Analysis of Secondary Objectives Other Than UACR section Updates to the Extent of Exposure section Updates to the Fluid-Related Measures section Updates to the Interim Analysis section Updates to the Analysis Sets part of Appendix B to clarify the interim analysis plan
1.7	07 Dec 22	Update to the baseline disease characteristics part of the Demographic and Other Baseline Characteristics section Updates to the Copy Reference Analysis section and the Jump to Reference Analysis section
2.0	07 Dec 22	Finalised version
2.1	05 Feb 23	Updates to the Echocardiography Assessment of Cardiac Structure and Function section Creation of new Global/Country Situation Summaries section from the previous COVID-19 Analysis and Ukraine/Russia Crisis Analysis sections Updates to the Protocol Deviations section Updates to the Primary Estimand for Primary Objective section Updates to the Primary Analysis of Primary Objective section, including the sensitivity analyses part and the subgroup analyses part Updates to the Tipping Point Analysis section Updates to the Jump to Reference Analysis section; removal of the Copy Reference Anaysis section and the BOCF-like Analysis section Updates to the Supplementary Analysis of Primary Objective section Updates to Extent of Exposure section

Version No.	Effective Date	Summary of Change(s)
2.2	21 Feb 23	Updates throughout SAP to make clear results for ET-1, copeptin and cortisol will not be reported in the CSR Updates throughout SAP to remove loss to follow up as an ICE and to include death as an ICE Updates to the Pharmacodynamics section within the Exploratory Variables section Updates to the Study Period section Updates to the Treatment Compliance section Updates to the Null Hypothesis for Primary Objective and Related Secondary Objective section Updates to the Primary Estimand for Primary Objective section Updates to the subgroup analyses part of the Primary Analysis of Primary Objective section Updates to the Tipping Point Analysis section Updates to the Jump to Reference Analysis section Updates to the Supplementary Analysis of Primary Objective section Updates to the eGFR part of the Analysis of Secondary Objectives Other Than UACR section Updates to Extent of Exposure section Updates to Adverse Events section Updates to Changes in the Conduct of the Study or Planned Analysis section

Version No.	Effective Date	Summary of Change(s)
2.3	16 Mar 23	Updates throughout SAP to make clear results for NT-proBNP will not be reported in the CSR Updates throughout SAP for how the second administrative interim analysis will be triggered Updates to the dose-response relationship secondary objective endpoints text in the Secondary Objectives section Updates to the Clinical Safety Laboratory Assessments section Updates to the Software section Updates to the Null Hypothesis for Primary Objective and Related Secondary Objective section Dose-response Testing for the Dose-response Relationship Secondary Objective removed Updates to reformulate the dose-response relationship secondary objective part of the Analysis of Secondary UACR Objectives section Updates to the Extent of Exposure section Updates to the Clinical Laboratory Evaluation section Updates to the Pharmacokinetics section Updates to the Analysis Sets section of Appendix B
2.4	30 Mar 23	Updated section 4.2.2 to specify the list of variables that are expected to be skewed. Updated section 4.6 to change “plasma concentration measurement post-randomisation” to “plasma concentration measurement post-treatment” to be in line with CSP. Updated sections 4.10.2.2 and 4.10.3 to replace continuous covariates of baseline eGFR (serum creatinine) by baseline eGFR strata (<= 45 versus > 45 mL/min/1.73 m2). Updated section 4.6 to remove the statement “all measurements for an included participant will be considered” from the last paragraph of the definition of the Pharmacokinetic Analysis Set. Updated section 4.15 to add deviations with CSP v3.0
3.0	05 May 2023	Updated section 4.10.3 to consider continuous covariates of baseline eGFR (serum creatinine) instead of baseline eGFR strata (<= 45 versus > 45 mL/min/1.73 m2).

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ABPM	ambulatory blood pressure monitoring
ACEi	angiotensin-converting enzyme inhibitor
AE	adverse event
AIC	Akaike's Information Criterion
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase/transaminase
BIS	bioimpedance spectroscopy
BMI	body mass index
BNP	B-type natriuretic peptide
BOCF	baseline observation carried forward
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CKD	chronic kidney disease
COVID-19	Coronavirus Disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT-proET-1	C-terminal pro-endothelin-1
DAE	adverse event leading to the discontinuation of study intervention
DBL	database lock
DKD	diabetic kidney disease
DM	diabetes mellitus
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELDP	endothelin-like domain peptide
ET-1	endothelin-1
FAS	Full Analysis Set
HF	heart failure
ICE	intercurrent event
IPD	important protocol deviation
LLOQ	lower limit of quantification
LVEF	left ventricular ejection fraction
MAR	missing at random
MCT	multiple contrast test
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed model for repeated measures
MNAR	missing not at random
MRA	mineralocorticoid receptor agonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PD	pharmacodynamic(s)
PEY	participant exposure year

Abbreviation / Acronym	Definition / Expansion
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PT	preferred term
QT	QT interval
QTcF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGLT2	Sodium-glucose co-transporter 2
SoA	Schedule of Activities
SoC	standard of care
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TLF	tables, listings and figures
UACR	urinary albumin to creatinine ratio
ULN	upper limit of normal
URC	Unblinded Review Committee
WHO-DD	World Health Organization - Drug Dictionary

1 INTRODUCTION

Patients with chronic kidney disease (CKD) have limited treatment options with current standard of care (SoC). The mechanisms of action of zibotentan and dapagliflozin are different and the outcome of combined treatment is expected to be synergistic, since the main biological effects of zibotentan are to block endothelin-1-dependent vasoconstriction and hypertension, to increase renal blood flow, and to reduce podocyte loss, vascular stiffness, endothelial dysfunction, fibrosis and inflammation; and of dapagliflozin are to inhibit sodium-glucose co-transporter 2 (SGLT2) to increase urinary excretion of glucose, sodium and water, to improve metabolic health, decrease vascular stiffness, improve endothelial function, and decrease oxidative stress and inflammation. Both mechanisms show efficacy in reducing albuminuria in CKD. However, unlocking the renal benefit of endothelin antagonists requires mitigation of their potential to cause fluid retention and to increase the risk of developing heart failure (HF) in some patients.
The primary objective of this study is to evaluate the effect of zibotentan 1.5 mg and dapagliflozin 10 mg in combination, compared to dapagliflozin 10 mg monotherapy, on urinary albumin to creatinine ratio (UACR). The secondary objectives are to determine the change in UACR for zibotentan 0.25 mg combined with dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy, and the change in office systolic and diastolic blood pressure (BP) for doses of zibotentan combined with dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy, to characterise the dose-response relationship of the different zibotentan/dapagliflozin doses and the UACR reduction, and to determine the effect of zibotentan and dapagliflozin in combination versus dapagliflozin 10 mg on eGFR.

This Statistical Analysis Plan (SAP) documents the variables to be analysed and the methods of analyses planned. The analyses of the following variables will be reported outside the clinical study report (CSR) and are therefore outside the scope of this SAP:

- Plasma concentration of zibotentan metabolites
- Blood and urine biomarkers relevant to cardiorenal mechanisms, inflammation, and fibrosis
- Genes/genetic variation that may influence response to treatment

An electronic case report form (eCRF) will be used to capture participant data into a secure, validated database. The following data are captured outside the eCRF and will be transferred electronically into the database periodically during the study:

- Safety laboratory data
- Electrocardiogram (ECG) data
- Plasma concentration of zibotentan and dapagliflozin
- Pharmacodynamic (PD) urine and blood samples
- Bioimpedance spectroscopy (BIS)
- Ambulatory blood pressure monitoring (ABPM)
- Hand-held electronic diary (eTablet) or paper diary (information may be entered in the eCRF based on the paper diary)
- Protocol deviations

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Amendment 2 (05 APR 2022)
- electronic Case Report Form, Version 8.0 (09 AUG 2022)

2 STUDY OBJECTIVES

2.1 Primary Objective

Primary Objective	Estimand Description/Endpoint
• To evaluate the effect of zibotentan 1.5 mg/dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy on UACR.	• Change in log-transformed UACR from baseline to Week 12. The primary estimand is a hypothetical estimand such that the treatment effect is quantified in the optimal situation where any potential confounder is avoided. The population of interest is the Full Analysis population. Participants will be included in the analysis if they have a non-missing baseline and at least one post-treatment visit UACR measurement. For the intercurrent events, if a participant dies, prematurely discontinues study treatment, or uses prohibited medication, the UACR data are treated as missing after the event and no imputation is performed. The summary measure being evaluated is the geometric mean reduction difference of UACR from baseline to Week 12.

Abbreviations: AE = adverse event; UACR = urinary albumin to creatinine ratio.

2.2 Secondary Objectives

Secondary Objectives[a]	Endpoints
• To evaluate the effect of zibotentan 0.25 mg/dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy on UACR.	• Change in log-transformed UACR from baseline to Week 12.
• To determine the change in office systolic and diastolic BP for doses of zibotentan combined with dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy.	• Change in BP from baseline (Visit 2) to Week 12.
• To characterise the dose-response relationship (relationship between different doses of zibotentan/a fixed dose of dapagliflozin and UACR reduction).	• Change in log-transformed UACR from baseline to Week 12.
• To determine the effect of different doses of zibotentan and dapagliflozin 10 mg in combination versus dapagliflozin 10 mg monotherapy on eGFR.	• Change in eGFR from baseline to Week 1. • Change in eGFR from baseline to Week 12. • Change in eGFR from baseline to Week 14. • Change in eGFR from Week 1 to Week 12.

Abbreviations: BP = blood pressure; eGFR = estimated glomerular filtration rate; UACR = urinary albumin to creatinine ratio
[a] The estimand for the secondary objectives is defined with the same approach as for the primary objective.

2.3 Safety Objective

Safety Objective	Measurements
• To assess the safety and tolerability of all doses of zibotentan combined with dapagliflozin 10 mg and dapagliflozin 10 mg monotherapy.	• AEs/SAEs/DAEs. • Vital signs. • Clinical laboratory tests. • 12-lead ECG assessment. • Echocardiography assessment. • Event of special interest (changes in fluid-related measures).

Abbreviations: AE = adverse event; DAE = adverse event leading to the discontinuation of study intervention; ECG = electrocardiogram; SAE = serious adverse event.

2.4 Exploratory Objectives

Exploratory Objectives	Endpoints
• To assess the pharmacokinetics of different doses of zibotentan and of dapagliflozin 10 mg in plasma.	• Plasma concentrations of zibotentan and dapagliflozin.
• Exploratory analysis of zibotentan metabolites.	• Plasma concentration of zibotentan metabolites. Results from this analysis will not be reported in the CSR.
• To assess body weight changes in response to different doses of zibotentan and dapagliflozin 10 mg in combination versus dapagliflozin 10 mg monotherapy.	• Change in body weight, as measured at the study site, throughout the interventional period.
• To explore the relationships between zibotentan dose/exposure and safety/PD variables.	• Dose/exposure of zibotentan relative to safety and PD variables. Safety/PD variables include blood assessment for NT-proBNP, BNP, creatinine, and cystatin C, and urine assessment of albumin and creatinine. Results for NT-proBNP will not be reported in the CSR.
• To assess the effect of zibotentan and dapagliflozin in combination versus dapagliflozin 10 mg monotherapy on plasma/serum K+, Na+, uric acid, BUN, fasting plasma glucose, haematocrit, haemoglobin, ET-1, ELDP, CT-proET-1, and copeptin levels.	• Change in plasma/serum concentrations of K+, Na+, uric acid, BUN, fasting plasma glucose, haematocrit, haemoglobin, ET-1, ELDP, CT-proET-1, and copeptin levels over time during the study. Results for ET-1, ELDP, CT-proET-1 and copeptin levels will not be reported in the CSR.
• To assess the effect of zibotentan and dapagliflozin in combination versus dapagliflozin 10 mg monotherapy on cardiovascular biomarkers in blood.	• Evaluation of changes in cardiovascular biomarkers in blood (NT-proBNP and BNP) over time during the study. Results for NT-proBNP will not be reported in the CSR.
• To assess the effect of zibotentan and dapagliflozin in combination versus dapagliflozin 10 mg monotherapy on body fluid volume and distribution status.	• Evaluation of changes in body fluid volume and distribution over the time course of the study. Change in total body water, extracellular water and intracellular water volumes. Results will be obtained from using bioimpedance spectroscopy.

Exploratory Objectives	Endpoints
• **Optional:** collect and store plasma, serum, and urine samples for potential future exploratory research aimed at exploring biomarkers involved in PK, PD, safety and tolerability related to zibotentan and dapagliflozin in combination versus dapagliflozin monotherapy or related to cardiorenal diseases.	• Evaluation of changes in blood and urine biomarkers relevant to cardiorenal mechanisms, inflammation, and fibrosis over the time course of the study. Results from this future analysis will not be reported in the CSR.
• **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. Results from this optional genetic research will not be reported in the CSR.

Abbreviations: BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CSR = clinical study report; CT-proET-1 = C-terminal pro-endothelin-1; ELDP = endothelin-like domain peptide; ET-1 = endothelin-1; K^+ = potassium; Na^+ = sodium; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PD = pharmacodynamics; PK = pharmacokinetics.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2b, multicentre, randomised, double-blind, active-controlled, parallel group dose-ranging study to assess the efficacy, safety and tolerability of zibotentan and dapagliflozin in participants with CKD with eGFR ≥ 20 mL/min/1.73 m^2, and UACR ≥ 150 mg/g and ≤ 5000 mg/g.

The study will be conducted in approximately 220 sites in North America, South America, Africa, Asia/Pacific, and European countries.

Participants will be randomised to 12 weeks of treatment plus 2 weeks follow-up, as shown in Figure 1. All the variables will be collected (eCRF and third party vendor data) to verify the inclusion and exclusion criteria and additional demographic data such as race/ethnicity, serum creatinine, and height.

Participants who meet the eligibility criteria will be randomised to study treatments in addition to receiving background local SoC therapy. To ensure blinding to treatment and zibotentan dose, daily dosing will consist of one dapagliflozin tablet, containing dapagliflozin 10 mg and one zibotentan capsule containing zibotentan 1.5 mg, zibotentan 0.25 mg or placebo.

A total of 495 participants will be randomised into this study, including participants randomised under the earlier study design. Four hundred and fifteen (415) participants will be randomised to have the following number of participants in the main analysis (marked as M in Table 4):

- Zibotentan 0.25 mg + Dapagliflozin 10 mg once daily, 83 participants
- Zibotentan 1.5 mg + Dapagliflozin 10 mg once daily, 166 participants
- Dapagliflozin 10 mg once daily, 166 participants

Participants who were previously randomised cannot be re-randomised.

Participants will be stratified by diabetes (diabetic kidney disease [DKD] versus non-diabetes mellitus [non-DM] CKD) and baseline eGFR (below or equal versus above 45 mL/min/1.73m^2) at the time of

randomisation to ensure an approximate balance between treatment arms within each sub-population. The strata are:

- Stratum 1: DKD participants with eGFR ≤ 45 mL/min/1.73m^2.
- Stratum 2: DKD participants with eGFR > 45 mL/min/1.73m^2.
- Stratum 3: non-DM CKD participants with eGFR ≤ 45 mL/min/1.73m^2.
- Stratum 4: non-DM CKD participants with eGFR > 45 mL/min/1.73m^2.

The number of randomised participants in each stratum will be monitored to ensure the non-DM CKD subpopulation is approximately a minimum of 30% and a maximum of 50% of the total number of participants randomised.

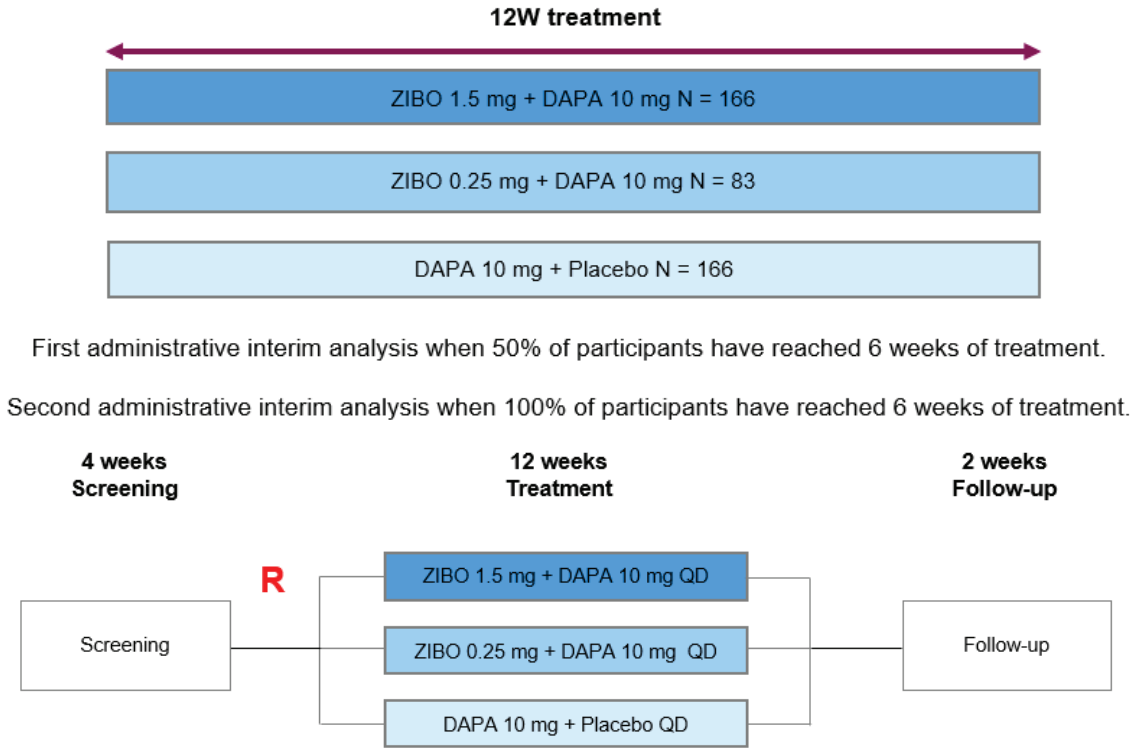
A first administrative interim analysis may be performed when 50% of participants have completed 6 weeks of treatment or at a time selected by the sponsor. A second administrative interim analysis may be performed after 100% of participants have completed the 6 weeks of treatment or at a time selected by sponsor / percentage of participants with a planned week 6 visit before data cut selected by sponsor. For further details on the interim analysis, see Section 4.13.

For each participant, the total duration of participation will be approximately 17 to 19 weeks. The screening period can be up to approximately 4 weeks in duration prior to randomisation. The first dose will be taken after randomisation at the baseline visit on Day 1. In addition to the baseline visit, the participant will visit the clinic 5 times during the following 12 weeks of treatment. Approximately 2 weeks after the last dose, the participant will visit the clinic again for a follow-up assessment.

The primary objective is to evaluate the effect of zibotentan 1.5 mg/dapagliflozin 10 mg as assessed by change from baseline in (log-transformed) UACR at Week 12, when compared to dapagliflozin 10 mg monotherapy as defined in Section 4.10.2.

The study schedule of assessments (SoA) can be found in Appendix A: Schedule of Activities.

Figure 1 Study Schema



DAPA = dapagliflozin; N = numbers of participants; QD = once daily; R = randomisation; SAP = Statistical Analysis Plan; W = week; ZIBO = zibotentan.

3.2 Endpoints

For a full list of all study assessments and the timings of the assessments, see the SoA in Appendix A: Schedule of Activities.

3.2.1 Efficacy Variables

3.2.1.1 Urinary Albumin to Creatinine Ratio (UACR)

The UACR is a key marker for assessing kidney function. The UACR is a ratio between 2 measured substances (urine albumin and creatinine), which estimates 24-hour urine albumin excretion.

The UACR is calculated as follows:

- UACR (mg/g) = urine albumin (mg/dL) / urine creatinine (g/dL)

Urine samples for the determination of albumin and creatinine levels and calculation of UACR will be collected at the time points described in the SoA in Appendix A: Schedule of Activities.

Spot urine from first morning void will be collected the day after screening and analysed centrally.

For subsequent visits, participants will collect first morning void samples at home on 3 consecutive days. Samples will be analysed centrally.

At each visit (except for screening), the geometric mean of the triplicate UACRs will be computed and used for all analysis of UACR. If any of the samples for a triplicate UACR is missing, then the geometric mean will be calculated based on the available samples for the triplicate.

3.2.1.2 Office/Clinic Blood Pressure Measurement

Blood pressure measurements for participants who receive dapagliflozin monotherapy or different doses of zibotentan combined with dapagliflozin 10 mg will be done during clinic visits at the time points for vital signs indicated in the SoA in Appendix A: Schedule of Activities.

3.2.1.3 Serum Analysis of Creatinine and Cystatin C (eGFR)

Estimated GFR is another measure that is considered as a standard for assessment of kidney function. Estimated GFR is calculated based on serum creatinine values using the widely validated and accepted CKD-EPI equation (Levey et al, 2009). Blood samples for estimation of serum creatinine (clinical chemistry) are collected at various time points during the course of the study as shown in the SoA in Appendix A: Schedule of Activities.

Estimated GFR, using serum creatinine, is calculated as follows:

- eGFR (mL/min/1.73 m^2) = 141 × min (SCr/κ, 1)$^{\alpha}$ × max (SCr/κ, 1)$^{-1.209}$ × 0.993^{Age} × (1.018 if female) × (1.159 if Black)

Where SCr = serum creatinine (in mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.

Alternatively, serum cystatin C provides GFR estimates that are nearly as accurate as serum creatinine adjusted for age, sex, and race thus providing an alternative GFR estimate that is not linked to muscle mass (Scholtes et al, 2020, Stevens et al, 2008). Blood samples will be collected for measurement of cystatin C, at specified time points as shown in the SoA in Appendix A: Schedule of Activities.

Estimated GFR, using cystatin C, is calculated as follows:

- eGFR = 133 × min (S_{cys}/0.8, 1)$^{-0.499}$ × max (S_{cys}/0.8, 1)$^{-1.328}$ × 0.996^{Age} × 0.932 [if female]

Where S_{cys} is standardized serum cystatin C (in mg/L), min indicates the minimum of S_{cys}/0.8 or 1, max indicates the maximum of S_{cys}/0.8 or 1, and age = years.

Estimated GFR calculations using the CKD-EPI formulae (in both ways, based on cystatin C and based on creatinine) will be performed by the central laboratory.

3.2.2 Safety Variables

Safety will be assessed by descriptive analysis of AEs (including serious adverse events [SAEs] and adverse events leading to the discontinuation of study intervention [DAEs]), vital signs, ECGs, laboratory assessments, echocardiography assessments and events of special interest.

Treatment-emergent throughout this document has the meaning of an event such as an AE or laboratory/ECG/vital sign value outside of predefined ranges occurring during on-treatment as defined in Section 4.2.1 and Section 4.11.2.

3.2.2.1 Adverse Events and Serious Adverse Events

Adverse events will be collected after the participant has received the first dose of study intervention throughout the interventional period and including the follow-up period (Visit 8).

SAEs will be recorded from the time of signing of the informed consent form.

3.2.2.2 Physical Examinations

Physical examination, and measurement of weight (analyses will be based on weight measured at the study site, not the home-based monitoring using the digital scales) and height will be conducted at the time points outlined in the SoA in Appendix A: Schedule of Activities. For further information on the physical examinations refer to Section 8.2.1 in the clinical study protocol (CSP).

The only information relating to physical examinations that will be included in the CSR are any associated AEs, the recording and reporting of which are specified in Section 8.3.5 of the clinical study protocol (CSP).

Body weight must be taken and reviewed before continuing treatment at each visit as indicated in the SoA in Appendix A: Schedule of Activities. Weight will be analysed as indicated in one of the exploratory objectives (the third bullet point in the table from Section 2.4).

3.2.2.3 Vital Signs

Vital signs will include resting BP, pulse, and respiratory rate measurements. For further information on vital signs refer to Section 8.2.2 in the CSP.

For information on how AEs based on vital sign results should be recorded and reported, refer to Section 8.3.5 in the CSP.

Notable changes from pre-dose at each post-dose time point for vital sign parameters will be identified. The predefined criteria for notable changes in vital signs values are displayed in Table 1

Table 1 Vital sign notable change predefined criteria

Vital sign		Observed value	Notable change from baseline
Systolic BP (mmHg)	High	≥ 140	Increase of ≥ 20
	Low	< 90	Decrease of ≥ 20
Diastolic BP (mmHg)	High	≥ 90	Increase of ≥ 10
	Low	< 60	Decrease of ≥ 10
Pulse Rate (bpm)	High	≥ 100	Increase of ≥ 20
	Low	< 50	Decrease of ≥ 20
Respiratory Rate (breaths/min)	High	> 20	
	Low	< 12	

BP = Blood pressure.

3.2.2.4 Electrocardiograms

Triplicate 12-lead ECGs will be performed after the participant has been resting in a supine position for at least 10 minutes, at the visits outlined in the SoA in Appendix A: Schedule of Activities. For further information on ECGs refer to Section 8.2.3 in the CSP.

Digital ECGs performed at site will be transferred to Clario (ERT), where they will be centrally read and stored. A digital ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTcF intervals will be used. Interpretation of the clinical safety digital ECG findings will be reviewed and confirmed by the investigator, classified as normal/abnormal and whether clinically significant, and recorded in the eCRF.

For information on how AEs based on ECG results should be recorded and reported, refer to Section 8.3.5 in the CSP.

Potentially clinically significant (PCS) ECG values will be identified from third party vendor data. The predefined criteria (based on severity) for PCS ECG values are displayed in Table 2.

Table 2 PCS ECG predefined criteria

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.
*Cut-off values for categorical analyses as recommended by ICH E14 (Note, more than one category for high range increases in QT/QTc values)
Note, no standard criteria are established for treatment emergent increases or decreases in RR intervals or heart rates, or for treatment emergent decreases in PR, QRS or QT/QTc intervals
Note, lower and upper RR interval limits and low and high RR interval reference ranges (all in ms), represent respectively the upper and lower heart rate limits and high and low heart rate reference ranges (all in bpm)

3.2.2.5 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the visits indicated in the SoA in Appendix A: Schedule of Activities.

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

The clinical chemistry, haematology, and urinalysis will be performed at a central laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

In addition, samples will also be collected for analysis of the following parameters:

- Screening samples for parameters needed to confirm eligibility:
  - For women only: serum pregnancy test (only included in listings).
- Samples for the determination of cystatin C by a central laboratory at the visits indicated in the SoA in Appendix A: Schedule of Activities.

Laboratory variables will be measured as indicated in Table 3.

Table 3 Laboratory Safety Variables

Haematology/Haemostasis (whole blood) [a]	**Clinical Chemistry (serum or plasma)** [a]
White blood cell (WBC) count	Serum sodium (Na^+)
Red blood cell (RBC) count	Serum potassium (K^+)
Haemoglobin (Hb)	Serum urea
Haematocrit	Blood urea nitrogen (BUN)
Neutrophils absolute count	Serum creatinine
Lymphocytes absolute count	Estimated glomerular filtration rate (eGFR), calculated by CKD-EPI formula [b]
Monocytes absolute count	Uric acid
Eosinophils absolute count	Albumin
Basophils absolute count	Calcium
Platelets	Phosphate
International normalised ratio (INR) (including prothrombin time, required to calculate INR)	Alkaline phosphatase (ALP)
	Alanine aminotransferase (ALT)
Urinalysis	Aspartate aminotransferase (AST)
Glucose	Total bilirubin (TBL)
Erythrocytes	Creatinine kinase (CK)
Protein	Chloride (Cl^-)
Albumin	Magnesium (Mg^+)
Creatinine	Glucose (fasting, refer to Section 5.3.1 of the CSP)
	HbA1c (fasting, refer to Section 5.3.1 of the CSP)
Other assessments [a]	Cholesterol and lipids (fasting, refer to Section 5.3.1 of the CSP)
Cystatin C (serum)	
Serum pregnancy test (women only, at screening)	

NB. In case a participant shows an AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN, refer to Appendix E in the CSP.

[a] Central laboratory for all visits.

[b] eGFR will be calculated by the central laboratory analysing the sample, using the CKD-EPI formulae in both ways, based on cystatin C and based on creatinine.

At each visit (except for screening), the geometric mean of the triplicate urine albumin and urine creatinine samples will be computed and used for summarising the parameters. If any of the samples for triplicate urine albumin or urine creatinine are missing, then the geometric mean will be calculated based on the available samples for the triplicate.

3.2.2.6 Echocardiography Assessment of Cardiac Structure and Function

An assessment of cardiac structure and function using echocardiography will be performed during the Screening period and at Week 12. The examination is non-invasive and prior preparation is not required.

The following parameters will be assessed:

- The left ventricular ejection fraction (LVEF) (%)
- Overall echocardiography evaluation (normal/abnormal)

- Left ventricular wall motion
- Method of left ventricular volume/ejection fraction calculation
- Mitral valve evaluation
- Aortic valve evaluation
- Tricuspid valve evaluation
- Pulmonic valve evaluation
- Mitral valve closure to open time (s)
- Tricuspid valve closure to open time (s).

3.2.2.7 Events of special interest

Changes in fluid-related measures (weight gain or BNP) meet the defined threshold to be considered as an event of special interest if they are as follows:

- BNP is increased > 100% from baseline and is greater than 200 pg/mL in a participant without atrial fibrillation or
- BNP is increased > 100% from baseline and is greater than 400 pg/mL in a participant with atrial fibrillation or
- More than 3% increase in study site body weight (at least 2.5% of which must be from total body water [increase of at least 2.5% in total body water from baseline as a percentage of baseline study site body weight] as measured by bioimpedance) from start of treatment (Day 1)

3.2.3 Exploratory Variables

3.2.3.1 Bioimpedance Spectroscopy

BIS will be performed at the site at the time points specified in the SoA in Appendix A: Schedule of Activities to monitor body fluid volumes: total body water, extracellular fluid, and intracellular fluid.

3.2.3.2 Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentrations of zibotentan and dapagliflozin, and exploratory zibotentan metabolite evaluation, as specified in the SoA in Appendix A: Schedule of Activities.

A sub-group of at least 20% of the overall study population will have 4 PK samples taken in addition to the pre-dose sample, spread over 4 different time points (0.5-1.0 h, 1.5-2.0 h, 2.5-3.0 h and 3.5-4.5 h post-dose). Zibotentan and dapagliflozin concentrations will be measured separately. As indicated in the SoA in Appendix A: Schedule of Activities, the additional samples will be taken at Visit 4. For further information on the PK sub-study refer to Section 8.5.1.1 in the CSP.

Samples for determination of zibotentan and dapagliflozin concentrations in plasma will be assayed by Labcorp Bioanalytical Services LLC on behalf of AstraZeneca, using appropriately validated bioanalytical methods. Zibotentan and dapagliflozin plasma concentrations will be measured separately. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Samples for zibotentan metabolite evaluation will be analysed by AstraZeneca. Results from this analysis may not be reported in the CSR.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

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

3.2.3.3 Pharmacodynamics

Urinary and serum/plasma parameters will be measured during the study for the evaluation of the exploratory endpoints.

The following parameters will be measured from the blood samples collected for safety (from Visit 2 to 8, analysed at a central laboratory, see Section 3.2.2.5):

- Plasma/serum K^+, Na^+, uric acid, BUN, and fasting plasma glucose as part of clinical chemistry.
- Haematocrit and haemoglobin, as part of haematology.

Urine samples will be collected and analysed by a central laboratory for the determination of the exploratory urinary parameters at the time points specified in the SoA in Appendix A: Schedule of Activities.

The urine samples collected on visit days for the analysis of UACR (see Section 3.2.1.1) will be split, so that they can also be used for the determination of Na+, K+, uric acid, urea, glucose, creatinine, osmolality and cortisol levels. Cortisol levels will not be reported in the CSR.

Blood samples will be collected at the time points specified in the SoA in Appendix A: Schedule of Activities and analysed by a central or local laboratory for the determination of the following parameters:

- Cystatin C, ET-1, ELDP, CT-proET-1, copeptin, NT-proBNP, and BNP. Results for ET-1, ELDP, CT-proET-1 and copeptin will not be reported in the CSR.
- Fasting plasma glucose (for fasting conditions, refer to Section 5.3.1 of the CSP).

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

4.2.1 Study Period

The following study periods are defined (if the specified visit did not take place, the date for planned visit should be used):

- Overall study period – from date of Visit 1 to date of Visit 8
- Screening period – from date of Visit 1 up to the day before Visit 2; this can be up to approximately 4 weeks in duration prior to randomisation
- Treatment (Interventional) period – from date of Visit 2 to date of Visit 7
- On-treatment period – from the same date as the first administration of study intervention until the earliest of: 28 days after last dose of zibotentan/placebo and/or dapagliflozin/placebo; end of study; lost to follow-up; and withdrawal of consent
- Off-treatment period – from more than 28 days after the last dose of study intervention
- Follow-up period – from day after Visit 7 to date of Visit 8

4.2.2 Data Presentation

All efficacy and safety variables will be summarised by study treatment arm using descriptive statistics. The type of analysis that will be performed for a treatment arm – main (M) or only descriptive (D) – depends on the protocol version and study part as specified in Table 4. Note that descriptive analysis will also be performed for M as a way of presenting data as detailed in this SAP.

For treatment arms marked with D in Table 4, a selection of descriptive statistics will be presented. The outputs will be identified in the tables, listings and figures (TLF) mock shells. The following information will be part of these selected outputs:

- Disposition
- Demographics
- Baseline characteristics
- UACR descriptive summary
- AEs/SAEs/DAEs
- Vital signs
- Clinical laboratory tests (including eGFR)
- 12-lead ECG assessment
- Event of special interest (changes in fluid-related measures)
- Study site body weight and total body water
- Exposure
- PK.

Table 4 Protocol version, study part, treatment arm and type of analysis

	Protocol Version 1.0 and CSP Amendment 1		**CSP Amendment 2**
Study part / Treatment arm	**A**	**B**	**-**
Placebo once daily	X/D	X/D	
Zibotentan 5 mg once daily	X/D	X/D	
Dapagliflozin 10 mg once daily	X/D	X/M	X/M
Zibotentan 5 mg + Dapagliflozin 10 mg once daily	X/D	X/D	
Zibotentan 1.5 mg + Dapagliflozin 10 mg once daily		X/M	X/M
Zibotentan 0.25 mg + Dapagliflozin 10 mg once daily		X/M	X/M

X marks whether the treatment arm is included under the corresponding protocol version and study part, M marks the treatment arms that are included in the main analysis and D marks the treatment arms that will only be presented with descriptive statistics.

For continuous variables, descriptive statistics will include the number of non-missing observations (n), mean, standard deviation (SD), median, minimum and maximum. For log-normal variables, the geometric mean (GeoMean) and coefficient of variation (CV) will be presented in addition to those already specified for continuous variables. Continuous data that are expected to be skewed (e.g. duration of exposure, time on study and laboratory variables) will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more

decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical variables will be summarised using frequency counts and percentages. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using the number of non-missing observations as the denominator, unless otherwise specified in the TLF mock shells. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

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".

Confidence intervals will be presented to one more decimal place than the raw data.

Data will be summarised by visit, as appropriate. For information on analysis visit windows, please refer to Section 4.2.3

'Baseline' is defined as the last non-missing value obtained prior to or on the same date as the administration of the first dose of study treatment, unless otherwise stated. For participants without a first dose, the last non-missing value obtained prior to or on the same date as the randomisation date will be used for 'baseline'. 'End of Study' is defined as the last available post-treatment assessment. '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

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

If the date of first dose of study treatment is not present, the randomisation date will be used in the above calculations.

4.2.3 Analysis Visit Windows

All visit-based summaries will use analysis visits. All post-randomisation scheduled and unscheduled visits (excluding Discontinuation visit), will be mapped to an appropriate analysis visit as shown in Table 5.

Table 5 Analysis Visit Windows

CRF Visit	Target Day[1]	Protocol Visit Window[1]	Actual Assessment Day[2]	Analysis Visit
Visit 3 (Wk 1)	D8	D7 to D9	D2 to D15	Week 1
Visit 4 (Wk 3)	D22	D20 to D24	D16 to D32	Week 3
Visit 5 (Wk 6)	D43	D41 to D45	D33 to D53	Week 6
Visit 6 (Wk 9)	D64	D62 to D66	D54 to D74	Week 9
Visit 7 (Wk 12)	D84	D82 to D86	D75 to D91	Week 12
Visit 8 (Wk 14)	D98	D95 to D101	D92 to D129	Follow-up

[1] Relative to the date of randomisation

[2] Relative to the date of first dose of study treatment or randomisation date if no first dose

For visit-based summaries, if there is more than one value per participant within a time window, then the closest value will be summarised, or the earliest in the event the values are equidistant from the

nominal visit date. The listings will highlight the value for that participant that went into the summary table, wherever feasible.

4.2.4 Global/Country Situation Summaries

The Coronavirus Disease of 2019 (COVID-19) pandemic was declared by the World Health Organisation on 11th March 2020 and is considered a global/country situation. The Ukraine/Russia crisis started on 24th February 2022 and is considered a global/country situation. Global/country situation summaries will be presented (see Section 4.5.1).

4.2.5 Japan-Specific Analysis

A subset of the planned outputs will be repeated for participants from Japan, as required for interactions with the Japanese Regulatory Agency. The outputs will be identified in the TLF mock shells.

4.3 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

4.4 Handling of Dropouts or Missing Data

Summary statistics will be based on non-missing values. Information on how missing data will be handled for UACR is provided in Section 4.10.2. Missing safety data will generally not be imputed. However, safety assessment values (vital signs, laboratory assessments excluding urine albumin, urine creatinine and UACR) of the form "<x" (i.e. below the lower limit of quantification [LLOQ]) or ">x" (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings. Measurements of urine creatinine, urine albumin and UACR which are displayed as "<x" will be imputed by using half of the "x" value, as this represents the LLOQ, justified by assuming that any value is equally likely between 0 and the LLOQ. These imputations are required in order to effectively calculate the geometric mean.

Partial or missing dates

If the start date of the concomitant medication or AE is missing, the following rules will be applied:

- If the year is missing, the year should be imputed as the year that participant received the first dose of study treatment.
- If the year is available and the month and day are missing, then impute the month as January and the day as 01.
- If the year and month are available and the day is missing, impute the day as 01 (the first day of the month).
- If any of the above puts the date before the date of first dose of study treatment, a conservative approach is followed, and the date is imputed using the date of first dose if the year matches the year of the date of first dose of study treatment when only the year is available or if the year and month matches the year and month of the date of first dose of study treatment when only the year and month are available.

If the stop date of the concomitant medication or AE is missing and there is an indication that there should be a stop date (ongoing flag marked as "N" for concomitant medication, outcome reported as resolved/fatal for AE), the following rules will be applied:

- If the year is missing, the year should be imputed as the year that participant received the last dose of study treatment.

- If the year is available and the month and day are missing, then impute the month as December and the day as 31.
- If the year and month are available and the day is missing, impute the day as the last day 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 or date of death, the date is imputed using the earliest of the date of end of study and the date of death.

It is not expected to have missing dates for unscheduled laboratory or ECG data. However, if there are missing dates, for any derivations, the dates should be imputed following the rules for concomitant medications and AEs.

4.5 Study Subjects

4.5.1 Disposition of Subjects

A clear accounting of the disposition of all participants who enter the study (signed the informed consent form) will be provided, from screening to study completion.

The following summaries will be provided:

- A summary of the number of participants screened, screen failures, randomised, treated, completed treatment (a participant who has not prematurely discontinued IP during the study), completed treatment period (a participant who has completed the last visit during the treatment period i.e. Visit 7, or a later visit) and completed study (a participant who has completed the follow-up visit at Week 14), by treatment arm and overall. In addition, reasons for not being treated, not completing the treatment period and not completing the study will be summarised by treatment arm and overall (Analysis set: Screened).
- A summary of subject disposition related to the global/country situation (Analysis set: Full Analysis Set).
- A summary of the number of participants randomised per region, country and centre, by treatment arm and overall (Analysis set: All randomised set).
- A summary of Interactive Response Technology (IRT) stratification factors i.e. diabetes (DKD participants versus non-DM CKD participants) and baseline eGFR ($\leq$ 45 mL/min/1.73 m^2 versus > 45 mL/min/1.73 m^2) at randomisation by treatment arm and overall (Analysis set: All randomised set).
- A summary of global/country situation study disruptions (Analysis set: Full Analysis Set).

By-participant listings of disposition details for discontinued participants, participants completing the study, participants affected by the global/country situation and participants with reported issues in the Clinical Trials Management System due to global/country situation will be provided. In addition, a by-participant listing of the randomisation scheme and codes will be provided.

4.5.2 Protocol Deviations

According to ICH E3 guidelines version dated 1995 (ICH 1995),

“Protocol deviations consist of any change, divergence or departure from the study design or procedures defined in the protocol. Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient’s rights, safety or well-being.”

The impact of important protocol deviations on the efficacy results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by important protocol deviations.

Important protocol deviations and any action to be taken regarding the exclusion of participants or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

For this study, the following general categories will be considered IPDs and will be summarised in the CSR:

- Deviation 1: Participants who did not meet the inclusion criteria or met exclusion criteria and received study treatment.
- Deviation 2: Participants assigned to treatment who received their assigned study treatment at an incorrect dose at one or more occasions or who received a study treatment to which they were not assigned.
- Deviation 3: Participants who received prohibited medications during study treatment period or as specified in Section 6.5.1 in the CSP.
- Deviation 4: Participants who met study treatment discontinuation criteria but continued study treatment.
- Deviation 5: Participants who persistently missed procedures related to key efficacy and safety objectives.
- Deviation 6: Missed visits, assessments, or treatments that, in the Investigator's opinion, were due to the COVID-19 pandemic and there was a significant effect on EITHER completeness, accuracy, and/or reliability of the participant's data, OR the participant's rights, safety or well-being.

In addition to classifying protocol deviations (PDs) as important or non-important, PDs are also evaluated for whether they can be classified as resulting from COVID-19 or the Ukraine/Russia crisis.

The number and percentage of participants with any IPD will be summarised for each IPD category based on the full analysis set (FAS). There will be additional sections of the summary for IPDs related to COVID-19 and the Ukraine/Russia crisis. Participants with more than one deviation in the same IPD category will be counted once for that IPD category. Any participants who have deviations in more than one IPD category will be counted once in the overall summary.

A list of all PDs, including those reported by monitors, will be reviewed and decisions regarding how to handle these deviations will be documented by the study team physician, clinical pharmacology scientist and statistician prior to database lock (DBL). The final classification will be made prior to database lock.

Programmable PDs will be detected from the data recorded in the clinical database and will be reviewed at regular PD review meetings. At this meeting, the programmatically derived PDs will be checked to ensure that they have been correctly classified as important or not important PDs.

On an ongoing basis throughout the study, monitoring notes or summaries will also be reviewed to determine any important post entry deviations that are not identifiable via programming.

The final classification of IPDs will be made prior to DBL or data cut-off for final analysis. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

A by-participant listing of important protocol deviations will be provided.

4.6 Analysis Sets

The following summaries will be provided:

- A summary of the number of participants in each analysis set by treatment arm and overall. Exclusions from each analysis set will also be summarised by reason.

By-participant listings of participants excluded from each analysis set and the reasons for exclusion from each analysis set will be provided.

Table 6 Analysis Sets

Population/ Analysis set	Data selection as indicated in Table 4	Description
Screened	D+M	All participants who signed the informed consent form.
Descriptive Analysis Set	D	All participants randomised and who are to be presented only descriptively as indicated with D in Table 4. Participants are evaluated according to the treatment assigned at randomisation.
All Randomised Set	M	All participants who are randomised. Participants are evaluated according to the treatment assigned at randomisation.
Full Analysis Set (FAS)	M	All participants who are randomised and receive any study treatment. Participants are evaluated according to the treatment assigned at randomisation.
Per Protocol Analysis Set (PPS)	M	A subset of the FAS consisting of all participants who completed at least 6 weeks of treatment and do not have any protocol deviations classified as important. All decisions to exclude participants from the PPS will be made and documented prior to the unblinding of the study.
Safety Analysis Set	M	All participants who are randomised and receive any study treatment. Participants are evaluated according to the actual treatment they received. If a participant received a different treatment dose than randomised throughout the study, they will be analysed according to the treated dose, not the randomisation dose. If a participant received investigational product from the wrong kit for only part of the treatment duration but they received the correct kit at some point during treatment duration, they will be analysed according to their planned randomisation arm. If a participant receives multiple incorrect kits and never receives the correct kit during treatment duration, they will be analysed according to their first treated dose. The Safety Analysis Set will be used for all safety analyses, unless otherwise specified.
Ambulatory Blood Pressure Monitoring Set	D	All participants in the Descriptive Analysis Set who have valid ambulatory BP data for change from baseline analyses.

Population/ Analysis set	Data selection as indicated in Table 4	Description
Pharmacokinetic Analysis Set	M	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 actual treatment they received. If a participant received a different treatment dose than randomised throughout the study, they will be analysed according to the treated dose, not the randomisation dose. If a participant received investigational product from the wrong kit for only part of the treatment duration but they received the correct kit at some point during treatment duration, they will be analysed according to their planned randomisation arm. If a participant receives multiple incorrect kits and never receives the correct kit during treatment duration, they will be analysed according to their first treated dose. The Pharmacokinetic Analysis Set will be used for all PK analyses.

Participants or sites identified prior to database lock with major Good Clinical Practice violations and where the integrity of the data is strongly questioned through thorough independent investigations will be excluded from all analyses and all analysis sets.

4.7 Demographic and Other Baseline Characteristics

Age will be taken from the demographics form in the eCRF.

Demographic and other baseline characteristics will be listed for all participants and summarised for the FAS as:

- Demographics (age [years], age group [≥18-<50, ≥50-<65, ≥65-<85, and ≥85 years], sex, race (if collected), country and ethnicity)
- Participant characteristics at baseline (height [cm], weight [kg], weight group [<40, ≥40-<75, ≥75-<90, ≥90-<120, and ≥120 kg], body mass index [BMI], BMI group [Underweight (<18.5 kg/m^2), Normal weight (≥18.5 - <25.0 kg/m^2), Overweight (≥25.0 - <30.0 kg/m^2), Obese (≥30.0 kg/m^2)], family history of premature cardiovascular disease [Y/N], and substance use [nicotine, alcohol, caffeine and drugs])
- Baseline disease characteristics:
    - T2DM diagnosis [Y/N] and T2DM duration [years] from medical history form in the eCRF
    - Derived CKD stage (eGFR category) [Stage 2 (60-89 mL/min/1.73m^2)/Stage 3a (45-59 mL/min/1.73m^2)/Stage 3b (30-44 mL/min/1.73m^2)/Stage 4 (15-29 mL/min/1.73m^2)/Stage 5 (<15 mL/min/1.73m^2)], eGFR (mL/min/1.73m^2), albuminuria [defined as 150-5000 mg albumin/g creatinine, with a further categorisation of 'moderate albuminuria' for 150-300 mg albumin/g creatinine and

'severe albuminuria' for >300-5000 mg albumin/g creatinine; count and percentage of participants meeting criteria], UACR (mg/g)

- CKD diagnosis, including primary renal diagnosis [Cystic kidney disease, Diabetic nephropathy, Ischaemic/Hypertensive nephropathy, Chronic glomerulonephritis, Renal artery stenosis, Chronic pyelonephritis (infectious), Chronic interstitial nephritis, Obstructive nephropathy, Unknown, Other (Specify)] and chronic glomerulonephritis type [IgA nephropathy, Focal segmental glomerulosclerosis (FSGS), Membranous nephropathy, Minimal change (which is part of exclusion criteria 1), Lupus nephritis, Other primary or secondary glomerulonephritis (Specify)] from CKD diagnosis form in the eCRF
- Angiotensin-converting enzyme inhibitor (ACEi) history [Y/N]
- Angiotensin receptor blocker (ARB) history [Y/N]
- Mineralocorticoid receptor agonist (MRA) history [Y/N]

Medical history and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later. The frequency and percentage of participants with each condition will be summarised by system organ class (SOC) and preferred term (PT). Participants with multiple unique terms will be counted once per each unique PT and unique SOC. A participant can have one or more PTs reported under a given SOC. Each summary will be sorted alphabetically by SOC and PT, unless otherwise stated.

By-participant listings of demographic data (including age, sex, race, baseline weight, baseline height and baseline BMI) and the baseline disease characteristics data detailed above will be provided.

4.8 Concomitant Medication

Any medication or vaccine (including over-the-counter or prescription medications, vitamins, and/or herbal supplements) that the participant is receiving on or after the date of first dose of randomised treatment (and could have started prior to or during treatment) will be recorded as concomitant. Medications starting after the date of discontinuation from study treatment/withdrawal from study will be listed but will not be classified or summarised. Medications completed prior to the date of first dose of randomised treatment will be listed but will not be classified or summarised.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of randomised treatment. Medications will be assumed to be concomitant unless there is clear evidence (through comparison of partial dates) to suggest that the medication stopped prior to first dose of randomised treatment.

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

- SGLT2i.
- Direct renin inhibitor (e.g. Aliskiren).
- Cyclosporin or tacrolimus.
- Receiving cytotoxic therapy, immunosuppressive therapy, or other immunotherapy for primary or secondary renal disease within 6 months prior to screening.

In addition to the above, the following medications cannot be initiated or any changes to dose made after the participant has consented, and until the participant has completed the study (or discontinued / withdrawn participation):

- ACEi.
- ARB.
- Angiotensin receptor neprilysin inhibitor (ARNi).
- MRA.

A medical review will be performed to determine whether a medication is classified as prohibited and this medically reviewed classification of prohibited medications will be used for any outputs involving prohibited medications.

Concomitant medications will be summarised for the FAS by drug class and (generic) drug name. A summary table by drug class and generic drug name will be generated for each of the following:

- all allowed concomitant medication taken during the study
- prohibited concomitant medication taken during the study

A by-participant listing of concomitant medications at study entry and taken during treatment will be presented.

4.9 Treatment Compliance

Treatment compliance will be assessed by direct questioning and counting returned zibotentan/placebo capsules and dapagliflozin/placebo tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of zibotentan/placebo capsules and dapagliflozin/placebo tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

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

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

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

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

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

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

$$\frac{Total\ study\ treatment\ dispensed - Total\ study\ treatment\ returned}{Total\ study\ treatment\ expected\ to\ be\ taken} \times 100$$

A participant is expected to take one capsule and one tablet each day while on study treatment as indicated by the dosage regimen in the CSP, such that interruptions could mean compliance of less than 100%. The number of capsules and/or tablets expected to be taken is based on the number of study days between every set of clinic visits from Visit 2 to the end of treatment/early discontinuation visit. For any visits where a participant is required to take study treatment in clinic, the study treatment would be included in the study treatment expected to be taken between the last visit and the current visit.

Participants taking ≥80% and ≤120% of planned study treatment are considered to be compliant.

Study compliance percentage for zibotentan/placebo, dapagliflozin/placebo and overall will be summarised for the FAS as follows:

- Descriptive statistics will be summarised by treatment arms and overall.
- Percent compliance will be categorised according to the following categories:
  - <80% (drug non-compliance)
  - ≥80% and ≤120% (drug compliance)
  - >120% (drug non-compliance)

A by-participant listing of treatment compliance data will be provided.

4.10 Efficacy Evaluation

4.10.1 Analysis and Data Conventions

4.10.1.1 Null Hypothesis for Primary Objective and Related Secondary Objective

This study is designed to test for superiority and assess the dose-response relationship. The null hypothesis for the primary treatment comparison will be that there is no difference between zibotentan 1.5 mg and dapagliflozin 10 mg in combination and dapagliflozin 10 mg monotherapy in UACR. The alternative hypothesis will be that there is a difference. Symbolically, this is expressed as follows:

H(0): μ(zibotentan 1.5 mg and dapagliflozin 10 mg in combination) = μ(dapagliflozin 10 mg monotherapy)

H(1): μ(zibotentan 1.5 mg and dapagliflozin 10 mg in combination) < μ(dapagliflozin 10 mg monotherapy)

Where μ represents the least squares mean change in log-transformed UACR from baseline to Week 12. A one-sided test with α=0.05 will be used to test this hypothesis.

The null and alternative hypotheses for the secondary efficacy treatment comparison of the difference between zibotentan 0.25 mg and dapagliflozin 10 mg in combination and dapagliflozin 10 mg monotherapy in UACR will be the same as described above for the primary efficacy treatment comparison (with the treatment arms updated as required).

4.10.1.2 Multi-centre Studies

No per centre (where the term ‘centre’ defines each investigator site) summaries or analyses will be performed.

4.10.1.3 Examination of Subgroups

When subgroup analyses are performed, it will be by diabetes (DKD versus non-DM CKD) and by stratification eGFR (≤ 45 mL/min/1.73m^2 versus > 45 mL/min/1.73m^2). No formal statistical testing will be performed within these subgroups.

4.10.2 Analyses of UACR Objectives

4.10.2.1 Primary Estimand for Primary Objective

The primary estimand is a hypothetical estimand such that the treatment effect is quantified in the optimal situation where any potential confounder is minimised. The analysis will be performed on the FAS. The endpoint being assessed is the change in log-transformed UACR from baseline to Week 12. Participants will be included in the analysis if they have a non-missing baseline and at least one non-missing post-treatment visit UACR measurement.

For the intercurrent events (ICEs), if a participant dies, prematurely discontinues study treatment, or uses prohibited medication, the UACR data are treated as missing after the event and no imputation will be performed. The summary measure being evaluated is the geometric mean reduction of UACR from baseline to Week 12.

The estimand is specified through the following definitions of population, variable, treatment condition, ICEs, and population-level summary:

Target population:	Defined by the inclusion/exclusion criteria.
Variable:	Change in log-transformed UACR from baseline to Week 12.
Treatment condition:	Zibotentan 1.5 mg combined with dapagliflozin 10 mg versus dapagliflozin 10 mg.
Intercurrent events:	Death, premature discontinuation from study treatment, or use of prohibited medication (Handled by hypothetical strategy i.e. UACR data are treated as missing after the event. Deaths are expected to be relatively few and will be handled in the context of missing data).
Population-level summary:	Difference in least squares mean change in log-transformed UACR from baseline to Week 12 between zibotentan 1.5 mg combined with dapagliflozin 10 mg and dapagliflozin 10 mg.

4.10.2.2 Primary Analysis of Primary Objective

The primary efficacy endpoint for this study is the change in log-transformed UACR from baseline to Week 12. As UACR is assumed to follow a log-normal distribution, it will be log-transformed for statistical analysis purposes. The mean log changes in UACR at Week 12 ($\hat{Y}_1, \hat{Y}_2$) for zibotentan 1.5 mg combined with dapagliflozin 10 mg and dapagliflozin 10 mg alone will be estimated using a mixed model repeated measures [MMRM] method (Weeks 3, 6, 9, and 12). The least squares means will be back transformed to give the geometric mean change from baseline to Week 12. The geometric means will be converted to percentage mean change for Week 12 from baseline on the original scale using the following formula:

$$(GeoMean(UACR_{Week12-Baseline}) - 1) \times 100$$

The change in UACR from baseline to Week 12 for zibotentan 1.5 mg combined with dapagliflozin 10 mg compared to the dapagliflozin 10 mg monotherapy arm will be presented as a geometric mean ratio. The analysis model will include the fixed categorical effects of CSP version (Amendment 2

versus pre-Amendment 2), diabetes (DKD versus non-DM CKD), treatment, visit, and treatment-by-visit interaction, plus baseline eGFR strata (<= 45 versus > 45 mL/min/1.73 m2), log(UACR) and baseline log(UACR)-by-visit interaction. An unstructured covariance structure will be used for the within-participant errors. The denominator degrees of freedom will be estimated using the Kenward-Roger approximation. If the MMRM model does not converge using an unstructured covariance structure, the Toeplitz, first-order autoregressive or compound symmetric covariance structure will be used. If that does not resolve the convergence issues, the analysis will be altered to use an analysis of covariance (ANCOVA) with a missing at random (MAR) multiple imputation (MI) method implemented (Section 4.10.2.3).

The geometric means, along with the conversion to percentage, for change from baseline to Week 12 from the model, and the 90% confidence intervals will be presented. The geometric mean ratio, which is the back-transformed least squares mean difference in change from baseline to Week 12 between two treatment arms, will be converted to adjusted percentage mean change between treatment arms as follows:

$$[(Geometric\ Mean\ Ratio\ -\ 1) \times 100]$$

The geometric mean ratio and the adjusted percentage mean change between treatment arms, as specified above, and the 90% confidence interval will be presented.

UACR will be summarised by treatment arm and visit in terms of absolute values and percentage change from baseline.

A plot showing the percentage mean change from baseline in UACR over time within each treatment arm will be provided.

A by-participant listing of the UACR data will be provided.

Sensitivity analyses

The following sensitivity analyses will be performed:

- The mean log change from baseline in UACR at Week 12 for zibotentan 1.5 mg combined with dapagliflozin 10 mg and dapagliflozin monotherapy on the PPS, using a MMRM method as described above.
- A multiple imputation analysis if not used as the primary analysis; see Section 4.10.2.3 for details.
- A tipping point analysis, depending on the results of the multiple imputation analysis; see Section 4.10.2.4 for details.
- A jump to reference analysis; see Section 4.10.2.5 for details.

Subgroup analyses

A forest plot will present the least squares mean and 90% CI overall and for each subgroup individually. The overall least square means will be taken from the primary analysis model and the subgroup least squares means will be taken from models including treatment arm by diabetes (DKD versus non-DM CKD) and treatment arm by stratification eGFR (below or equal versus above 45 mL/min/1.73m^2), respectively. Homogeneity assessments between the DKD and the non-DM CKD sub-populations, and between the stratification eGFR below or equal to 45 mL/min/1.73m^2 and the stratification eGFR above 45 mL/min/1.73m^2 sub-populations, will be performed by visual inspection of the subgroups in the forest plot and by assessing the interaction p-values from the models.

4.10.2.3 Multiple Imputation

The MI method specified in this section will either be a sensitivity analysis based on the primary estimand strategy or will be the primary efficacy analysis if no covariance structures for the MMRM converge. The MI will be performed on the FAS. It will involve the following steps:

Step 1 – Imputation Preparation

The dataset of participants with observed values, excluding any values after the ICEs specified in Section 4.10.2, and those needing estimation by multiple imputation will be created. The UACR values will be log-transformed.

Step 2 – Imputation

Imputation is the generation of multiple copies of the original dataset by replacing missing values by using an appropriate stochastic model. The missing data will be imputed using the Fully Conditional Specification (FCS) method. The FCS method is based on an iterative algorithm; at each iteration and for each variable of the prediction model, there is a prediction step and an imputation step. The models used for prediction and imputation will be linear regression models. A total of 200 imputations will be performed using a seed of 12345.

The imputation model will include treatment arms, CSP version (Amendment 2, pre-Amendment 2), diabetes (DKD, non-DM CKD), baseline eGFR strata (<= 45 versus > 45 mL/min/1.73 m2), baseline log(UACR), and the log(UACR) at each previous post-baseline visit.

Step 3 – Analysis

The analysis step is performed for each of the imputed datasets. The statistical method for analysis of the change in log-transformed UACR from baseline to Week 12 will be ANCOVA and will include the same covariates as the MMRM that is specified in Section 4.10.2.2, except that the visit and by-visit interaction variables – for treatment and baseline log(UACR) – will not be included.

Step 4 – Pooling

Pooling is the combination of the different parameter estimates across the multiple imputed datasets based on Rubin's rules (Rubin, 2004
2004) to produce a unique point estimate and standard error taking into account the uncertainty of the imputation process.

4.10.2.4 Tipping Point Analysis

In order to check the assumption that the missing data is not MAR, a tipping point analysis will be conducted based on the multiple imputation analysis in Section 4.10.2.3. The objective of the tipping point analyses is to identify assumptions about the missing data under which the conclusions from the main analysis change. These tipping point analyses will only be performed if the multiple imputation analysis results show a reduction in UACR for zibotentan 1.5 mg and dapagliflozin 10 mg in combination versus dapagliflozin 10 mg monotherapy.

If there is a reduction in UACR for zibotentan 1.5 mg and dapagliflozin 10 mg in combination versus dapagliflozin 10 mg monotherapy, additional tipping point analyses will be repeated after increasing the imputed log(UACR) values in the zibotentan 1.5 mg and dapagliflozin 10 mg in combination arm by ascending log(UACR) (1, 2, 3… etc.), with the goal to find the "tipping point" that will significantly reverse the analysis result. The smallest delta, for which a reduction in UACR cannot be shown anymore, will be the "tipping point". The delta will only be applied to the Week 12 imputed values for all missing data regardless of the reason for imputation.

For each value of delta, summary tables will include number of participants, the estimates described in Section 4.10.2.2 (such as geometric mean and geometric mean ratio) and their 90% CIs, and corresponding p-values.

This sensitivity analysis will be performed on the FAS.

4.10.2.5 Jump to Reference Analysis

The jump to reference analysis assumes that the participants who experience ICEs in the active zibotentan treatment arms immediately change to the mean of the dapagliflozin 10 mg arm at the relevant time point, where the participant's residual relative to that of their treatment arm prior to the ICE is taken into account.

A sequential modelling approach will be used to implement the jump to reference analysis. Firstly, all missing values will be imputed under the MAR assumption as described in Section 4.10.2.3 (Steps I and II). Then data after an ICE in the active zibotentan treatment arms will be reset to missing. Missing data in the active zibotentan treatment arms will be imputed sequentially by visit using observed and imputed data from the reference arm. One imputation will be performed for each imputation already performed under the MAR assumption, thereby maintaining the overall number of imputations at 200, using a seed of 12345. The analysis and pooling steps will then be performed as described in Section 4.10.2.3.

4.10.2.6 Supplementary Analysis of Primary Objective

The treatment policy estimand is specified through the following definitions of population, variable, treatment condition, ICEs, and population-level summary:

Target population:	Defined by the inclusion/exclusion criteria.
Variable:	Change in log-transformed UACR from baseline to Week 12.
Treatment condition:	Zibotentan 1.5 mg combined with dapagliflozin 10 mg versus dapagliflozin 10 mg.
Intercurrent events:	Death, premature discontinuation from study treatment, or use of prohibited medication (Handled by the treatment policy strategy i.e. UACR data after the event will be included if collected. Deaths are expected to be relatively few and will be handled in the context of missing data).
Population-level summary:	Difference in least squares mean change in log-transformed UACR from baseline to Week 12 between zibotentan 1.5 mg combined with dapagliflozin 10 mg and dapagliflozin 10 mg.

The primary analysis in Section 4.10.2.2, excluding the sensitivity and subgroup analyses, will be replicated for the treatment policy estimand, with the exceptions that the analyses will be performed on the All Randomised Set and that step 1 in the MI (Section 4.10.2.3) will not exclude any UACR values from after an ICE.

4.10.2.7 Analysis of Secondary UACR Objectives

Comparison of zibotentan 0.25 mg and dapagliflozin 10 mg combined to dapagliflozin monotherapy (Secondary Objective Related to Primary Objective)

The geometric mean ratio of UACR for the zibotentan 0.25 mg combined with 10 mg dapagliflozin versus 10 mg dapagliflozin alone from baseline to Week 12 will be assessed. The MMRM model as described in Section 4.10.2.2 will be used to extract the results.

The results of the model parameters (estimates, p-values and 90% CIs) will be presented. Analyses and definitions described in Section 4.10.2.1, 4.10.2.2, 4.10.2.3, 4.10.2.4, 4.10.2.5 and 4.10.2.6 will be followed with the treatment arm adjusted as appropriate.

Dose-response Relationship Secondary Objective

The dose-response relationship between different doses of zibotentan/a fixed dose of dapagliflozin and UACR reduction will be characterised by assessing the UACR reduction analysed in the primary objective and the secondary objective related to the primary objective.

In order to select the dose for future studies, a more comprehensive PK analysis, including additional dose and exposure response models and modelling of safety events, will be performed by the AstraZeneca PK team based on subject level data. This will only be done where there is sufficient data that allows the AstraZeneca PK team to perform the modelling.

4.10.3 Analysis of Secondary Objectives Other Than UACR

The secondary efficacy variables will be based on a similar estimand to the primary estimand for the primary objective in Section 4.10.2.1, with the variable and population-level summary updated to be relevant to the secondary efficacy variable specified.

Office systolic and diastolic BP

The change from baseline to Week 12 in office systolic and diastolic BP will be assessed for doses of zibotentan combined with dapagliflozin 10 mg compared to dapagliflozin 10 mg monotherapy. This will be analysed using the MMRM method specified in Section 4.10.2.2, adjusting for the same variables, though with baseline BP replacing baseline log(UACR). The FAS will be used for this analysis and BP will be evaluated on the original scale.

The results of each MMRM will be presented by treatment arm. A summary of change from baseline of office systolic and diastolic BP results will be presented by treatment arm and a by-participant listing of office systolic and diastolic BP results at each visit will be provided. Plots of the mean office systolic and diastolic BP over time up to follow-up visit will be presented.

As a sensitivity analysis, a MMRM will be performed for office systolic and diastolic BP up to Week 12, analysed on the PPS, similarly to that described above.

eGFR

The effect of different doses of zibotentan and dapagliflozin in combination compared to dapagliflozin 10 mg monotherapy on eGFR will be determined from the change in eGFR from baseline to Week 1, from baseline to Week 12, from baseline to Week 14 and from Week 1 to Week 12. Change from baseline to Week 1, baseline to Week 12, baseline to Week 14 and Week 1 to Week 12 will be analysed using the MMRM methodology specified in Section 4.10.2.2. Change from baseline to Week 1, change from baseline to Week 3, change from baseline to Week 6, change from baseline to Week 9, change from baseline to Week 12 and change from baseline to Week 14 will be included in the model, adjusting for the fixed categorical effects of CSP version (Amendment 2 versus pre-Amendment 2), diabetes (DKD versus non-DM CKD), treatment visit, and treatment-by-visit interaction, plus the continuous covariates of baseline eGFR and baseline eGFR-by-visit interaction. The FAS will be used for these analyses and eGFR will be evaluated on the original scale.

The results of each MMRM will be presented by treatment arm. A summary of change from baseline of eGFR results will be presented by treatment arm and a by-participant listing of eGFR results at each visit will be provided. A plot of the least squares means by treatment arm over time will be presented.

As a sensitivity analysis, a MMRM will be performed for eGFR from baseline to Week 1, from baseline to Week 12, from baseline to Week 14 and from Week 1 to Week 12, analysed on the PPS, similarly to that described above.

A visual inspection of the plot of the least squares means, mentioned above, will be used to examine the eGFR slope from baseline to Week 12.

4.10.4 Exploratory Evaluations

The exploratory efficacy variables will be based on a similar estimand to that described for the primary efficacy variable in Section 4.10.2.1, with the variable and population-level summary updated to be relevant to the exploratory efficacy variable specified.

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

- Body weight changes in response to different doses of zibotentan and dapagliflozin in combination versus dapagliflozin 10 mg monotherapy, throughout the interventional period.
- Evaluation of changes in body fluid volume and distribution over time during the study. Change in total body water, extracellular fluid, and intracellular fluid volumes will be analysed.

Descriptive summary statistics, including change from screening, by treatment arm based on the ABPM set will be presented for:

- Mean 24-hour systolic and diastolic BP in ABPM at screening, Week 6 and Week 12.

4.11 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Analysis Set as defined in Section 4.6 and the on-treatment period as defined in Section 4.2.1, unless otherwise specified. Safety summaries will be presented by treatment arm.

Change from baseline will be calculated as the difference between the post-dose value at each time point and the last non-missing value prior to or on the same date as administration of the first dose of investigational products.

Individual safety and tolerability data will be provided in data listings and summarised as appropriate by treatment and overall. Continuous variables (laboratory parameters, ECG, and vital signs) will be summarised using descriptive statistics (n, mean, SD, minimum, median, and maximum) as appropriate by scheduled assessment time point. Where applicable, data will be summarised for the observed value, and for the corresponding change from baseline/screening. Categorical variables will be summarised in frequency tables (counts and percentage) as appropriate by scheduled assessment time point.

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

4.11.1 Extent of Exposure

The extent of exposure (days) will be derived for zibotentan and dapagliflozin, combined, as follows:

$$Duration\ of\ exposure\ (days) = Date\ of\ last\ dose - Date\ of\ first\ dose + 1$$

The following extent of exposure summaries will be provided for zibotentan and dapagliflozin (combined):

- Duration of exposure (days)

- A summary of the duration of exposure to treatment (days) and cumulative exposure over time (≥1 day, ≥8 days, ≥22 days, ≥43 days, ≥64 days, ≥85 days), by treatment arm.
- Time on study (days) defined as:
  $Time\ on\ study\ (days) = (Date\ of\ last\ study\ assessment\ or\ Date\ of\ withdrawal) - Date\ of\ randomisation + 1.$

A listing for study drug administration according to protocol and the reason if the study drug administration is not according to protocol will be produced for the Safety Analysis Set.

A Kaplan-Meier figure for time to premature study drug discontinuation will be produced for the Safety Analysis Set. Time to premature study drug discontinuation (days) will be defined as:

- $Date\ of\ premature\ discontinuation\ from\ study\ drug - Date\ of\ first\ dose + 1$ for participants who prematurely discontinue study drug
- $Date\ of\ last\ visit\ day\ in\ the\ treatment\ period - Date\ of\ first\ dose + 1$ for participants who do not prematurely discontinue study drug but are lost to follow-up during the treatment period
- $Minimum(Withdrawal\ of\ consent\ date, Date\ of\ death, Date\ of\ Visit\ 7, Date\ of\ study\ day\ 86) - Date\ of\ first\ dose + 1$ for any other participants who do not prematurely discontinue study drug.

4.11.2 Adverse Events

Adverse events will be coded using MedDRA version 25.0 or a later version, if available.

AEs (and also separately SAEs) will be summarised by study treatment arm in incidence summaries by MedDRA SOC and PT. AEs will be assigned to the period where they start and will be summarised for the Safety Analysis Set. SAE collection will begin after the participant signs the informed consent document, and all AE collection will begin after the participant has received the first dose of the study intervention. The SAE/AE collection will last until the end of the participant's follow-up period.

All AEs will be listed and assigned to on/off treatment period as:

- Prior treatment: The SAE occurred before the first administration of study intervention. Only applicable for SAEs.
- On treatment: The AE occurred on the same date or after the first administration of study intervention until the earliest of: 28 days after last dose of zibotentan/placebo and/or dapagliflozin/placebo; end of study; lost to follow-up; and withdrawal of consent.
- Off treatment: The AE occurred more than 28 days after the last dose of study intervention.
- On + off treatment: The AE occurred on the same date or after the first administration of study intervention.

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

An overview of AEs will be presented for each treatment arm; the number and percentage of participants with any AE, any AE with outcome of death, any SAE, any DAE, any AE leading to study treatment dose interruptions, any AE leading to withdrawal from the study, and any AE possibly related to study treatment, as well as the number of individual occurrences in those categories.

The number and percentage of participants reporting AEs, SAEs and DAEs in each treatment arm will be tabulated by SOC and PT. If more than one event occurs with the same preferred term for

the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarisation by intensity and by relationship to the study treatment.

The distribution of AEs by intensity and relationship to study treatment will be summarised by treatment arm.

The incidence of common (≥5% of participants in any treatment arm) AEs will be summarised by PT and treatment arm, sorted in decreasing overall (across treatments) frequency. For each participant and each AE, the worst intensity recorded will be attributed and used in the by-intensity summaries. Similarly, the worst causality will be attributed and used in the by-causality summaries. Multiple occurrences of an AE in the same participant will only be counted once overall. Non-serious AEs occurring in more than 5% of participants will be presented by treatment arm.

In addition, a tabulation of AEs, by PT, relevant for assessment of potential proarrhythmic effect will be provided based on the SMQ "Torsade de pointes/QT prolongation" (narrow and broad scope) and PT Seizure. A tabulation of AEs by PT will be provided for the SMQ "Haemodynamic oedema, effusions and fluid overload" (narrow scope).

Listings will be presented of participants with SAEs, AEs leading to discontinuation, and participants who died. A listing will be presented of participants with AEs, detailing whether these are SAEs, AEs leading to discontinuation, or result in death. Listings will include on- and off-treatment categorisation.

4.11.3 Deaths, Serious Adverse Events, and Adverse Events Leading to the Discontinuation of Study Intervention

The following summaries will be provided:

- A summary of the number and percentage of participants reporting an AE with outcome of death by treatment arm, SOC and PT
- A summary of key participant information for participants reporting an AE with outcome of death
- A summary of the number of SAEs reported by treatment arm, SOC and PT
- A summary of the number and percentage of participants reporting a SAE by treatment arm, SOC and PT
- A summary of key participant information for participants reporting a SAE
- A summary of the number and percentage of participants reporting a DAE by treatment arm, SOC and PT
- A summary of key participant information for participants reporting a DAE.

4.11.4 Clinical Laboratory Evaluation

The following summaries will be provided:

- A summary, which will cover n, mean, SD, minimum, Q1, median, Q3, and maximum, of the observed values and change from baseline for all clinical chemistry (including cystatin C), haematology and quantitative urinalysis parameters by treatment arm and time point
- A summary of baseline to maximum observation on treatment in each clinical chemistry (including cystatin C) and haematology laboratory parameter by treatment arm (shift table)

- A summary of baseline to minimum observation on treatment in each clinical chemistry (including cystatin C) and haematology laboratory parameter by treatment arm (shift table)
- A plot of ALT versus total bilirubin, expressed as multiples of upper limit of normal (ULN)
- A plot of AST versus total bilirubin, expressed as multiples of ULN
- A summary of the number and percentage of participants reporting maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's Law criteria
- A summary of individual participant data for participants with Potential Hy's Law i.e. participants with combined ALT or AST, and bilirubin elevations
- A summary of key participant information for participants with treatment-emergent changes in laboratory parameters (refers to clinical chemistry and haematology, other laboratory parameters are in supportive listings) outside of pre-defined criteria
- A summary of treatment-emergent laboratory changes (see Appendix C: Treatment-Emergent Changes in Relevant Laboratory Parameters)
- A summary of baseline versus maximum value on treatment for urinalysis by treatment arm (shift table)
- A summary of treatment-emergent urinalysis changes

Treatment-emergent changes in relevant laboratory parameters outside pre-defined criteria for this study are provided in Appendix C: Treatment-Emergent Changes in Relevant Laboratory Parameters. Treatment-emergent urinalysis changes are defined as: negative/trace at baseline to ++, +++, ++++ at any visit after baseline or an increase of at least ++, for example + to +++, ++ to ++++.

By-participant listings of all laboratory data will be provided including participant identifier, treatment, age, sex, race, visit, category, lab test name, result, change from baseline (where appropriate) and standard units. Laboratory reference ranges will also be listed and out of range values will be flagged.

BNP values from local laboratories will only be presented in listings; the central laboratory values will be used for summary tables and presented in listings. Results for central NT-proBNP will not be reported in the CSR.

4.11.5 Vital Signs, Electrocardiograms, Echocardiography and Other Observations Related to Safety

The number and percentage of participants with normal and abnormal ECG readings by visit will be presented by treatment arm. Abnormal ECG results and reasons entered into the eCRF will be listed by participant and by visit.

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each applicable scheduled visit will be summarised.

The following summaries will be provided:

- A summary, which will cover n, mean, SD, minimum, Q1, median, Q3, and maximum, of the observed absolute values and change from baseline for all vital sign parameters by treatment arm and time point.
- A summary of key participant information for participants reporting notable changes outside predefined criteria for all vital sign parameters.

- A summary of the number and percentage of participants experiencing notable changes from baseline outside predefined criteria, by vital sign parameter and treatment arm.
- A summary of the observed absolute values and change from baseline in each ECG parameter (excluding QTcB) by treatment arm and time point.
- A summary of ECG assessment (normal/abnormal [clinically significant, not clinically significant]), baseline versus last observation on treatment.
- A summary of key participant information for participants reporting PCS ECG values (excluding QTcB) outside predefined criteria.
- A summary of the number and percentage of participants reporting PCS ECG values (excluding QTcB) outside predefined criteria, by ECG parameter and treatment arm.
- A summary of the overall evaluation for echocardiography (normal/abnormal) and LVEF by treatment arm and time point.

By-participant listings of vital sign parameters, ECG parameters, ECG findings, echocardiography parameters, and weight, height and BMI will also be provided.

4.11.5.1 Fluid-Related Measures

Changes in fluid-related measures (weight gain or BNP) meet the defined threshold to be considered as an event of special interest if they meet the criteria defined in Section 3.2.2.7.

A summary of the number, percentage, incidence rate per participant exposure year (PEY) and incidence rate per participant year of participants reporting fluid-related events of special interest will be produced for the Safety Analysis Set, by treatment arm. The relative risk and one-sided 80% CI, where the standard error of the relative risk is based on the Katz-log method, for the composite of any fluid-related events of special interest compared to the dapagliflozin 10 mg arm will be presented.

The incidence rate per 100 PEY is defined as below for on-treatment:

$$\left(\frac{number\ of\ subjects\ with\ event\ of\ special\ interest\ on\text{-}treatment}{time\ at\ risk\ (days)\ for\ an\ event\ of\ special\ interest}\right) \times 365.25 \times 100$$

The time at risk, in days, for each participant for a fluid-related event of special interest is:

- $Min(Date\ of\ last\ dose + 28, end\ of\ study, lost\ to\ follow\text{-}up, withdrawal\ of\ consent) - Date\ of\ first\ dose + 1$ for participants who do not have an on-treatment event
- $Date\ of\ first\ occurrence\ of\ event\ of\ special\ interest\ on\text{-}treatment - Date\ of\ first\ dose + 1$ for participants who have an on-treatment event.

The denominator is calculated per participant then summed.

The incidence rate per 100 participant years is defined as below for on+off treatment:

$$\left(\frac{number\ of\ subjects\ with\ event\ of\ special\ interest\ on{+}off\ treatment}{time\ in\ study\ (days)\ up\ to\ an\ event\ of\ special\ interest}\right) \times 365.25 \times 100$$

The time in study, in days, for each participant for a fluid-related event of special interest is:

- $Date\ of\ end\ of\ study - Date\ of\ first\ dose + 1$ for participants who do not have an on+off treatment event
- $Date\ of\ first\ occurrence\ of\ event\ of\ special\ interest\ on{+}off\ treatment - Date\ of\ first\ dose + 1$ for participants who have an on+off treatment event.

A by-participant listing of percentage weight gain from baseline, total body water change from baseline as a percentage of baseline weight, percentage change from baseline in BNP, BNP value and atrial fibrillation indicator will be provided.

4.12 Other Analyses

4.12.1 Pharmacokinetics

'Baseline' is defined as the last non-missing value obtained prior to the administration of the first dose of study treatment, taking into account both the date and time of the non-missing value and the first dose of study treatment.

The following exploratory PK endpoints will be summarised by treatment arm, visit and timepoint based on the Pharmacokinetic Analysis Set:

- Plasma concentration of zibotentan and dapagliflozin.
- Dose of zibotentan relative to safety and PD variables (blood NT-proBNP, BNP, creatinine, and cystatin C, and urine albumin and creatinine).

Summary tables will be provided covering the results of the PK sub-study at Week 3.

All PK summary tables will include samples from visits for participants who had not previously permanently discontinued study treatment. PK listings will include samples from participants regardless of whether they were from visits after the participant had discontinued study treatment.

Additional PK analyses may be conducted as appropriate. Results for NT-proBNP will not be reported in the CSR.

The summary of plasma concentration of zibotentan metabolites are outside the scope of this SAP.

4.12.2 Pharmacodynamics

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

- Change in plasma/serum concentrations of K^+, Na^+, uric acid, BUN, fasting plasma glucose, haematocrit, and haemoglobin over time during the study. Results for ET-1, ELDP, CT-proET-1 and copeptin will not be reported in the CSR.
- Evaluation of changes in cardiovascular biomarkers in blood (NT-proBNP and BNP) over time during the study. Results for NT-proBNP will not be reported in the CSR.

4.12.3 Potential Future Exploratory Research and Optional Genetic Research

The following analyses will not be part of the CSR:

- Evaluation of changes in blood and urine biomarkers relevant to cardiorenal mechanisms, inflammation, and fibrosis over the time course of the study.
- Optional exploratory research into genes/genetic variation that may influence response to treatment.

Analyses for these exploratory objectives are outside the scope of this SAP.

4.13 Interim Analysis

Up to 2 administrative interim analyses may be performed. The first interim analysis may occur after 50% of participants (only considering the 415 participants randomised to the three treatment arms still in the CSP Amendment 2 study design and specified as part of the main analysis in Table 4) have completed 6 weeks of treatment or at a time selected by the sponsor, and a second interim analysis may be performed after 100% of participants have completed 6 weeks of treatment or at a time selected by sponsor / percentage of participants with a planned week 6 visit before data cut selected by sponsor. The objective of the administrative interim analyses will be to decide if an CCI zibotentan/dapagliflozin project activities CCI on the interim data.

An internal URC of AstraZeneca representatives is set up for this study for ongoing safety monitoring and reviewing the unblinded interim results. Changes in fluid-related measures (weight gain or BNP) that meet the defined threshold (see Section 4.11.5.14.11.5) will be reported as an event of special interest.

Full details of the URC are described in a separate URC charter.

The blinding maintenance plan and the study integrity plan document study roles which have access to and receive unblinding study data. A separate unblinded study team will be implemented at Parexel to run and deliver unblinded outputs to a separate independent unblinded team at AstraZeneca. Further details of the logistics of the interim within AstraZeneca are included in the URC charter, which will be stored in the AstraZeneca eTMF.

The interim analysis will be performed on data that is clean to the required level, such that the data for the participants included in the administrative interim analyses will be cleaned and fully coded, where appropriate. The outputs for the interim analysis will include a subset of the outputs for the primary analysis, as well as some unique outputs. These will be clearly marked in the mock shells.

See Appendix B for further details on the interim analysis.

4.14 Determination of Sample Size

With a 1-sided type I error rate of 5%, 150 evaluable participants in the zibotentan 1.5 mg and dapagliflozin 10 mg arm and dapagliflozin 10 mg monotherapy arm will have approximately CCI% power to detect a dapagliflozin-corrected UACR reduction of CCI% or more assuming a SD of CCI on the natural log-scale. In the DKD sub-population (which will be about 70% of the total population), the power to detect the same reduction is estimated to be CCI%.

For the dose-response models (not part of CSR), the sample size below will have at least CCI% power across multiple dose-response models to detect dose-response significance. This assumes a 1-sided type I error of 5% and a maximum UACR reduction of CCI% for the zibotentan 1.5 mg and dapagliflozin 10 mg combination arm relative to dapagliflozin 10 mg.

- Zibotentan/Dapagliflozin dose = 0/10 mg: n = 150.
- Zibotentan/Dapagliflozin dose = 0.25/10 mg: n = 75.
- Zibotentan/Dapagliflozin dose = 1.5/10 mg: n = 150.

A total of 495 participants will be randomised into this study, including participants randomised under the earlier design. Four hundred and fifteen (415) participants will be randomised, accounting for 10% drop-outs, to have the following number of participants in the main analysis (marked as M in

Table 4): 166 participants in the zibotentan 1.5 mg/dapagliflozin 10 mg combination arm and dapagliflozin 10 mg monotherapy arm, and 83 participants in the zibotentan 0.25 mg/dapagliflozin 10 mg combination arm.

A participant is considered to be evaluable if the participant received at least one dose of study intervention, has baseline UACR, and at least one post-treatment UACR result available.

The sample size was calculated using nQuery (version 8.2.0.0) for the pairwise comparisons. The sample size was calculated using the "DoseFinding" package (version 0.9-16) in R (version 3.5.3) for the dose-response models.

4.15 Changes in the Conduct of the Study or Planned Analysis

Echocardiography is included as an exploratory variable for efficacy assessments in the CSP but is included as a safety variable related to the safety objective in this SAP.

The CSP states that for the primary endpoint, no imputation is performed for UACR data that is treated as missing after the ICEs. If there are convergence issues with the MMRM proposed for the primary analysis, an ANCOVA with MI will be performed, meaning there is the possibility of imputation being performed. Regardless of the approach that will be taken for the primary analysis, sensitivity analyses will be performed that includes imputation for UACR data that is treated as missing after the ICEs.

The CSP states that the secondary variables of BP and eGFR will be analysed using ANCOVA but they will be analysed using a MMRM for consistency with the primary efficacy variable analysis, with an option for ANCOVA if none of the covariance structures converge.

The CSP does not include the phrase "or at a time selected by the sponsor" in relation to the first interim analysis for the planned timings of the interim analysis.

The CSP states that lost to follow-up is an ICE but it is not defined as an ICE in this SAP. It will be handled in the framework of missing data.

The CSP states that ABPM includes all participants in the FAS who have valid ambulatory BP data for change from baseline analysis, but as per SAP this analysis set will include all participants in the Descriptive Analysis Set who have valid ambulatory BP data for change from baseline analyses.

The CSP states that changes from baseline of ECG parameters will be listed, but as per SAP only the abnormalities (values outside the reference ranges) will be presented in the listings.

5 REFERENCES

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6 APPENDICES

Appendix A: Schedule of Activities

Schedule of Activities (Part B)

Procedure	Screening	Interventional period						Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7 (ED)**	**8**	
Week	**-4**	**0**	**1**	**3**	**6**	**9**	**12**	**14**	
Day	**-28**	**1**	**8**	**22**	**43**	**64**	**84**	**98**	
Day Visit Window	**+7/ -14**		**±1**	**±2**	**±2**	**±2**	**±2**	**±3**	
Informed consent	X								
Inclusion and exclusion criteria	X	X							Recheck clinical status before randomisation.
Screening in IRT/RTSM	X								
Randomisation in IRT/RTSM		X							Diaries will be given to the participants and they will be asked to fill in the dose intake information (date and time) at home.
Routine clinical procedures									
Demography and baseline characteristics (smoking history and alcohol consumption included)	X								
Physical examination	X	X	X	X	X	X	X	X	A complete physical examination will be done at screening, randomisation and Week 12. A brief physical examination will be done at Weeks 1, 3, 6, 9, 14.
Medical/surgical history, which includes substance usage and family history of premature cardiovascular disease	X								Substances: drugs, alcohol, tobacco, and caffeine

Procedure	Screening	Interventional period						Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7 (ED)**	**8**	
Week	**-4**	**0**	**1**	**3**	**6**	**9**	**12**	**14**	
Day	**-28**	**1**	**8**	**22**	**43**	**64**	**84**	**98**	
Day Visit Window	**+7/ -14**		**±1**	**±2**	**±2**	**±2**	**±2**	**±3**	
Height	X								
Serology (HIV I and II, Hepatitis B surface antigen, Hepatitis C virus antibody, central lab)	X								Results need to be available before randomisation.
FSH/LH and serum pregnancy test (females only, central lab)	X								Results need to be available before randomisation.
Local test for SARS-CoV-2	X								Testing is also required if participants show COVID-19 symptoms during the study.
Concomitant medication	X	X	X	X	X	X	X	X	
Efficacy assessments									
Spot urine from first morning void: albumin and creatinine (central lab)	X								Results need to be available before randomisation. A single sample for analysis is sufficient at screening.
Spot urine from first morning void over 3 consecutive days: albumin, creatinine (central lab)		X		X	X	X	X	X	Spot urine from first morning void over 3 consecutive days, ideally on day of clinic visit and preceding 2 days, collected at home in provided vials. Analysis will be done in all 3 samples at central laboratory and averaged.
Spot urine from first morning void: Na^+, K^+, uric acid, urea, glucose, creatinine, osmolality, and cortisol (central lab)		X		X	X	X	X	X	Spot urine from first morning void, only from the third day sample (day of clinic visit), collected at home in provided vial. Analysis will be done at central laboratory.

Procedure	Scree-ning	Interventional period						Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7 (ED)**	**8**	
Week	**-4**	**0**	**1**	**3**	**6**	**9**	**12**	**14**	
Day	**-28**	**1**	**8**	**22**	**43**	**64**	**84**	**98**	
Day Visit Window	**+7/ -14**		**±1**	**±2**	**±2**	**±2**	**±2**	**±3**	
Body weight	X	X	X	X	X	X	X	X	Body weight must be taken and reviewed before treatment at each dosing visit.
Echocardiography	X						X		Screening and Week 12 only. ECHO will be performed locally and sent to central reader.
Bioimpedance spectroscopy		X	X	X	X	X	X	X	
Home-based monitoring									
Daily digital body weight measurement		Daily home measurement using a digital device from randomisation to end of follow up.							Home body weight measurements should start 2 days before randomisation (same as for spot urine).
Pharmacodynamics									
Plasma/serum K^+, Na^+, uric acid, BUN, fasting plasma glucose, cystatin C, haematocrit, haemoglobin, ET-1, ELDP, CT-proET-1, copeptin, NT-proBNP, and BNP (central lab)		X	X	X	X	X	X	X	Results for central BNP testing must be reviewed within 24 hours of receipt by the investigator.
BNP or NT-proBNP (local laboratory)	X								Results need to be available before randomisation.
Safety assessments									
Adverse event review	X SAEs only	X	X	X	X	X	X	X	
Vital signs (blood pressure, pulse, respiratory rate)	X	X	X	X	X	X	X	X	Vital signs at Visit 2 need to be performed and the results reviewed before randomisation in IWRS.

Procedure	Screening	Interventional period						Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7 (ED)**	**8**	
Week	**-4**	**0**	**1**	**3**	**6**	**9**	**12**	**14**	
Day	**-28**	**1**	**8**	**22**	**43**	**64**	**84**	**98**	
Day Visit Window	**+7/ -14**		**±1**	**±2**	**±2**	**±2**	**±2**	**±3**	
Digital 12-lead safety	X	X	X	X	X	X	X	X	ECGs will be centrally read. ECG read out from Visit 2 to be reviewed by the investigator before randomisation as central report will not be available on the day. Unscheduled ECGs may be added if clinically indicated.
Clinical chemistry and haematology (central lab)	X	X	X	X	X	X	X	X	Central lab results must be reviewed by investigator within 48 hours from receipt of result, and eGFR and creatinine calculations made, and participant discontinued if required. Clinical chemistry includes creatinine and eGFR calculation using the CKD-EPI formula in both ways: based on cystatin C and based on creatinine.
Urinalysis (central lab)	X	X			X		X	X	
HbA1c, cholesterol and lipids (central lab)	X	X					X	X	
Study intervention									
Study intervention dispensed		X		X	X	X			
Study intervention account				X	X	X	X		

Procedure	Scree-ning	Interventional period						Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7 (ED)**	**8**	
Week	**-4**	**0**	**1**	**3**	**6**	**9**	**12**	**14**	
Day	**-28**	**1**	**8**	**22**	**43**	**64**	**84**	**98**	
Day Visit Window	**+7/ -14**		**±1**	**±2**	**±2**	**±2**	**±2**	**±3**	
Study intervention intake at the clinic		X		X		X			Between the clinic visits and at Visits 3, 5 and 7, participants will take their study intervention at home. At Visits 4 and 6, study intervention will be taken in the clinic irrespective of participation in the PK sub-study.
Pharmacokinetics									
4-hour PK blood sample profile				X					Total of 5 samples, spread over 5 time points: Pre-dose, 0.5-1.0 h, 1.5-2.0 h, 2.5-3.0 h, 3.5-4.5 h post-dose. Performed in the morning. Dose taken at clinic. Participants to arrive fasted at clinic (light breakfast provided). Participants to stay at clinic until last PK post-dose sample has been taken. Zibotentan and dapagliflozin plasma concentrations will be measured separately. If participants or investigators do not wish to participate in this sub-study, only one pre-dose sample will be taken instead of the whole profile.
Post-dose PK plasma sample for all participants at a convenient day, time			X		X		X		Dose at home, sampling at clinic (any day, time). Zibotentan and dapagliflozin plasma concentrations will be measured separately. Document actual clock times of dosing at home and of sampling at clinic.

Procedure	Scree-ning	Interventional period						Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7 (ED)**	**8**	
Week	**-4**	**0**	**1**	**3**	**6**	**9**	**12**	**14**	
Day	**-28**	**1**	**8**	**22**	**43**	**64**	**84**	**98**	
Day Visit Window	**+7/ -14**		**±1**	**±2**	**±2**	**±2**	**±2**	**±3**	
Pre-dose PK plasma sample for all participants						X			Perform in the first half of the day. Dose taken at clinic, sampling before dose. Zibotentan and dapagliflozin plasma concentrations will be measured separately. Document actual clock times of dosing and sampling at clinic
Exploratory metabolite evaluation for all participants				X					Pre-dose plasma sample. Dose taken at clinic. Samples to be sent to AstraZeneca Gothenburg for exploratory zibotentan metabolite evaluation.
Exploratory biomarkers									
Collect and store serum and plasma samples for future exploratory assessment of biomarkers		X	X	X	X		X	X	
Collect and store urine samples for future exploratory assessment of biomarkers		X	X	X	X		X	X	
Optional genetic sample									
Optional genetic sampling (blood)		X							

Abbreviations: BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CKD-EPI = chronic kidney disease epidemiology collaboration; COVID-19 = coronavirus disease 2019; CSP = Clinical Study Protocol; CT-proET-1 = C-terminal pro-endothelin-1; ECG = electrocardiogram; ECHO = echocardiogram; ED = Early Discontinuation; eGFR = estimated glomerular filtration rate; ELDP = endothelin-like domain peptide; ET-1 = endothelin-1; FSH = follicle stimulating hormone; HbA1c = glycated haemoglobin; HIV = human immunodeficiency virus; IRT = Interactive Response Technology; IWRS = interactive web response system; K^+ = potassium; LH = luteinising hormone; Na^+ = sodium; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PK = pharmacokinetic; RTSM = Randomisation and Trial Supply Management, SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Appendix B: Interim Analysis Plan

This section describes definitions of analysis sets, key efficacy endpoints and statistical methods for the interim analyses (IAs). Further details of the interim analysis are included in the URC charter.

The first interim analysis may occur after 50% of participants have completed at least 6 weeks of treatment or at a time selected by the sponsor, and a second interim analysis may be performed after 100% of participants have completed at least 6 weeks of treatment or at a time selected by sponsor / percentage of participants with a planned week 6 visit before data cut selected by sponsor. The objective of the administrative interim analyses will be to decide if an CCI zibotentan/dapagliflozin project activities CCI on the interim data.

The decision-making framework of the interim analyses is based on CCI

B.1. Analysis Sets

The analysis sets are defined as follows.

Analysis Set	Data selection as indicated in Table 4	Description	Data Period
First Administrative Interim FAS	M	All participants who were randomised at least 44 days ago i.e. reached study day 45, and who have received any study treatment at the time of the first interim analysis data cut-off. Participants are evaluated according to the treatment assigned at randomisation.	Baseline to Week 6 data
First Administrative Interim Safety Analysis Set	M	All participants who have received any study treatment at the time of the first interim analysis data cut-off. Participants are evaluated according to the actual treatment they received.	All data
First Administrative Interim All Randomised Set	M	All participants who are randomised at least 44 days ago i.e. reached study day 45 at the time of the first interim analysis data cut-off. Participants are evaluated according to the treatment assigned at randomisation.	Baseline to Week 6 data
Second Administrative Interim FAS	M	All participants who were randomised at least 44 days ago i.e. reached study day 45, and who have received any study treatment at the time of the second interim analysis data cut-off. Participants are evaluated	Baseline to Week 6 data*

		according to the treatment assigned at randomisation.	
Second Administrative Interim Safety Analysis Set	M	All participants who have received any study treatment at the time of the second interim analysis data cut-off. Participants are evaluated according to the actual treatment they received.	All data
Second Administrative Interim All Randomised Set	M	All participants who are randomised at least 44 days ago i.e. reached study day 45 at the time of the second interim analysis data cut-off. Participants are evaluated according to the treatment assigned at randomisation.	Baseline to Week 6 data*

*Some outputs will be based on longer data periods (not just baseline to Week 6)

B.2. Fluid-related Analysis

Changes in fluid-related measures (weight gain or BNP) meet the defined threshold to be reported as an event of special interest if they meet the criteria defined in Section 3.2.2.7.

In the examination of the fluid-related safety CCI [redacted] The examination depends on the actual number of participants with a fluid-related event of special interest and the total number of participants in the zibotentan/dapagliflozin arm and in the dapagliflozin 10 mg monotherapy arm.

Assuming CCI participants in each arm for the first interim analysis, the scenario analysis is illustrated below where the CCI [redacted] is used to estimate CCI [redacted]

CCI [redacted]

This will be performed for zibotentan/dapagliflozin 1.5/10 mg vs dapagliflozin 10 mg as well as for zibotentan/dapagliflozin 0.25/10 mg vs dapagliflozin 10 mg.

B.3. Efficacy Analysis

In the administrative interim analyses, the primary efficacy endpoint is the UACR reduction difference from baseline to Week 6, where the comparison will be made for each active zibotentan

arm (1.5 mg and 0.25 mg) vs the dapagliflozin 10 mg monotherapy arm. The UACR reduction will be analysed by means of the MMRM approach as described in Section 4.10.2.2 using the Administrative Interim FAS. The least square estimate of the dapagliflozin-adjusted UACR reduction and its SE will be used CCI UACR reduction difference.

The CCI in terms of the UACR reduction difference are calculated as

CCI

CCI

CCI

In total, 2 CCI will be created:

- UACR reduction difference at Week 6 for zibotentan/dapagliflozin 1.5/10 mg vs dapagliflozin 10 mg
- UACR reduction difference at Week 6 for zibotentan/dapagliflozin 0.25/10 mg vs dapagliflozin 10 mg

CCI

CCI

With reference to the CCI, the URC will evaluate CCI [redacted]

CCI [redacted]

Note that the above will be done for each active treatment arm in the main analyses, zibotentan/dapagliflozin 1.5/10 mg and zibotentan/dapagliflozin 0.25/10 mg, CCI [redacted]

B.4. General Safety Analysis

General safety analysis will be based on the Administrative Interim Safety Analysis Set. Selected safety outputs will be presented by treatment arm and overall.

A summary of AEs in any category will be presented by treatment. The number and percentage of participants reporting AEs, SAEs and AEs leading to discontinuation of study treatment in each treatment arm will be tabulated by SOC and PT, sorted in decreasing overall (across treatments) frequency.

Listings may be presented of participants with SAEs, AEs leading to discontinuation of study treatment, and participants who died. A listing may be presented of participants with AEs, detailing whether these are SAEs, AEs leading to discontinuation of study treatment, or result in death.

Summary statistics of laboratory data (as described in Section 4.11.4) will be presented. Participants with laboratory values which are highlighted as abnormal will be listed. Summary statistics of vital signs and ECG data will be summarised (as described in Section 4.11.5).

Reference:

CCI [redacted]

Appendix C: Treatment-Emergent Changes in Relevant Laboratory Parameters

The treatment-emergent changes in relevant laboratory parameters for this study are as follows:

Laboratory Parameter	Range	Limits
Creatinine		≥1.5xBaseline Serum Creatinine ≥2xBaseline Serum Creatinine
Sodium		<120 mmol/L <130 mmol/L >150 mmol/L
Potassium		≤2.5 mmol/L ≥6.0 mmol/L
Creatine Kinase		>5xULN >10xULN
Haemoglobin		<9 g/dL

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