Clinical Study Protocol	
Study Intervention	Zibotentan and Dapagliflozin
Study Code	D4325C00001
Version	Amendment 3
Date	22 Mar 2023

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

Sponsor Name: AstraZeneca

Legal Registered Address: AstraZeneca AB, SE-15185 Södertälje, Sweden

Regulatory Agency Identifier Numbers

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

Protocol Number: D4325C00001

Amendment Number: 3

Study Intervention: Zibotentan and Dapagliflozin

Study Phase: 2b

Brief Title: Zibotentan and Dapagliflozin for the Treatment of CKD (ZENITH-CKD trial)

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	22 Mar 2023
Amendment 2	05 Apr 2022
Amendment 1	03 Dec 2021
Version 1.0	14 Sep 2020

Amendment 3 (22 Mar 2023)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The amended CSP (Amendment 2, dated 05 April 2022) was updated to provide clarification, align wording with recent CSP template, and to reflect that some of the exploratory endpoints will not be reported in the CSR.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis	Updated the title to "Brief Title" as per the recent CSP template	Following a CSP waiver from the CSP process owner, this report aligns to the mandatory implementation requirement for all protocols being updated but NOT including a template transfer to v7	Non-substantial
	Updated the title to "Objectives, Endpoints and Estimands" as per the recent CSP template	Following a CSP waiver from the CSP process owner, this report aligns to the mandatory implementation requirement for all protocols being updated but NOT including a template transfer to v7	Non-substantial
	Updated the wording for secondary estimand description / endpoint	For clarification since endpoints should be defined on patient-level	Non-substantial
	Updated the wording for the second administrative interim analysis	For clarification	Non-substantial
	Deleted information about MCP-Mod approach to investigate the dose response. Updated the wording for dose-relationship between different doses of zibotentan / a fixed dose of dapagliflozin and UACR reduction.	MCP-Mod analysis is not recommended when there are only 2 active arms	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.2 Figure 1 Study Schema	Updated footnote wording to the second administrative interim analysis completion	For clarification	Non-substantial
Section 3 Objectives, Endpoints and Estimands Synopsis	Updated the title to "Objectives, Endpoints and Estimands" as per the recent CSP template	Following a CSP waiver from the CSP process owner, this report aligns to the mandatory implementation requirement for all protocols being updated but NOT including a template transfer to v7	Non-substantial
	Updated the wording for secondary estimand description / endpoint	For clarification since endpoints should be defined on patient-level	Non-substantial
	Exploratory endpoint updated to confirm that results for NT-proBNP, ET-1, ELDP, CT-proET-1 and copeptin levels will not be reported in the CSR	For clarification	Non-substantial
Section 4.1 Overall Design	Updated the wording to the second administrative interim analysis	For clarification	Non-substantial
Section 4.4 End of Study Definition	Updated the wording for a participant considered to have completed the study	For clarification	Non-substantial
Section 6.1.1 Investigational Products Table 4	Unit Dose Strength for Dapagliflozin 10 mg was updated to remove NA.	For clarification	Non-substantial
	Table 4 footnote was updated to include and expand abbreviation	For clarification	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 6.1.2 Medical Devices	Instructions for medical device wording was updated	For clarification	Non-substantial
Section 8.5.3.1 Collection of Samples	Included the text that results for urine cortisol will not be reported in the CSR	For clarification	Non-substantial
Section 9.4.2.1 Primary Endpoint	Updated the wording to the analysis model inclusion criteria	For clarification	Non-substantial
Section 9.4.2.2 Secondary Endpoints	Deleted information about MCP-Mod approach to investigate the dose response. Updated the wording for dose-relationship between different doses of zibotentan / a fixed dose of dapagliflozin and UACR reduction	MCP-Mod analysis is not recommended when there are only 2 active arms	Non-substantial
Section 9.4.4 Other Analyses	Included the analyses that will not be reported in the CSR	For clarification	Non-substantial
Section 9.5 Interim Analyses	Updated the wording to the second administrative interim analysis completion	For clarification	Non-substantial
Section 10 Appendix A1: Regulatory and Ethical	Expanded the first use of IRB and IEC and text updated	For clarification	Non-substantial
	A new sub-section was added to include the mandatory wording and section for Regulatory Reporting Requirements for Serious Breaches	Following a CSP waiver from the CSP process owner, this report aligns to the mandatory implementation requirement for all protocols being updated but	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		NOT including a template transfer to v7	
Section 10 Appendix B4: Medication Error, Drug Abuse and Drug Misuse	Updated the title to include "Drug Abuse and Drug Misuse" as per the recent CSP template	Following a CSP waiver from the CSP process owner, this report aligns to the mandatory implementation requirement for all protocols being updated but NOT including a template transfer to v7	Non-substantial
	New sub-sections were added to include the mandatory wordings and sections for Drug Abuse and Drug Misuse	Following a CSP waiver from the CSP process owner, this report aligns to the mandatory implementation requirement for all protocols being updated but NOT including a template transfer to v7	Non-substantial
Section 10 Appendix H: Protocol Amendment History	Moved Amendment 2 text to Appendix H	For template alignment	Non-substantial
Section 11 References	Deleted Pinheiro et al, 2006 from references	To align with the CSP amendment	Non-substantial

BNP = B-type natriuretic peptide; CKD = chronic kidney disease; CSP = Clinical Study Protocol; CSR = Clinical Study Report; CT-proET-1 = C-terminal pro-endothelin-1; GCP = Good Clinical Practice; IA = interim analysis; ELDP = endothelin-like domain peptide; ET-1 = endothelin-1; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRA = mineralocorticoid receptor agonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PK = pharmacokinetic; QTcF = QT interval corrected using Fridericia's formula; SGLT2 = sodium-glucose co-transporter 2; SoA = Schedule of Activities; SoC = standard of care; T2DM = type 2 diabetes mellitus; UACR = Urinary Albumin to Creatinine Ratio; URC = Unblinded Review Committee.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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

Brief Title: Zibotentan and Dapagliflozin for the Treatment of CKD (ZENITH-CKD trial)

Rationale: 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.

Objectives, Endpoints and Estimands:

Objectives	Estimand Description/Endpoints
Primary	
• 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 is lost to follow up, prematurely discontinues study treatment, or uses a 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 of UACR from baseline to Week 12.

Objectives	Estimand Description/Endpoints
Secondary[a]	
• To evaluate the effect of zibotentan 0.25 mg/dapagliflozin 10 mg versus dapagliflozin 10 mg 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.
Safety	
• 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. • Event of special interest (changes in fluid-related measures).

AE = adverse event; BP = blood pressure; DAE = adverse event leading to the discontinuation of study intervention; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; SAE = serious adverse event; UACR = urinary albumin to creatinine ratio.

[a] The estimand for the secondary objectives is defined with the same approach as for the primary objectives.

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

Overall Design:

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.

An internal Unblinded Review Committee (URC) of AstraZeneca representatives is set up for this study for ongoing safety monitoring and reviewing the unblinded interim results. In addition to general safety/tolerability, the URC will focus on potential risks related to hypotension and hospitalisations due to HF. Changes in fluid-related measures (weight gain or B-type natriuretic peptide [BNP]) that meet the defined threshold will be reported as an event of special interest.

Participants will be randomised to 12 weeks of treatment plus 2 weeks follow-up.

Participants who meet the eligibility criteria will be randomised to study treatments in addition to receiving background local SoC therapy. 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 number of randomised participants in each stratum will be monitored to ensure the non-DM CKD sub-population is approximately a minimum of 30% and a maximum of 50% of the total number of participants randomised.

Disclosure Statement:

The study is participant, investigator, and Sponsor (with the exception of the URC) blinded. Participants will be randomised into one of the three arms (zibotentan 1.5 mg/dapagliflozin 10 mg combination arm, zibotentan 0.25 mg/dapagliflozin 10 mg combination arm or dapagliflozin 10 mg monotherapy arm) in a 2:1:2 allocation.

Number of Participants:

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 to have 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.

Intervention Groups and Duration:

Eligible participants will be randomised to either of the following treatments, in addition to receiving background local SoC therapy:

- Zibotentan 0.25 mg + Dapagliflozin 10 mg once daily.
- Zibotentan 1.5 mg + Dapagliflozin 10 mg once daily.

- Dapagliflozin 10 mg once daily.

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.

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.

Data Monitoring Committee:

An internal URC of AstraZeneca representatives is set up for this study for ongoing safety monitoring and reviewing the unblinded interim results.

Statistical Methods:

The primary hypothesis for this study is that zibotentan 1.5 mg and dapagliflozin 10 mg in combination will reduce UACR compared with dapagliflozin 10 mg monotherapy. The secondary hypothesis for this study is that zibotentan 0.25 mg combined with dapagliflozin 10 mg will reduce UACR compared with dapagliflozin 10 mg monotherapy. Dose-response for the reduction in UACR, as a function of the zibotentan dose, as combined with dapagliflozin, will be evaluated.

With a 1-sided 5% type I error, 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, 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.

- Zibotentan/Dapagliflozin dose = 0/10 mg: n = 150.
- Zibotentan/Dapagliflozin dose = 0.25/10 mg: n = 77.
- Zibotentan/Dapagliflozin dose = 1.5/10 mg: n = 150.

A first administrative interim analysis will be performed when 50% of participants have completed 6 weeks of treatment of the study. A second administrative interim analysis will be performed after 100% of participants have completed the 6 weeks 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 is CCI on the interim data.

The analysis of all efficacy variables will be performed on the Full Analysis Set (FAS) with a hypothetical estimand. In addition, the primary efficacy endpoint will also be analysed using the Per Protocol Analysis Set (PPS), and a treatment policy estimand as sensitivity analyses.

The primary efficacy endpoint for this study is the change in log-transformed UACR from baseline to Week 12 for zibotentan 1.5 mg combined with dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy. UACR will be log-transformed and analysed using a mixed model repeated measures (MMRM) method. The values will be back transformed onto the original scale to give the geometric mean relative change from baseline to Week 12. The analysis model will include the fixed categorical effects of stratification factor, treatment, visit, and treatment-by-visit interaction, plus the continuous covariates of baseline log(UACR) and baseline log(UACR)-by-visit interaction. An unstructured covariance structure will be used for the within-participant errors.

As a secondary efficacy endpoint for this study, the change in UACR for doses of 0.25 mg zibotentan combined with dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy from baseline (Visit 2) to Week 12 (Visit 7) will be assessed. A MMRM model similar to that described for the primary endpoints will be fitted.

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 primary and first secondary objective.

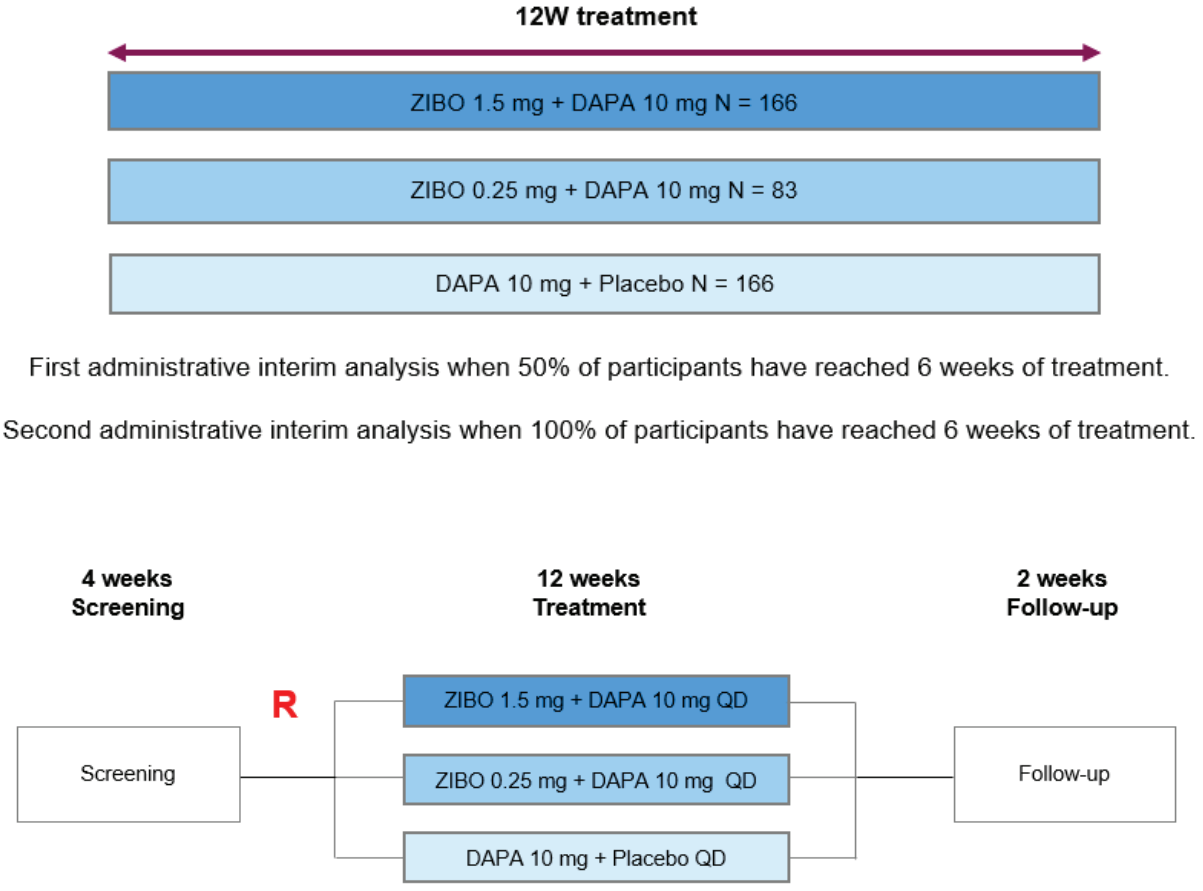
The change from baseline (Visit 2) to Week 12 (Visit 7) in office systolic and diastolic blood pressure (BP) will be assessed for doses of zibotentan combined with dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy.

The effect of different doses of zibotentan and dapagliflozin in combination versus dapagliflozin 10 mg monotherapy on eGFR will be determined from the change in eGFR from baseline to Week 1, Week 12, and Week 14, and from Week 1 to Week 12.

These secondary variables of BP and eGFR will be analysed using ANCOVA, adjusting for stratification factors, treatment arm, and baseline. The FAS will be used for these analyses.

1.2 Schema

Figure 1 Study Schema



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

Four hundred and fifteen (415) participants will be randomised to have 166 participants in the zibotentan 1.5 mg/dapagliflozin 10 mg combination arm and dapagliflozin 10 mg monotherapy arm, and 83 participants in the zibotantan 0.25 mg/dapagliflozin 10 mg combination arm.
First administrative interim analysis at 6 weeks of treatment (n = 50% of participants).
Second administrative interim analysis at 6 weeks of treatment (n = 100% of participants, or at a time selected by sponsor / percentage of participants with a planned week 6 visit before data cut selected by sponsor).
Details described in the SAP.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Screening	Interventional period						Follow-up	Notes	Details in CSP Section/Appendix
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									Section 5.1; Appendix A 3
Inclusion and exclusion criteria	X	X							Recheck clinical status before randomisation.	Sections 5.1 and 5.2
Screening in IRT/RTSM	X									Section 6.3
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.	Section 6.3 and 6.4
Routine clinical procedures										
Demography and baseline characteristics (smoking history and alcohol consumption included)	X									Sections 5.1 and 5.2
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.	Section 8.2.1

Procedure	Screening	Interventional period						Follow-up	Notes	Details in CSP Section/Appendix
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**		
Medical/ surgical history, which includes substance usage and family history of premature cardiovascular disease	X								Substances: drugs, alcohol, tobacco, and caffeine	Sections 5.1 and 5.2
Height	X									Sections 5.1, 5.2 and 8.2.1
Serology (HIV I and II, Hepatitis B surface antigen, Hepatitis C virus antibody, central laboratory)	X								Results need to be available before randomisation.	Section 8.2.4
FSH/LH and serum pregnancy test (females only, central laboratory)	X								Results need to be available before randomisation.	Section 8.2.4
Local test for SARS-CoV-2	X								Testing is also required if participants show COVID-19 symptoms during the study.	Section 8.2.4
Concomitant medication	X	X	X	X	X	X	X	X		Section 6.5
Efficacy assessments										
Spot urine from first morning void: albumin and creatinine (central laboratory)	X								Results need to be available before randomisation. A single sample for analysis is sufficient at screening.	Section 8.1.1

Procedure	Screening	Interventional period						Follow-up	Notes	Details in CSP Section/Appendix
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**		
Spot urine from first morning void over 3 consecutive days: albumin, creatinine (central laboratory)		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.	Section 8.1.1
Spot urine from first morning void: Na^+, K^+, uric acid, urea, glucose, creatinine, osmolality, and cortisol (central laboratory)		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.	Sections 8.5.3 and 8.5.3.1
Body weight	X	X	X	X	X	X	X	X	Body weight must be taken and reviewed before treatment at each dosing visit.	Sections 8.2.2 and 5.1
Echocardiography	X						X		Screening and Week 12 only. ECHO will be performed locally and sent to central reader. Results need to be available before randomisation.	Section 8.1.3.3
Bioimpedance spectroscopy		X	X	X	X	X	X	X		Section 8.1.3.2
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).	Section 8.1.3 and Section 8.2.1

Procedure	Screening	Interventional period						Follow-up	Notes	Details in CSP Section/Appendix
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**		
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 laboratory)	X	X	X	X	X	X	X	X	Results for central BNP testing must be reviewed within 24 hours of receipt by the investigator.	Section 8.2.4 and 8.5.3.1
BNP or NT-proBNP (local laboratory)	X								Results need to be available before randomisation.	Section 8.2.4
Safety assessments										
Adverse event review	X SAEs only	X	X	X	X	X	X	X		Section 8.3
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.	Section 8.2.2 and 8.1.2.1
Digital 12-lead safety ECG	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.	Section 8.2.3

Procedure	Screening	Interventional period						Follow-up	Notes	Details in CSP Section/Appendix
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**		
Clinical chemistry and haematology (central laboratory)	X	X	X	X	X	X	X	X	Central laboratory 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.	Sections 8.1.2.2 and 8.2.4
Urinalysis (central laboratory)	X	X			X		X	X		Section 8.2.4
HbA1c, cholesterol and lipids (central laboratory)	X	X					X	X		Section 8.2.4
Study intervention										
Study intervention dispensed		X		X	X	X				Section 6.2, 6.3, 6.4
Study intervention account				X	X	X	X			Section 6.2, 6.4
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.	Section 6.2, 6.3, 6.4

Procedure	Screening	Interventional period						Follow-up	Notes	Details in CSP Section/Appendix
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**		
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 (separate tubes for zibotentan and dapagliflozin) will be taken instead of the whole profile.	Section 8.5.1.1
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.	Section 8.5.1

Procedure	Screening	Interventional period						Follow-up	Notes	Details in CSP Section/Appendix
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.	Section 8.5.1
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.	Section 8.5.1
Exploratory biomarkers										
Collect and store serum and plasma samples for future exploratory assessment of biomarkers		X	X	X	X		X	X		Section 8.6
Collect and store urine samples for future exploratory assessment of biomarkers		X	X	X	X		X	X		Section 8.6

Procedure	Screening	Interventional period						Follow-up	Notes	Details in CSP Section/Appendix
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**		
Optional genetic sample										
Optional genetic sampling (blood)		X								Section 8.7

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.

2 INTRODUCTION

Zibotentan is a selective ETA receptor antagonist, originally investigated for cardiovascular and oncology indications. Zibotentan is currently being investigated as a treatment for CKD in combination with dapagliflozin.

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

2.1 Study Rationale

Patients with CKD have limited treatment options with current SoC.

The mechanisms of action (MoA) 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 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 HF in some patients.

2.2 Background

Chronic Kidney Disease

CKD is a serious progressive condition defined by decreased kidney function (shown by reduced eGFR), or markers of kidney damage (eg, albuminuria), or both, for at least 3 months. CKD is associated with increased risk of HF (Dhingra et al, 2011), CV and all-cause death (Munter et al, 2002; Webster et al, 2017), therapy resistant hypertension (Tanner et al, 2013), and chronic fluid overload (Agarwal, 2012). Most patients with CKD stages 3-4 will die of CV causes rather than progress to ESKD and die of renal failure; when a patient does progress to ESKD, decline of kidney function has progressed to a point where dialysis or transplantation is required. The most common causes of CKD are diabetes (42%) and hypertension (17%); glomerulonephritis of varying aetiologies accounts for a further 18% of cases (Xie et al, 2018).

Potential for SGLT2 Inhibitors (SGLT2i) in CKD

Guidelines are starting to adopt SGLT2i as SoC. Kidney Disease Improving Global Outcomes guidelines will recommend SGLT2 inhibitors as SoC for patients with type 2 diabetes mellitus

(T2DM) and CKD (KDIGO, 2022). National Institute for Health and Care Excellence guidelines will recommend dapagliflozin be used as an add-on to optimised standard care (NICE, 2022). Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) have been used as SoC for decades but confer incomplete protection. Sodium-glucose co-transporter 2 inhibitors also slow CKD progression, in part by lowering intraglomerular pressure (Wanner et al, 2016). It has been postulated that the kidney protection and natriuretic effects induced by SGLT2i may account for the reductions in HF hospitalisation in the EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 studies (Zelniker et al, 2019). Moreover, the reduction in HF hospitalisation in these studies was greater in patients with worse baseline renal function: a 40% reduction in HF hospitalisation was observed in patients with eGFR < 60 mL/min/1.73 m^2 compared with 31% in patients with eGFR between 60 to 90 mL/min/1.73 m^2 and 12% in patients with eGFR > 90 mL/min/1.73 m^2 (Zelniker et al, 2019). Dapagliflozin also reduced UACR by 21% in T2DM patients in the DELIGHT study (Pollock et al, 2019). In the recent DAPA-HF study, dapagliflozin demonstrated a reassuring safety profile over a broad range of renal functions (including patients with eGFR < 45 and a few < 30 mL/min/1.73 m^2). Dapagliflozin was investigated in patients with CKD in the DAPA-CKD study (NCT03036150) which demonstrated a 39% reduction in the primary outcome: a composite of a sustained decline in estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes (Heerspink et al, 2020).

Hypertension and Endothelial Dysfunction in CKD

Hypertension is common in CKD and is an independent risk factor for CKD progression: 75% of patients with eGFR < 30 mL/min/1.73 m^2 have BP values > 140/90 mmHg (Bakris et al, 2000). The majority of CKD patients fail to reach target BP (NICE, 2022) despite a predominantly antihypertensive MoA with current SoC (ACEi or ARB).

Endothelial dysfunction makes a significant contribution to cardiovascular risk in CKD (Linden et al, 2008) and can be linked to production of the potent vasoconstrictor endothelin-1 (ET-1). Plasma ET-1 levels are inversely correlated with eGFR (Dhaun et al, 2015). ET-1 signals through the ETA and ETB receptors. ETA receptor blockade lowers BP, increases renal perfusion, reduces intraglomerular pressure, and also has an anti-inflammatory effect in the kidney. ETB blockade is less desirable because this receptor has an important and beneficial effect in clearing circulating ET-1 via the lungs. Furthermore, preclinical and clinical data have identified a likely class effect of both ETA and ETB antagonists to reduce the natriuretic effect of ET-1 in the renal collecting duct.

Rationale for the Development of Zibotentan

Endothelin-1, an agonist of the ETA and ETB receptors synthesised by vascular endothelial cells, is one of the most potent vasoconstrictors in humans and can worsen renal function in CKD (De Miguel et al, 2016). ETA receptor antagonists have shown efficacy for urine

albumin to creatinine ratio reduction in patients with CKD (Heerspink et al, 2019, Mann et al, 2010, De Zeeuw et al, 2014). Recently, the ETA receptor antagonist atrasentan reported a 35% reduction in a renal composite endpoint in the SONAR trial, although the trial was stopped due to too few renal endpoint events (Heerspink et al, 2019). The main biological effects of zibotentan relevant for treatment of CKD would be to block ETA-driven hypertension, reduce vascular stiffness, improve renal blood flow and endothelial function, and decrease podocyte loss, inflammation, and fibrosis.

However, unlocking the potential of ETA receptor antagonists in the treatment of CKD requires mitigation of their potential sodium and fluid retention risk. The zibotentan CKD development programme is investigating zibotentan in combination with dapagliflozin. Coadministration of dapagliflozin with zibotentan is expected to mitigate zibotentan's potential sodium and fluid retention due to the intrinsic diuretic and natriuretic effects of SGLT2 inhibition. Further, dapagliflozin and other SGLT2i have demonstrated nephroprotective effects (Mosenzon et al, 2019, Perkovic et al, 2019, Scholtes et al, 2020); SGLT2 inhibition leads to a physiological adaptation in the kidney due to altered glucose, sodium, and water handling, and improved metabolic flexibility, mitochondrial function, and overall fluid balance. The combination of zibotentan and dapagliflozin for treatment of CKD is expected to be additive, since their mechanisms of action are different.

Detailed descriptions of the chemistry, pharmacology, efficacy, and safety of zibotentan and dapagliflozin are provided in the respective Investigator's Brochures.

2.3 Benefit/Risk Assessment

Fluid retention is believed to be a class effect of endothelin receptor antagonists that limits their potential use as monotherapy. Clinical data and scientific rationale support a zibotentan/dapagliflozin fixed dose combination (FDC) that combines 2 different and complementary MoAs targeting the underlining mechanisms of CKD progression. The potential fluid retention risk from zibotentan is believed to be mitigated by a lower dose than 5 mg zibotentan, combined with the diuretic and natriuretic effects of dapagliflozin. The interim analyses and frequent site visits will also mitigate the known risks of zibotentan.

An internal Unblinded Review Committee (URC) of AstraZeneca representatives is set up for this study for ongoing safety monitoring and reviewing the unblinded interim results. In addition to general safety/tolerability, the URC will focus on potential risks related to hypotension and hospitalisations due to HF. Changes in fluid-related measures (weight gain or BNP) that meet the defined threshold (Section 7.1) will be reported as an event of special interest.

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

2.3.1 Risk Assessment

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Dapagliflozin		
Diabetic ketoacidosis in patients with diabetes mellitus	Diabetic ketoacidosis was only observed in patients with diabetes mellitus: • Type 2 diabetes mellitus: In the cardiovascular outcome study DECLARE TIMI-58 in T2DM, 8574 patients received dapagliflozin 10 mg and 8569 patients received placebo, for a median exposure time of 48 months. Events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a T2DM population. In clinical trials in subjects with heart failure (DAPA-HF) or chronic kidney disease (DAPA-CKD) with and without T2DM, events of ketoacidosis were only observed in subjects with T2DM. In the DAPA-HF study, events of DKA were reported in 3 patients with T2DM in the dapagliflozin group and none in the placebo group. In the DAPA-CKD study, events of DKA were not reported in any patient in the dapagliflozin group and in 2 patients with T2DM in the placebo group. • Type 1 diabetes mellitus: In the 2 placebo-controlled clinical trials of dapagliflozin in type 1 diabetes mellitus, patients were advised to monitor blood ketones in case of suspected symptoms of DKA and seek medical advice/attention if their self-measured blood ketone reading was ≥ 0.6 mmol/L. In the pooled 24-week data, events of DKA were reported in 11 (1.9%) patients in the dapagliflozin 10 mg group and 3 (0.6%) patients in the placebo group. DKA events occurred evenly distributed over the study period. Inadequate insulin doses (missed insulin dose or insulin pump failure) were the most common precipitating factors. Three of the 11 patients with DKA in the dapagliflozin 10 mg group had blood glucose in the euglycemic range (< 14 mmol/L or 250 mg/dL). Patients with DKA events responded to conventional treatment for DKA. In addition, there have been post marketing reports of ketoacidosis, including diabetic ketoacidosis, in patients with T1DM and T2DM taking dapagliflozin or other SGLT2i.	Patients with T1DM are excluded from the study (see exclusion criteria #10). DKA including euglycemic DKA have been reported with use of dapagliflozin. Consider temporary interrupting study treatment if DKA is suspected. The participant should be promptly evaluated. If diabetic ketoacidosis is confirmed, study intervention should be discontinued permanently. If diabetic ketoacidosis is not confirmed, restart of study intervention should be considered (see Section 7.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Zibotentan (in context of dapagliflozin combination treatment)		
Fluid retention	Peripheral oedema has been very commonly reported in patients receiving zibotentan and tend to develop within a month of commencing the drug. Most cases are mild (CTC Grade 1/2) and tend to resolve with continued dosing.	The potential fluid retention risk from zibotentan will be mitigated by administering a dose lower than 5 mg of zibotentan, combined with the diuretic and natriuretic effects of dapagliflozin. Interim analyses are performed to assess changes in fluid-related measures (weight gain or BNP). Changes in fluid-related measures that meet the defined threshold will be reported as an event of special interest. Discontinuation from study intervention if fluid retention criteria are met (see criteria for weight or BNP in Section 7.1).
Heart failure	Endothelin receptor antagonists have the potential to cause fluid retention and risk of increased incidence of HF.	Exclusion criteria related to presence or risk of HF (see Section 5.2, exclusion criteria #3 to #8 and #30). Administration of a dose lower than 5 mg of zibotentan, combined with the diuretic and natriuretic effects of dapagliflozin. An internal URC of AstraZeneca representatives is set up for this study for ongoing safety monitoring and reviewing the unblinded interim results. In addition to general safety/tolerability, the URC will focus on potential risks related to hospitalisations due to HF. Discontinuation based on heart failure or the defined BNP elevation criteria (see Section 7.1).
Hypotension	Adverse clinical effect of hypotension is largely due to zibotentan's pharmacologically mediated effects of ET receptor antagonism resulting in vasodilation. Hypotension (small reductions in systolic and diastolic BP of approximately 5 mmHg) has been reported with zibotentan but this has usually been asymptomatic.	Monitoring of BP according to the SoA. The URC will focus on potential risks related to hypotension. Discontinuation from study intervention if criteria for symptomatic hypotension is met (systolic BP < 90 mmHg and/or diastolic BP < 60 with symptoms).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
COVID-19 pandemic risks	There is currently an outbreak of respiratory disease (COVID-19) caused by a novel SARS-CoV-2, for which the World Health Organization declared a pandemic situation on 12 March 2020. The mechanism of action of either zibotentan and/or dapagliflozin are unlikely to impact the course of infection with SARS-CoV-2. Therefore, the risk to participants of exposure to SARS-CoV-2 or of suffering from COVID 19 is expected to be similar to the background population with the same co-morbidities as those in the study, in particular CKD. The risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).	Exclusion of participants with COVID-19 infections. Further risk mitigation measures are detailed in Appendix F.

BNP = B-type natriuretic peptide; BP = blood pressure; COVID -19 = corona virus disease-2019; CTC = Common Toxicity Criteria; DAPA-CKD = dapagliflozin chronic kidney disease; DAPA-HF = dapagliflozin heart failure; DKA = diabetic ketoacidosis; HF = heart failure; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SoA = Schedule of Activities; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; URC = Unblinded Review Committee.

2.3.2 Benefit Assessment

Based on available clinical data with zibotentan and dapagliflozin, it is expected that participants in this study will benefit from treatment with dapagliflozin and zibotentan:

- Recently, a member of the SGLT2i class, canagliflozin, demonstrated efficacy in patients with diabetic nephropathy (Perkovic et al, 2019) and received indications for reductions of renal outcomes in adults with T2DM and diabetic nephropathy and albuminuria. Nephroprotective effects were reported for dapagliflozin (Mosenzon et al, 2019, Scholtes et al, 2020). New clinical guidelines on the management of CKD have established SGLT2 inhibitors as a SoC.
- Coadministration of dapagliflozin with zibotentan is expected to mitigate zibotentan's potential sodium and fluid retention, and the combination as a treatment for CKD is expected to have additive nephroprotective effects, since their mechanisms of action are different.

2.3.3 Overall Benefit: Risk Conclusion

The overall clinical evidence suggests that the combination of zibotentan and dapagliflozin would have clinical benefit, and an acceptable safety profile in patients with CKD and that

further drug development, with appropriate risk mitigation strategies for any potential for excess fluid retention, is warranted.

3 OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 3 Objectives and Endpoints

Objectives	Estimand Description/Endpoints
Primary	
• 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 is lost to follow up, 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 of UACR from baseline to Week 12.
Secondary[a]	
• 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.

Objectives	Estimand Description/Endpoints
Safety	
• 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. • Event of special interest (changes in fluid-related measures).
Exploratory	
• 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 may 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 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 over time during the study. Results for NT-proBNP will not be reported in the CSR.

Objectives	Estimand Description/Endpoints
• 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.
• **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.

AE = adverse event; BNP = B-type natriuretic peptide; BP = blood pressure; BUN = blood urea nitrogen; CSR = Clinical Study Report; CT-proET-1 = C-terminal pro-endothelin-1; DAE = adverse event leading to the discontinuation of study intervention; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ELDP = endothelin-like domain peptide; ET-1 = endothelin-1; K^+ = potassium; Na^+ = sodium; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; UACR = urinary albumin to creatinine ratio.

[a] The estimand for the secondary objectives is defined with the same approach as for the primary objectives.

4 STUDY DESIGN

4.1 Overall Design

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. All the variables will be collected to verify the inclusion 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 166 participants in 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.

- Zibotentan 0.25 mg + Dapagliflozin 10 mg once daily.
- Zibotentan 1.5 mg + Dapagliflozin 10 mg once daily.
- Dapagliflozin 10 mg once daily.

Participants who were previously randomised cannot be re-randomised.

Participants will be stratified by diabetes (DKD versus 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 number of randomised participants in each stratum will be monitored to ensure the non-DM CKD sub-population is approximately a minimum of 30% and a maximum of 50% of the total number of participants randomised.

A first administrative interim analysis will be performed when 50% of participants have completed 6 weeks of treatment. A second administrative interim analysis will be performed

after 100% of participants have completed the 6 weeks treatment or at a time selected by sponsor / percentage of participants with a planned week 6 visit before data cut selected by sponsor.

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.

4.2 Scientific Rationale for Study Design

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 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 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.

UACR was chosen as a surrogate for renal outcomes based on the analyses presented at the 2018 National Kidney Foundation (NKF)/FDA workshop on endpoints in CKD, which noted a strong and consistent relationship between change in UACR and the clinical outcome of kidney disease progression (Levey et al, 2020).

The study will evaluate general safety and tolerability of treatment with zibotentan and dapagliflozin in combination, compared with dapagliflozin monotherapy, with special focus on hypotension and hospitalisations due to HF. Changes in fluid-related measures (weight gain or BNP) that meet the defined threshold (Section 7.1) will be reported as an event of special interest.

Exploratory objectives include assessment of PK, change in body weight, dose/exposure of zibotentan relative to safety and PD variables, 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, change in cardiovascular biomarkers in blood (NT-pro-BNP, BNP), and change in body fluid volume and distribution status. In addition, plasma, serum and urine samples will be collected and stored for potential future exploratory research aimed at exploring biomarkers relevant to cardiorenal mechanisms, inflammation, and fibrosis. Optional blood samples will be collected and stored for genetic research (according to each country's local and ethical procedures).

This study is randomised and double-blinded to prevent bias in treatment allocation and in the subjective assessment of effect of the study intervention in the intended study population. A randomised, blinded, multicentre, active-controlled study design is considered the best design to achieve the objectives of the study, from both safety and efficacy perspectives.

4.3 Justification for Dose

Zibotentan

Zibotentan doses of 0.25, 1.5, and 5 mg (hereafter referred to as low, intermediate, and high dose, respectively) were initially selected to characterise the dose-UACR response relationship for zibotentan. Predictions were made using an exposure-UACR response model of clinical data from other ETA receptor antagonists, taking into account differences in PK and potency between the different compounds. Based on this model, 5 mg zibotentan was predicted to achieve a maximal UACR response. In participants with severe renal impairment, a dose of 5 mg will result in plasma exposure similar to that of 10 mg in subjects with normal renal function. Since 10 mg was associated with an increased fluid retention risk in earlier clinical studies, 5 mg was initially selected to be the highest dose used in this study involving a participant population with renal impairment. Based on the rate of fluid retention observed in an ad hoc safety interim analysis, randomisation to 5 mg zibotentan (both monotherapy and in combination with dapagliflozin) has been discontinued. The zibotentan 1.5 mg dose is predicted to cause less fluid retention than 5 mg, while at the same time producing meaningful UACR response, according to the model predictions. The zibotentan 0.25 mg dose was selected to be a minimally clinically relevant dose because it is predicted to produce a 20% or less reduction in UACR in addition to that with dapagliflozin.

Dapagliflozin

Dapagliflozin 10 mg is the approved dose for T2DM, CKD, and HF. 10 mg is the dose tested in DAPA-CKD for patients with CKD and an eGFR > 25 mL/min/1.73m^2 (NCT03036150).

Based on available preclinical and clinical data, the risk for metabolic drug-drug interactions between zibotentan and dapagliflozin is regarded as low.

4.4 End of Study Definition

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

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and screening criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

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

Age

1 Participant must be 18 years of age or older at the time of signing the informed consent.

Type of Participant and Disease Characteristics / Laboratory Parameters

2 Diagnosis of CKD, defined as:

(a) eGFR (CKD-EPI) ≥ 20 mL/min/1.73 m^2 (by CKD-EPI formula, see Section 8.1.2.2) AND

(b) Urine albumin to creatinine ratio (UACR) ≥ 150 and ≤ 5000 mg albumin/g creatinine, based on a single first morning void spot urine sample at screening.

Medical Treatment

3 No current or prior (within 1 month of screening) medical treatment with an SGLT2i or any FDC with SGLT2i (such as SGLT2i + metformin).

4 If ACEi and/or ARB and/or MRA are prescribed, the dose must be stable ≥ 4 weeks before screening. Participants who have been deemed unable to tolerate ACEi or ARB therapy due to allergy or complications can be enrolled.

5 No current or prior treatment within 6 months prior to screening with cytotoxic therapy, immunosuppressive therapy or other immunotherapy for primary or secondary kidney disease.

Weight

6 Body mass index (BMI) ≤ 40 kg/m^2.

Sex

7 Male or female of non-childbearing potential.

Reproduction

8 Female participants must have a negative pregnancy test at screening, must not be lactating, and must be of non-childbearing potential, confirmed at screening by fulfilling one of the following criteria:

(a) Postmenopausal defined as amenorrhoea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH and LH levels in the postmenopausal range.

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

9 Male participants must be surgically sterile, abstinent, or in conjunction with a female sexual partner, using a highly effective method of contraception for the duration of the study (from the time they sign consent) and for 3 months after the last dose of investigational product to prevent any pregnancies. Male study participants must not donate or bank sperm during this same time period (see Section 8.3.8.2).

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered highly effective birth control methods such as:

- Combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progesterone-only hormonal contraception associated with inhibition of ovulation:
  - Oral.
  - Injectable.
  - Implantable.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion of female partner.
- Male vasectomy.
- True sexual abstinence.

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

Informed Consent

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

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

12 Provision of signed and dated written Genetic informed consent prior to collection of samples (optional) for genetic analysis.

5.2 Exclusion Criteria

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

Medical Conditions

1 Minimal change disease, unstable rapidly progressing renal disease, and/or renal disease requiring significant immunosuppression, autosomal dominant or autosomal recessive polycystic kidney disease.

2 Participants with NYHA functional HF class III or IV.

3 Acute coronary syndrome (ACS) events within 3 months prior to screening.

4 Participants with a BNP ≥ 200 pg/mL or NT-proBNP ≥ 600 pg/mL (BNP ≥ 400 pg/mL or NT-proBNP ≥ 1200 pg/mL, respectively, if associated with atrial fibrillation) measured by local laboratory at screening (Visit 1).

5 Participants with unstable HF requiring hospitalisation for optimisation of HF treatment and/or who have not been stable on HF therapy within 6 months prior to screening.

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

7 High output HF (eg, due to hyperthyroidism or Paget's disease).

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

9 Participants with uncontrolled diabetes mellitus (HbA1c > 12%).

10 Participants with T1DM.

11 Hyponatremia, defined as serum Na^+ < 135 mmol/L at the time of screening (Visit 1).

12 Intermittent or persistent second or third degree atrioventricular (AV) block after sinus node dysfunction, with clinically significant bradycardia or sinus pause when not treated with pacemaker.

13 Prolonged QT interval (QTcF > 470 ms) on ECG at screening (Visit 1) or randomisation visit (Visit 2), known congenital long QT syndrome or history of QT prolongation associated with other medications.

14 History of any life-threatening cardiac dysrhythmia (continuous or paroxysmal or uncontrolled ventricular rate in participants with atrial fibrillation or atrial flutter).

15 Cardiac surgery or non-elective percutaneous coronary interventions (PCI/TAVI) (within 3 months) or open chest coronary artery bypass grafting or valvular repair/replacement (within 3 months) prior to screening or is planned to undergo any of these procedures after randomisation.

16 Heart transplantation or left ventricular assist device at any time.

17 Kidney or any organ transplantation.

18 History or ongoing allergy/hypersensitivity, as judged by the investigator, to SGLT2i (eg, dapagliflozin, canagliflozin, empagliflozin) or drugs with a similar chemical structure to zibotentan.

19 Any clinically significant disease or disorder (eg, cardiovascular, gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, psychiatric, major physical impairment) which, as judged by the investigator, might put the participant at risk because of participation in the study, or probable alternative primary reason for participant's symptoms in judgment of investigator, including but not limited to:

   (a) Isolated pulmonary arterial hypertension (defined as mean PAP ≥ 25 mmHg at rest) or right ventricular failure; in the absence of left-sided HF.

   (b) Anaemia defined as haemoglobin (Hb) level < 100 g/L or 10 g/dL at screening (Visit 1).

   (c) Severe chronic obstructive pulmonary disease (COPD) or other lung disease including but not limited to pulmonary fibrosis requiring chronic O_2 therapy, regular nebuliser use, or oral steroid therapy.

20 Stroke, transient ischemic attack, carotid surgery, or carotid angioplasty within previous 3 months prior to screening.

21 Active malignancy requiring treatment (except for basal cell or squamous cell carcinomas of the skin) and malignancies 5 years prior to screening.

22 Severe hepatic impairment (Child-Pugh class C Hepatic impairment), aspartate transaminase [AST] or alanine transaminase [ALT] > 2x the upper limit of normal [ULN]; or total bilirubin > 2x ULN at time of screening. An isolated increase in bilirubin in participants with known Gilbert's syndrome is not a reason for exclusion.

23 Participants with newly detected pathological laboratory values or an ongoing disease condition requiring investigation and/or initiation or adjustment of current treatment (in the opinion of the investigator).

24 Drug or alcohol abuse, either current or within 12 months before screening.

25 Positive hepatitis C antibody or hepatitis B virus surface antigen at screening.

26 Positive human immunodeficiency virus (HIV) test.

27 Participants treated with strong or moderate CYP3A4 inhibitor or inducer.

28 Any condition outside the renal and CV disease area, such as but not limited to malignancy, with a life expectancy of less than 2 years based on investigator's clinical judgment.

29 Confirmation of COVID-19 infection:

(a) Participant has a positive test result for SARS-CoV-2 during screening. Participants who are not hospitalised for COVID-19 infections can be re-screened 4 weeks after they have recovered.

(b) Participant has been previously hospitalised with COVID-19 infection.

30 Ejection fraction < 50% measured by ECHO at screening.

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

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

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

34 Previous randomisation into the present study.

35 Plasma donation within 1 month of the visit at the clinic or any blood donation/blood loss > 500 mL during the 3 months prior to any visit at the clinic.

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

Genetic Sampling (Optional)

Participants can decline to participate in the genetic research and may still participate in the study. Exclusion from this optional genetic research may be for any of the exclusion criteria specified for the main study or any of the following:

37 Previous allogeneic bone marrow transplant.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

1 Participants will be advised to adhere to diet as per clinical recommendations by dietician.

2 Investigational products should be taken at approximately the same time each morning (no later than 12:00), and the time recorded by the participant in the diary (can be digital recording).

3 On certain days when participants will attend the study site for a study visit and assessments, they will be asked to not take their investigational products prior to attending the study visit (see Table 1). The participant will take the investigational product at the site, provided they are permitted to continue in the study following assessments.

4 On the day of the short PK profile assessments (sub-study), participants will be asked to come to the study site fasted and will be given a light standardised breakfast after taking the dose. This light meal should be approximately 350 kilocalories and should be sourced locally to meet cultural requirements.

5 Participants should fast prior to the collection of blood samples for HbA1c, cholesterol, and lipids, on the days specified in the SoA. Fasting is defined as no caloric intake for at least 8 hours prior to the collection of the sample. Still or sparkling, unflavoured water is allowed during this period.

5.3.2 Tobacco

Participants who use tobacco products will be instructed that use of such products may be restricted while they are in the clinical unit.

5.3.3 Activity

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

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be fully re-screened once. However, a second re-screening is allowed if the participant was excluded due to a criterion that is not applicable any more in the current protocol version or if the participant was a screen failure due to the recruitment halt based on recommendation of the AstraZeneca URC. No more than two re-screenings are allowed for any participant. Re-screened participants should re-sign informed consent and be assigned the same participant

number as for the initial screening.

Where the values for the following investigations are outside the usual range for a participant during screening, based on their medical history, re-testing may be undertaken on one occasion without requiring a re-screen: blood pressure, eGFR, spot urine for ACR, ALT, AST, bilirubin, and serum sodium.

6 STUDY INTERVENTION

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

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Participants who meet the eligibility criteria will be randomised to either of the following treatments, in addition to receiving background local SoC therapy:

- Zibotentan 0.25 mg + Dapagliflozin 10 mg once daily.
- Zibotentan 1.5 mg + Dapagliflozin 10 mg once daily.
- Dapagliflozin 10 mg once daily.

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.

Table 4 Investigational Products

Intervention Name	**Zibotentan 1.5 mg/placebo**	**Zibotentan 0.25 mg/placebo**	**Dapagliflozin 10 mg**
Type	Drug/placebo	Drug/placebo	Drug
Dose Formulation	Capsule	Capsule	CCI tablet
Excipients	Contains gelatin with ingredients coming from pigs and cows in quantities that adhere to regulatory requirements.		Contains lactose, in quantities not likely to cause discomfort in lactose-intolerant individuals.
Unit Dose Strength(s)	1.5 mg/NA	0.25 mg/NA	10 mg
Dosage Level(s)	1.5 mg: 1 zibotentan capsule	0.25 mg: 1 zibotentan capsule	10 mg: 1 dapagliflozin tablet
	Placebo: 1 placebo capsule		

Intervention Name	Zibotentan 1.5 mg/placebo	Zibotentan 0.25 mg/placebo	Dapagliflozin 10 mg
Route of Administration	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental
IMP and NIMP	IMP	IMP	IMP
Sourcing	Zibotentan, dapagliflozin, and matching placebo treatments will be supplied centrally through AstraZeneca.		
Packaging and Labelling	For each strength, zibotentan and matching placebo will be provided in bottles containing 28 capsules.		Dapagliflozin will be supplied in HDPE bottles containing 28 tablets.
	All bottles will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.		

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

6.1.2 Medical Devices

1) No AstraZeneca manufactured medical devices (or medical devices manufactured for AstraZeneca by a third party) are provided for use in this study.
2) Other medical devices (not manufactured by or for AstraZeneca) provided for use in this study are:
   (a) Home-based body weight digital scales.
   (b) Bioimpedance spectroscopy (BIS).
   (c) Hand-held electronic diary (eTablet).
3) Instructions for medical device used by the participants are provided to each participant. All devices provided for the study will be returned by the participant on or before the final safety follow-up visit.
4) All medical device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation and appropriately managed by the sponsor.
   In this study any deficiency observed with a third-party medical device will be collected and reported to the manufacturer. A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer. The manufacturers medical device complaint report will be used to collect the deficiency.

6.2 Preparation/Handling/Storage/Accountability

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants having signed the ICF for the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4) Further guidance and information for the final disposition of unused study interventions are provided in the Study Intervention Handling Instructions.

6.3 Measures to Minimise Bias: Randomisation and Blinding

All participants will be centrally assigned to randomised, blinded study intervention using an Interactive Response Technology/Randomisation and Trial Supply Management (IRT/RTSM). Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site.

Participants will be stratified by diabetes (DKD versus 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.

- 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 that the non-DM CKD sub-population is approximately 30 to 50% of the total number of participants randomised in the study.

Study intervention will be dispensed at the study visits summarised in the SoA (Table 1). Returned study intervention should not be re-dispensed to the participants.

The IRT/RTSM will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit.

Routines for this will be described in the IRT/RTSM user manual that will be provided to each centre.

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

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

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

- Personnel carrying out the packaging and labelling of investigational treatment.
- Personnel generating the randomisation list.
- Personnel analysing the pharmacokinetic samples.

The IRT/RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

Unblinded Study Data

Unblinded study data will be reported to the AstraZeneca internal URC for assessment at each of the interim analyses. These data will be clearly defined in the URC charter for individual analysis parameters but will include unblinded PK data on each occasion.

Unblinded study data may also be reported to the URC for emergent safety issues. The information provided will be pertinent to the safety concern being reviewed (eg, change in fluid-related measures for fluid retention events).

Unblinded AstraZeneca or Vendor staff members will be identified before the first subject is

screened. Access to unblinded study data by individual roles will be defined in the URC charter and these roles will not take part in blinded data decisions.

6.4 Study Intervention Compliance

Participants will take treatment at the clinic on indicated visit days and at home on all other occasions.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study interventions at home, compliance with study intervention will be assessed at each visit. Diaries will be given to the participants at the randomisation visit and the participants will be asked to fill in the dose intake information (date and time) at home (can be digital recording). The diaries will be checked by study site personnel at the study visits and data transferred to the eCRF.

Compliance will be assessed by direct questioning and counting returned zibotentan/placebo capsules and dapagliflozin 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 tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.5 Concomitant Therapy

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

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

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

6.5.1 Prohibited Concomitant Medications

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 (eg, 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.
- ARNi.
- MRA.

6.5.2 Medications Inducing Hypoglycaemia

Participants using medications that can cause hypoglycaemia in T2DM patients, including insulin or sulfonylurea (SU), may be required to reduce insulin by 10% to 20% (total daily dose) and SU by 25% to 50%. In addition, more frequent blood glucose monitoring may be considered in participants receiving insulin and/or SU and with baseline HbA1c $\leq$ 7% at randomisation.

6.5.3 Background Standard of Care Therapy

Prescribed SoC treatment for CKD (eg, ACEi and/or ARB) should be stable for at least 4 weeks prior to screening (see inclusion criterion #4) and remain stable during the study.

It is preferable that any background medical therapy (eg, antidiabetic or antihypertensive therapy [including diuretics] or therapy with statins) does not change during study intervention; ie, between the screening visit and the last dose of investigational product. However, if this is necessary, the participant does not need to be withdrawn from study intervention.

6.5.4 Rescue Medicine

If a participant's medical condition requires rescue therapy, the participant should be treated,

and withdrawn from investigational product administration at the investigator's discretion. Rescue therapy should be recorded in the eCRF.

Diabetic participants may require adjustment of their other glucose-lowering treatments on commencing blinded investigational product (due to the potential of dapagliflozin treatment) to avoid hypoglycaemia as described in Section 6.5.2.

6.6 Dose Modification

No dose modifications are permitted during the study due to its short duration. However, investigational product dose(s) may be withheld if clinically necessary. In the case of a delayed or missed dose for any reason, subsequent doses should be administered according to the original schedule (ie, at the planned time point relative to the first dose of investigational product).

6.7 Intervention After the End of the Study

After the end of the study (safety follow-up visit), participants will no longer receive zibotentan and/or dapagliflozin.

Participants should maintain their other prescribed treatments at the discretion of the investigator.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

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

- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- An AE that, in the opinion of the investigator or AstraZeneca, warrants discontinuation from further dosing.
- Severe non-compliance with the CSP.
- Safety reasons as judged by the investigator and/or sponsor where continued treatment may put participant at undue risk.

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

- If BNP is increased > 100% from baseline AND is greater than 200 pg/mL; or if BNP is increased > 100% from baseline AND is greater than 400 pg/mL in a participant with atrial fibrillation.
- If the participant or male participant's partner becomes pregnant during the course of the study, investigational products should be discontinued immediately, and an AZ representative notified.
- Diabetic ketoacidosis: DKA including euglycemic DKA have been reported with use of dapagliflozin. Consider temporary interrupting study treatment if DKA is suspected. The participant should be promptly evaluated. If diabetic ketoacidosis is confirmed, investigational product(s) should be discontinued permanently. If diabetic ketoacidosis is not confirmed, restart of study intervention should be considered (see Section 7.1.1 for details).
- Symptomatic hypotension (defined as systolic BP < 90 mmHg OR diastolic BP < 60 mmHg with symptoms).
- eGFR reduction: investigational study products must be discontinued in case of confirmed eGFR reduction from baseline >50% and/or any confirmed decrease below 15 mL/min/1.73m^2.
  If an unexpected, acute decline in kidney function is observed, the participant should be promptly evaluated. Volume depletion, hypotension, intercurrent medical problems and concomitant drugs may cause increases in blood creatinine. Urinary tract infection and urinary obstruction should be considered. Several drugs may cause a decline in kidney function, especially non-steroidal anti-inflammatory drugs and certain antibiotics such as trimethoprim. If any drug is suspected of causing or contributing to worsening kidney function, their use should be reconsidered.
- More than 3% increase in weight (at least 2.5% must be from total body water as measured by bioimpedance) from start of treatment (Day 1).
- Heart failure.

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

If study interventions are permanently discontinued, the participant will continue with the study visits and complete further evaluations as per the SoA (Table 1).

7.1.1 Ketoacidosis in Participants with T2DM

Pre-disposing factors to ketoacidosis include a low beta-cell function reserve resulting from

pancreatic disorders (eg, type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction, reduced caloric intake or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in these participants.

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

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timings are summarised in the SoA. Protocol waivers or exemptions are not allowed.
- Emerging safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from an individual participant over the duration of the study, including any PK assessments that may be required, will not exceed 500 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Primary/Secondary Variable: 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 (Table 1):

- At screening, containers to collect the urine samples will be dispensed to the participants. A spot urine from first morning void will be collected the next day and analysed centrally.
- For subsequent visits, containers to collect the urine samples will be dispensed to the participants. Participants will collect first morning void urine samples at home on 3 consecutive days (ideally day of visit and preceding 2 days [refrigerated overnight] which will be returned on the day of visit). Samples will be analysed centrally.
  Note: The samples collected on visit days will also be used for the determination of exploratory urinary parameters (see Section 8.5.3.1).
- At each visit (except for screening), the geometric mean of the triplicate UACRs will be computed and used for all analysis of UACR.

8.1.2 Other Secondary Variables

8.1.2.1 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 (Table 1 and Section 8.2.2).

8.1.2.2 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. 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 (Table 1).

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

- eGFR (mL/min/1.73 m²) = 141 × min (SCr/κ,1) α × max (SCr/κ,1)$^{-0.209}$ × 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 in the SoA (Table 1).

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

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

Where S_{cys} is standardised 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.

8.1.3 Exploratory Variables

8.1.3.1 Electronic Scale Measurement of Body Weight

Home-based body weight monitoring will be performed each morning using the provided digital scales from 2 days before randomisation to end of follow-up (Visit 8) (Table 1 and Section 6.1.2) (also refer to Section 8.2.1).

8.1.3.2 Bioimpedance Spectroscopy

Bioimpedance spectroscopy (BIS) will be performed at the site at the time points specified in the SoA to monitor body fluid volumes (Table 1).

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

8.1.3.3 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 LVEF threshold for inclusion ≥ 50% with no evidence of significant ventricular wall motion abnormality or severe cardiac valve abnormalities.

The echocardiography data will be analysed by a blinded central reader.

8.2 Safety Assessments

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

8.2.1 Physical Examinations

Physical examination, and measurement of weight and height will be conducted at the time points outlined in the SoA.

- For weight and height measurements, the participant will be allowed to wear indoor, daytime clothing with no shoes and no coats/jackets and removal of heavy objects from pockets.
- A complete physical examination will include: assessments of general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems and an assessment of the presence and extent of peripheral (ankle/leg) oedema.
- A brief physical examination will include: assessment of skin (colour, turgor), lungs (breathing rate and breath sounds), cardiovascular system (HR, JVP, sounds), and abdomen (liver and spleen to detect any increase) in addition to vital signs, and an assessment of the presence and extent of peripheral (ankle/leg) oedema.

For information on how AEs based on physical examination findings should be recorded and reported, see Section 8.3.5.

Body weight will be monitored at home using an electronic scale measurement throughout the interventional period as detailed in Section 8.1.3 at the times outlined in the SoA.

8.2.2 Vital Signs

Vital signs will include resting BP, pulse, and respiratory rate measurements.

Routine BP, pulse, and respiratory rate will be assessed at the study site, as outlined in the SoA, prior to blood collection for laboratory tests with the participant resting in a supine position using a completely automated device. Manual techniques will be used only if an automated device is not available.

Vital sign measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones) and will consist of 1 pulse, 1 respiratory rate, and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded on the eCRF.

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

There will be real-time safety monitoring of body weight online data from home monitoring devices by the study physician. The study physician will alert the respective investigator if any significant weight gain is seen. The investigator will also have direct access to the online data for their participants.

The investigator will contact the participant immediately and arrange a clinic visit to assess health status.

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

8.2.3 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 (Table 1). Three individual ECGs will be recorded per time point, 1 minute apart or maximum within 2 minutes from the previous measurement. The mean value of the 3 measurements will be used will be used (eg, QTcF interval requirement will be the mean of the three ECGs).

Digital ECGs performed at site will be transferred to, centrally read, and stored by ERT. 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 and recorded in the eCRF.

Investigators will assess participants' eligibility according to the Screening ECG report (Visit 1) but also be vigilant for any abnormal findings at the randomisation clinic visit (Visit 2), prior to the centrally read report being available. Abnormal ECG findings will be evaluated by the investigator and the participant screen failed if required.

Throughout the study, clinically relevant new findings or worsening of a pre-existing finding

in the ECGs (parameters or abnormal findings in the tracing) must be considered an AE and must be recorded in the AE CRF form.

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

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the visits indicated in the SoA (Table 1).

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: FSH, LH, and serum pregnancy test.
  - Local test for SARS-CoV-2.
  - Serology test for HIV I and II, Hepatitis B surface antigen, Hepatitis C virus antibody.
  - Local laboratory BNP or NT-proBNP.
- Samples for the determination of cystatin C by a central laboratory at the visits indicated in the SoA.

Laboratory variables will be measured as indicated in Table 5.

Table 5 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)	Alkaline phosphatase (ALP)
Urinalysis	Alanine aminotransferase (ALT)
Glucose	Aspartate aminotransferase (AST)
Erythrocytes	Total bilirubin (TBL)
Protein	Creatine kinase (CK)
Albumin	Chloride (Cl^-)
Creatinine	Magnesium (Mg^+)
	Glucose (fasting, see Section 5.3.1)
	HbA1c (fasting, see Section 5.3.1)
	Cholesterol and lipids (fasting, see Section 5.3.1)
Serology (serum or plasma), at screening [a]	**Other assessments** [a]
Hepatitis B virus surface antigen	Cystatin C (serum)
Hepatitis C antibodies	Test for SARS-CoV-2 (at screening) [c]
Human immunodeficiency virus (HIV)	Follicle stimulating hormone (FSH) and luteinising hormone (LH) (women only, at screening)
	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 please refer to Appendix E - Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law - for further instructions.

[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.
[c] Any SARS-CoV-2 test except for antibody tests will be acceptable.

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

8.3 Adverse Events and Serious Adverse Events

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

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

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

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

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.

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

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim).
- The date and time when the AE started and stopped.
- Maximum intensity.
- Whether the AE is serious or not.
- Investigator causality rating against the investigational products (yes or no).
- Action taken with regard to investigational products.
- AE caused participant's withdrawal from study (yes or no).
- Outcome.

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

- Date AE met criteria for SAE.
- Date investigator became aware of SAE.
- AE is serious due to.
- Date of hospitalisation.

- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Causality assessment in relation to study procedure(s).
- Causality assessment to other medication.

8.3.3 Causality Collection

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

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

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

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

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms,

the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination, as compared with the baseline assessment, will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.7 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

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

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

The reference document for definition of expectedness/listedness is the IB for both AstraZeneca investigational products.

8.3.8 Pregnancy

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

8.3.8.1 Maternal Exposure

Zibotentan, in common with other ET antagonists, has been demonstrated to induce teratogenic effects in animals. Pregnant or breastfeeding women must not receive the compound. To prevent potential exposure via semen, men receiving zibotentan who are sexually active with a woman of childbearing potential should employ the use of condoms together with other highly effective methods of contraception.

Dapagliflozin must not be used in the second and third trimesters of pregnancy. In the time period corresponding to second and third trimester of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. There are no adequate and well-controlled studies of dapagliflozin in pregnant women.

Women of childbearing potential will not be included in this study (for definition see inclusion criteria, Section 5.1). Should a pregnancy still occur, the investigational product should be discontinued immediately, and the pregnancy reported to AstraZeneca.

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

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** for SAEs (see Section 8.3.7) and **within 30 days** for all

other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.8.2 Paternal Exposure

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

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

See Section 5.1 for methods that can achieve a failure rate of less than 1% per year when used consistently and correctly, and are considered highly effective birth control methods:

Male participants should not donate or bank sperm for the duration of the study and for at least 3 months after the study follow-up visit.

Male participants will be instructed that if they father a pregnancy during the study, this should be reported to the investigator and the study intervention should be discontinued. If the male participant fathers a pregnancy within 3 months after last dose of the study intervention, it should also be reported to the investigator. In the event that a participant's partner is subsequently found to be pregnant after the study participant is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery.

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

8.3.9 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an

SAE associated with the medication error (see Section 8.3.7) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.4 Overdose

Dapagliflozin has been well tolerated at doses up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy volunteers and patients with type 2 diabetes. Only suspected single intake of more than 500 mg dapagliflozin or repeated intake of more than 100 mg dapagliflozin should be reported on the eCRF overdose module.

Presently there is no information regarding overdose of zibotentan in humans. For the purposes of this study, an overdose will be defined as the use of investigational product in doses in excess of that specified in the protocol.

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

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** for overdoses associated with an SAE (see section 8.3.7) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

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

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

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

8.5.1 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 (Table 1; also Section 8.5.1.2).

Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Backup PK samples may be used to evaluate safety or efficacy aspects during or after the study.

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

8.5.1.1 PK Sub-Study

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 (Table 1), the additional samples will be taken at Visit 4. Participants will be asked to come to the site in the morning and fasted. They will be given a light standardised breakfast after taking the dose. Participants need to stay in the clinic until the last PK post-dose sample has been taken for measurement of zibotentan and dapagliflozin plasma concentrations.

The sub-study will be performed in all participants that agree to it, if the site investigators deem it feasible. When the target of evaluable PK profiles in at least 20% of the study population has been reached, or if recruitment is deemed too slow, the sites may be notified that further inclusions are not necessary. While participants are encouraged to take part in the PK sub-study, hesitation to take part should never be a hindrance to recruiting of the overall study. If participants or investigators choose not to take part in the PK sub-study or when the target number of samples has been reached, a single pre-dose PK sample will be taken instead of the short profile. In all cases, the dose will be administered in the clinic.

8.5.1.2 Determination of Drug Concentration

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.

8.5.2 Immunogenicity Assessments

Immunogenicity analysis will not be done in this study.

8.5.3 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 8.2.4):

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

8.5.3.1 Collection of Samples

Urine Samples

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.

The urine samples collected on visit days for the analysis of UACR (see Section 8.1.1) 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.

Results for urine cortisol will not be reported in the CSR.

Blood Samples

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

Central laboratory:

- Cystatin C, ET-1, ELDP, CT-proET-1, copeptin, NT-proBNP, and BNP.
- Fasting plasma glucose (for fasting conditions, see Section 5.3.1).

Local laboratory:

- BNP or NT-proBNP.

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

For storage, re-use and destruction of pharmacodynamic samples see Section 8.5 and Appendix C.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study, the participant consents to the mandatory research components of the study. However, biomarker samples collected for future analyses are seen as optional; participants are able to participate in the study even if they do not consent to the purpose of collection for the below samples:

- Plasma or serum sample collection for future analysis to assess the effect of zibotentan and dapagliflozin in combination versus dapagliflozin monotherapy on cardiovascular biomarkers in blood by a central laboratory.
- Plasma, serum, and urine samples for future analysis 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 by a central laboratory.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA and is subject to agreement in the participant's Informed Consent Form.

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

study.

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

For storage and destruction of genetic samples see Appendix D.

8.8 Health Economics OR Medical Resource Utilisation and Health Economics (Not Applicable)

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary hypothesis for this study is that zibotentan 1.5 mg and dapagliflozin 10 mg in combination will reduce UACR compared with dapagliflozin 10 mg monotherapy.

The secondary hypothesis for this study is that zibotentan 0.25 mg combined with dapagliflozin 10 mg will reduce UACR compared with dapagliflozin 10 mg monotherapy. Dose-response for the reduction in UACR, as a function of the zibotentan dose, as combined with dapagliflozin, will be evaluated.

9.2 Sample Size Determination

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 [redacted]% power to detect a dapagliflozin-corrected UACR reduction of [redacted]% or more assuming a SD of [redacted] 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 [redacted]%.

For the dose-response models, the sample size below will have at least [redacted]% 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 [redacted]% 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 = 77.
- Zibotentan/Dapagliflozin dose = 1.5 mg/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 to have 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.

9.3 Populations for Analyses

The following populations are defined:

Table 6 Populations for Analysis

Population/Analysis set	Description
Screened	All participants who signed the ICF.
Full Analysis Set (FAS)	All participants who are randomised and receive any study intervention. Participants are evaluated according to the treatment assigned at randomisation. The FAS will be used for all analyses of demographic baseline characteristics and efficacy data.
Per Protocol Analysis Set (PPS)	A subset of the FAS consisting of all participants who completed at least 6 weeks of treatment and do not violate the terms of the protocol in a way that may affect the primary efficacy endpoint significantly. All decisions to exclude participants from the per protocol analysis set will be made and documented prior to the unblinding of the study.
Safety Analysis Set (SAS)	All participants who are randomised and receive any study intervention. Participants are evaluated according to the actual treatment they received. If a participant received a different treatment dose than randomised throughout the study, they will be analysed according the treated dose, not the randomisation dose. If a participant received investigational product from the wrong kit for only part of the treatment duration, they will be analysed according to their randomisation dose. The SAS will be used for all safety analyses.
Ambulatory Blood Pressure Monitoring population	All participants in the FAS who have valid ambulatory BP data for change from baseline analyses.
Pharmacokinetic Analysis Set	All participants in the FAS who have at least one detectable zibotentan or dapagliflozin plasma concentration measurement post-treatment. The Pharmacokinetic Analysis Set will be used for all PK analyses.

Additional analysis sets may be defined in the Statistical Analysis Plan (SAP) for exploratory analyses. Participants or sites identified prior to database lock with major GCP 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.

9.4 Statistical Analyses

The SAP will be finalised prior to first participant in, and it will include a more technical and

detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

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

Demographic and baseline characteristics as well as prior and concomitant medication will be presented. For continuous variables, the number of non-missing observations, mean, SD, median, first and third quartiles, minimum, and maximum will be presented. For categorical variables: counts (n) and percentages (%) (where specified) will be presented. These summaries will be provided by time point of assessment, as appropriate.

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

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

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

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

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

9.4.2 Efficacy

The analysis of all efficacy variables will be performed on the FAS with a hypothetical estimand. In addition, the primary efficacy endpoint will also be analysed using the PPS, and a treatment policy estimand as sensitivity analyses.

9.4.2.1 Primary Endpoint

The primary efficacy endpoint for this study is the change in log-transformed UACR from baseline to Week 12 for zibotentan 1.5 mg combined with dapagliflozin 10 mg versus

dapagliflozin 10 mg.

For the intercurrent events, if a participant is lost to follow-up, prematurely discontinues study treatment, or uses prohibited medication, the UACR data are treated as missing after the event and no imputation is performed.

UACR will be log-transformed and analysed using a mixed model repeated measures (MMRM) method. The values will be back transformed onto the original scale to give the geometric mean relative change from baseline to Week 12. The analysis model will include the fixed categorical effects of stratification factor, CSP version (Amendment 2 versus pre-Amendment 2), treatment, visit, and treatment-by-visit interaction, plus the continuous covariates of baseline log (UACR) and baseline log(UACR)-by-visit interaction. An unstructured covariance structure will be used for the within-participant errors.

9.4.2.2 Secondary Endpoints

The change in UACR for zibotentan 0.25 mg combined with dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy from baseline (Visit 2) to Week 12 (Visit 7) will be assessed. A MMRM model similar to that described for the primary endpoint will be fitted.

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 primary and first secondary objective.

The change from baseline (Visit 2) to Week 12 (Visit 7) in office systolic and diastolic BP will be assessed for doses of zibotentan combined with dapagliflozin 10 mg compared to dapagliflozin 10 mg monotherapy.

The effect of different doses of zibotentan and dapagliflozin in combination on eGFR will be determined from the change in eGFR from baseline to Week 1, Week 12, and Week 14, and from Week 1 to Week 12.

These secondary variables of BP and eGFR will be analysed using ANCOVA, adjusting for stratification factors, treatment arm, and baseline. The FAS will be used for these analyses. More details will be provided in the SAP.

9.4.2.3 Exploratory Endpoints

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 water, and intracellular water volumes will be analysed.

9.4.3 Safety

Safety analyses will be performed using the SAS. Safety data will be presented using descriptive statistics unless otherwise specified.

In general, the baseline value for statistical analysis is the last non-missing value prior to or on the same date as administration of the first dose of investigational products. Details are described in the SAP.

9.4.3.1 Adverse Events

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

Adverse events will be presented for each treatment arm by system organ class (SOC) and/or PT covering number and percentage of participants reporting at least 1 event and number of events, where appropriate.

Adverse events will be presented in summary tables. Serious AEs occurring prior to start of study intervention will be included in data listings.

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

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

An additional table will present number and percentage of participants with most common

AEs. Most common (eg, frequency of > 5%) will be defined in the SAP.

In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of participants in any treatment arm.

Key participant information will be presented for participants with AEs with outcome of death, SAEs, and AEs leading to discontinuation of investigational product.

An AE listing for the SAS will cover details for each individual AE; an AE listing for participants who were not exposed to investigational product is presented separately.

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

9.4.3.2 Vital Signs

Vital sign parameters (office/clinic BP, pulse, and respiratory rate) will be presented for each treatment arm. Summary statistics for continuous variables will cover n, mean, SD, minimum, Q1, median, Q3, and maximum.

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

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

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

9.4.3.3 Laboratory Assessments

Laboratory parameters will be presented for each treatment arm. Summary statistics for continuous variables will cover n, mean, SD, minimum, Q1, median, Q3, and maximum. Frequency tables will cover number and percentage of participants in the respective category.

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

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

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

For urinalysis, a frequency table will present number of participants reporting at least

1 treatment-emergent increase in baseline category and/or a shift table will present the baseline assessment against the maximum on-treatment category.

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

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

9.4.3.4 Electrocardiograms

Descriptive statistics will be produced at each scheduled assessment time point for all quantitative ECG parameters (heart rate, PR, RR, QRS, QT, and QTcF intervals) for both observed absolute values and changes from baseline.

Electrocardiogram findings will also be listed.

An analysis of potentially clinically significant ECG values for QT, QTcF, QRS, and PR interval, and heart rate will be performed. The number and percentage of participants with potentially clinically significant ECG values will be tabulated across time and treatment arm. The criteria based on severity will be defined in the SAP.

Outliers with respect to QTcF will also be tabulated for the following categories:

- Absolute value > 450 ms.
- Absolute value > 480 ms.
- Absolute value > 500 ms.
- Increase from baseline > 30 ms.
- Increase from baseline > 60 ms.

9.4.4 Other Analyses

9.4.4.1 Exploratory PK Endpoints

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

- Plasma concentration of zibotentan and dapagliflozin.
- Plasma concentration of zibotentan metabolites (results from this analysis may not be reported in the CSR).
- Dose/exposure of zibotentan relative to safety and PD variables (BNP, creatinine, and cystatin C, and urine albumin and creatinine).

The following analysis will not be part of the CSR:

- Dose/exposure of zibotentan relative to blood NT-proBNP.

Additional PK analyses may be conducted as appropriate but will not be reported in the CSR.

Further details of this will be provided in the SAP.

9.4.4.2 Exploratory PD and Biomarker Endpoints

The following exploratory PD and biomarker 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.
- Evaluation of changes in cardiovascular biomarkers in blood over time during the study.

The following analyses will not be part of the CSR:

- Change in plasma/serum concentrations of ET-1, ELDP, CT-proET-1, and copeptin levels over time during the study.
- Change in cardiovascular biomarker NT-proBNP over time during the study.

9.4.4.3 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 will be described in a separate analysis plan and results will be presented separately from the main CSR.

9.5 Interim Analyses

Up to 2 administrative interim analyses may be performed. The first interim analysis may occur after 50% of participants have completed 6 weeks of treatment, 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 [redacted] zibotentan/dapagliflozin project activities is [redacted] 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.

The SAP will describe the planned interim analyses in greater detail.

9.6 Data Monitoring Committee

An internal URC of AstraZeneca representatives is set up for this study for ongoing safety monitoring and reviewing the unblinded interim results. In addition to general safety/tolerability, the URC will focus on potential risks related to hypotension and hospitalisations due to HF. Changes in fluid-related measures (weight gain or BNP) that meet the defined threshold (Section 7.1) will be reported as an event of special interest.

For details on the review committee, refer to Appendix A.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochures, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

Regulatory Reporting Requirements for Serious Breaches

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

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant underwent any study-specific procedures, the study identifier, and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Participants who are re-screened are required to sign a new ICF.

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

A 4 Data Protection

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

A 5 Committees Structure

An internal URC is set up for this study in accordance with the AstraZeneca charter for data review committees.

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

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

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

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and included into the study (ie, who signed consent) at any study site and will be the study start date.

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

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

B 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

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

- Results in death.
- Is immediately life-threatening.
- Requires in-participant hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

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

Important Medical Event or Medical Treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used. Below are some examples of events that may be considered medically important based on the investigator's judgment:

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

Intensity Rating Scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

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

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred.
- Was identified and intercepted before the participant received the drug.
- Did not occur, but circumstances were recognised that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, for example, wrong route or wrong site of administration.
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature.
- Wrong participant received the medication (excluding IRT/RTSM errors).
- Wrong drug administered to participant (excluding IRT/RTSM errors).

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

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

- Accidental overdose (will be captured as an overdose).
- Participant failed to return unused medication or empty packaging.
- Errors related to background and rescue medication, or SoC medication in open label studies, even if an AstraZeneca product.

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

Drug Abuse

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

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

Examples of drug abuse include but are not limited to:

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

Drug Misuse

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

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person

- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

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

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on zibotentan and dapagliflozin or other AstraZeneca investigational products of the same classes or for these indications continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

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

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the CSP and must provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

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

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

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants at Visit 2, at or after randomisation. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

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

Ethical and Regulatory Requirements

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

Informed Consent

- The genetic component of this study is optional, and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The principal investigators are responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

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

Data Management

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

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

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

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

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 × Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of investigational product irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law
AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN.
- AST ≥ 3 × ULN.
- TBL ≥ 2 × ULN.

Central Laboratories Being Used:

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

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

- Notify the AstraZeneca representative.
- Request a repeat of the test (new blood draw) by the central laboratory without delay.
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result.

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

- Determine whether the participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

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

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

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

date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

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

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory Tests

Hy's Law Laboratory Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; GGT = gamma-glutamyltransferase; HAV = hepatitis A virus; HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalised ratio; LDH = lactate dehydrogenase; RNA = ribonucleic acid.

[a] HBV DNA is only recommended when IgG anti-HBc is positive.

[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly.

E 7 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

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

Appendix F COVID-19 Specifics

F 1 Background to COVID-19

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

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

F 2 Risk Assessment for COVID-19 Pandemic

The mechanism of action of either zibotentan and/or dapagliflozin are unlikely to impact the course of infection with SARS-CoV-2. Dapagliflozin is an anti-glycaemic agent and zibotentan is an ETA receptor antagonist; neither is expected to cause immune suppression. Therefore, risk for the participants to be exposed to SARS-CoV-2 or to suffer from COVID-19 is expected to be similar to the background population with the same co-morbidities, in particular CKD. The risk of exposure to infected people cannot be completely excluded as the participants may need to be in public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

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

- This study is going to start including participants only when the sponsor and CRO in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic imposed by the local authorities are compatible with safe conduct of the study.
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.

- Participants will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnoea, sore throat, and fatigue throughout the study during the pandemic. Once clinical signs of infection are reported by participants, the investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. The decision to continue with dosing the participant with the investigational products in the event of him/her showing symptoms of COVID-19 infection will be per investigator's discretion.
- The probability of virus transmission will be controlled as much as possible by:
  - Advice for participant to adhere to local requirements for reduction of the public exposure while ambulatory.
  - Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on investigator's discretion.
  - Requesting all participants are contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected reports. In addition, participants are asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, participants will be referred to the local health care system for further follow-up and treatment.
  - Physical distancing and person-to-person contact restrictions will be applied during site visits.
  - Where physical distancing is not possible, personal protective equipment will be used by study participants (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the investigators and site staff and guided by local requirements.
  - Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.
- If site visits are not possible due to local restrictions, home nursing visits may be considered after discussion with and approval by the sponsor.

F 3 Restrictions Related to COVID-19

During the COVID-19 pandemic, participants are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory. If applicable, prior to screening (Visit 1), potential participants should be called to confirm they are not experiencing any COVID-19 symptoms and signs and are asked not to attend the site in case of suspected infection. If appropriate, participants will be referred to the local health care system. Physical distancing and person-to-person contact restrictions will be applied and explained to participants while staying at the study site. Where physical distancing is not possible, study

participants will be asked to use surgical face masks and/or gloves if deemed appropriate by the investigator and site staff and guided by local requirements.

F 4 Data Quality Assurance Related to COVID-19

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

F 5 References

Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic, EMA, Version 3 (28/04/2020). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, March 2020, Updated on July 02, 2020 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

Appendix G Abbreviations

Abbreviation or special term	Explanation
ABPM	ambulatory blood pressure monitoring
ABV	alcohol by volume
ACEi	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCA	anti-neutrophil cytoplasm antibody
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
ARNi	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase/transaminase
AV	atrioventricular
BIS	bioimpedance spectroscopy
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
BUN	blood urea nitrogen
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology collaboration
COPD	chronic obstructive pulmonary disease
COVID-19	corona virus disease-2019
CRF	case report form (electronic/paper)
CRO	contract research organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT-proET-1	C-terminal pro-endothelin-1
CV	cardiovascular
CYP	cytochrome P450
DILI	Drug Induced Liver Injury
DKA	diabetic ketoacidosis
DKD	diabetic kidney disease
DM	diabetes mellitus

Abbreviation or special term	Explanation
DNA	deoxyribonucleic acid
DUS	Disease Under Study
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
eGFR	estimated glomerular filtration rate
ELDP	endothelin-like domain peptide
EMA	European Medicines Agency
ERT	eResearch Technology
ESKD	end-stage kidney disease
ET-1	endothelin-1
ETA	endothelin A
ETB	endothelin B
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	haemoglobin
Hb1Ac	glycated haemoglobin
HDPE	high density polyethylene
HF	heart failure
HL	Hy's Law
IA	Interim analysis
IATA	International Airline Transportation Association
IB	Investigator's Brochure
IC50	concentration required to inhibit 50% of the activity
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology

Abbreviation or special term	Explanation
LH	luteinising hormone
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MoA	mechanism of action
MRA	mineralocorticoid receptor agonist
NICE	National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association classification
PD	Pharmacodynamic(s)
PHL	Potential Hy's Law
PK	pharmacokinetic(s)
PPS	Per Protocol Analysis Set
QT	QT interval
QTcF	QT interval corrected using Fridericia's formula
RTSM	Randomisation and Trial Supply Management
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCr	serum creatinine
SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
SGLT2i	sodium-glucose co-transporter 2 inhibitor
SoA	Schedule of Activities
SoC	standard of care
SOC	system organ class
SU	sulfonylurea
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
UACR	urinary albumin to creatinine ratio
ULN	upper limit of normal
URC	Unblinded Review Committee

Appendix H Protocol Amendment History

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

Amendment 2 (05 Apr 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The amended CSP (Amendment 1, dated 03 December 2021) was updated to implement recommendations of an AstraZeneca URC following an ad hoc safety interim analysis on 11 February 2022. The recommendation was to close further randomisation of participants to both the zibotentan 5 mg monotherapy arm and the zibotentan 5 mg/dapagliflozin 10 mg arm due to the rate of fluid retention events in these two treatment arms. Fluid retention is a known risk with zibotentan. The study had to be temporarily halted for recruitment until the IXRS system was updated for this change. Participants that were already randomised at the time of discontinuation were allowed to continue with their randomised treatment allocation based on the assessment schedule provided in CSP Amendment 1. The dapagliflozin 10 mg arm and placebo arm were not affected by the halt. Principal investigators, regulatory authorities and IRBs were informed about the recruitment halt in the high dose zibotentan arms and temporary halt in the other treatment arms due to IXRS update.

Additionally, new clinical guidelines on the management of CKD have established SGLT2 inhibitors as a SoC which has led to the need to reconsider the inclusion of a placebo treatment arm in the study. As a result, dapagliflozin 10 mg will be used in the new design as primary active comparator instead of placebo, thus further randomisation of participants to the placebo arm was closed. Following this change, participant numbers in the remaining treatment arms were redistributed to ensure the study would achieve the desired level of statistical power. At the time of discontinuation of the zibotentan high dose monotherapy arm, high dose zibotentan/dapagliflozin combination arm and placebo comparator arm, 54 participants were randomised into Part A and 52 participants had already been randomised into Part B. Approximately 26 out of the 52 participants were randomised to the treatment arms that have been closed to further randomisation. Data from Part A will be reported descriptively and separately from Part B within the CSR, unless specified otherwise.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Title Page	Changed "Placebo-Controlled" to "Active-Controlled".	Dapagliflozin 10 mg will be used as primary active comparator instead of placebo in the new design.	Substantial
	Replaced Bergur Stefansson with Glenn Carlson as AstraZeneca Study Physician.	Change within study team.	Non-substantial
Section 1.1 Synopsis	The synopsis was revised to align with revisions in the CSP sections.	Revisions were made for consistency.	Non-substantial
Section 1.2 Schema	Updated study schema and footnote with the remaining treatment arms, and number and timing of IAs.	To reflect new study design.	Substantial
Section 1.3 Schedule of Activities	Deleted SoA for Part A.	To reflect new study design as dapagliflozin 10 mg will be used as primary active comparator instead of placebo.	Substantial
	Removed End of Treatment visit.	To collect 12 weeks' data in all participants irrespective of premature study intervention discontinuation.	Substantial
	Updated text to refer to "diaries" instead of "diary cards".	To allow for either paper diary cards or electronic diaries to be used.	Non-substantial
	Deleted that home body weight measurement will be used to establish baseline body weight.	Body weight measurements at the study site will be used for baseline body weight.	Non-substantial
Section 2.2 Background	Added information on the SoC for patients with T2DM and CKD.	New clinical guidelines on the management of CKD have established SGLT2 inhibitors as a SoC.	Non-substantial
Section 2.3 Benefit/Risk Assessment	Updated the mitigation strategy for potential fluid retention risk from zibotentan.	Updated due to safety issues related to fluid retention in participants receiving high dose of zibotentan.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	The planned URC is now set up to monitor ongoing safety in the study.	To clarify.	Non-substantial
Section 2.3.1 Risk Assessment, Table 2	Updated risk assessment data and mitigation strategy for dapagliflozin and zibotentan.	To align CSP with new information which became available.	Non-substantial
Section 2.3.2 Benefit Assessment	Updated text to state that new clinical guidelines on the management of CKD have established SGLT2 inhibitors as a SoC.	To align CSP with new information which became available.	Non-substantial
Section 3 Objective and Endpoints, Table 3	Updated objectives and endpoints.	To reflect new study design as dapagliflozin 10 mg will be used as primary active comparator instead of placebo.	Substantial
Section 4.1 Overall Design	Updated number of study sites to be used and overall study design: further randomisation of participants to the placebo arm was closed and dapagliflozin 10 mg became the primary active comparator, redistributed participant numbers in the remaining treatment arms and updated the number and timing of IAs.	To reflect new study design.	Substantial
Section 4.2 Scientific Rationale for Study Design	Updated doses for remaining treatment arms. Removed placebo as control and added dapagliflozin as primary active comparator.	To reflect new study design.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 4.3 Justification for Dose	Updated the initially selected dose range.	Updated based on observations in ad hoc safety interim analysis.	Substantial
Section 5.1 Inclusion Criteria	Added that participants on a stable dose of MRA may be included in the study.	To clarify.	Substantial
Section 5.2 Exclusion Criteria	Updated exclusion criteria regarding BNP and NT-proBNP.	To clarify.	Non-substantial
Section 5.3.1 Meals and Dietary Restrictions	Removed time range during which investigational products should be taken and stated that it should be taken approximately at the same time each morning, but no later than 12:00.	To allow flexibility.	Non-substantial
	Removed reference to study Part A and Part B.	Not applicable for new study design.	Non-substantial
Section 5.4 Screen Failures	Added that a participant who was a screen failure due to the recruitment halt based on recommendation of the AstraZeneca URC, can be re-screened.	To facilitate recruitment.	Non-substantial
Section 6.1.1 Investigational Products, Table 4	Updated doses for remaining treatment arms and investigational product information.	To reflect new study design.	Substantial
Section 6.3 Measures to Minimise Bias: Randomisation and Blinding	Removed information regarding sub-population for Part A.	Not applicable for new study design.	Non-substantial
	Added list of personnel who will be unblinded as to the exact content of	To clarify.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	investigational treatments.		
Section 6.4 Study Intervention Compliance	Updated text to refer to "diaries" instead of "diary cards".	To allow for either paper diary cards or electronic diaries to be used.	Non-substantial
	Removed information regarding placebo tablets.	Not applicable for new study design.	Non-substantial
Section 6.5.1 Prohibited Concomitant Medications	Added MRA to the medications allowed in the study on stable doses.	To clarify.	Substantial
Section 7.1 Discontinuation of Study Intervention	Updated discontinuation criteria regarding BNP and NT-proBNP, diabetic ketoacidosis, and hypotension.	To clarify.	Substantial
	Described procedure to be followed when study interventions are permanently discontinued.	To clarify.	Non-substantial
Section 7.1.1 Ketoacidosis in Participants with T2DM	Updated information regarding ketoacidosis in participants with T2DM.	To clarify.	Non-substantial
Section 7.2 Participant Withdrawal from the Study	Updated study visit name.	To clarify and for consistency within the CSP.	Non-substantial
Section 8.1.2.1 Office/Clinic Blood Pressure Measurement	Updated description of different treatment arms.	To reflect new study design.	Non-substantial
Section 8.2.3 Electrocardiograms	Added that QTcF interval requirement will be the mean of the three ECGs.	To clarify.	Non-substantial
Section 8.3.8.2 Paternal Exposure	Removed list of contraception methods and added reference to Section 5.1.	Already included in Section 5.1.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Added that if a male participant fathers a pregnancy within 3 months after last dose of study intervention, it should be reported to the investigator.	To clarify paternal exposure.	Non-substantial
Section 8.5.1 Pharmacokinetics	Removed reference to study Part A and Part B.	Not applicable for new study design.	Non-substantial
	Removed that analysis of PK samples is planned only for actively treated participants and may be analysed for placebo participants, if necessary.	Not applicable for new study design.	Non-substantial
Section 8.5.1.1 PK Sub-study	Removed reference to study Part B.	Not applicable for new study design.	Non-substantial
Section 8.5.1.2 Determination of Drug Concentration	Removed reference to study Part B.	Not applicable for new study design.	Non-substantial
Section 8.6.1 Collection of Mandatory Samples for Biomarker Analysis	Clarified that biomarker samples collected for future analyses will be optional and participants will be able to participate in the study even if they do not consent to the purpose of collection for these samples.	To clarify.	Non-substantial
	Removed placebo as control and added dapagliflozin as primary active comparator.	Dapagliflozin 10 mg will be used as primary active comparator instead of placebo in the new design.	Substantial
Section 9.1 Statistical Hypotheses	Updated doses for remaining treatment arms. Removed placebo as control and added dapagliflozin as primary active comparator.	To reflect new study design.	Substantial
Section 9.2 Sample Size Determination	Updated sample size determination based on new study design.	To reflect new study design.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Sample 9.3 Populations for Analyses	Added that participants or sites identified prior to database lock with major GCP violations and where the integrity of the data is strongly questioned will be excluded from all analyses and all analysis sets.	To reflect handling of data with questionable quality.	Substantial
Section 9.4.1 General Considerations	Added that the baseline value for statistical analysis can also be the last non-missing value on the same date as administration of the first dose of investigational products.	To clarify.	Non-substantial
Section 9.4.2	Updated description of efficacy analyses.	To clarify.	Non-substantial
Section 9.4.2.1 Primary Endpoint	Updated primary endpoint based on new study design.	To reflect new study design.	Substantial
Section 9.4.2.2 Secondary Endpoints	Updated secondary endpoints based on new study design.	To reflect new study design.	Substantial
Section 9.4.2.3 Exploratory Endpoints	Updated exploratory endpoints based on new study design.	To reflect new study design.	Substantial
Section 9.4.3 Safety	Added that the baseline value for statistical analysis can also be the last non-missing value on the same date as administration of the first dose of investigational products.	To clarify.	Non-substantial
Section 9.4.4.1 Exploratory PK Endpoints	Removed reference to study Part B.	Not applicable for new study design.	Non-substantial
	Added that possible additional PK analyses will not be reported in the CSR.	To clarify.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 9.5 Interim Analyses	Updated number and timing of IAs.	To reflect new study design.	Substantial
	The planned URC is now set up.	To clarify.	Non-substantial
Section 9.6 Data Monitoring Committee	The planned URC is now set up.	To clarify.	Non-substantial
Section 10 Supporting Documentation and Operational Considerations Appendix A: A 5	The planned URC is now set up.	To clarify.	Non-substantial
Section 10 Supporting Documentation and Operational Considerations Appendix H	Moved Protocol Amendment Summary of Changes Table for previous amendment to appendix section.	Template requirement.	Non-substantial
Section 11 References	Added reference to websites referring to in Section 2.2.	To provide source for newly added information.	Non-substantial
Throughout	Minor editorial and document formatting revisions.	Minor, therefore, have not been summarised.	Non-substantial

BNP = B-type natriuretic peptide; CKD = chronic kidney disease; CSP = Clinical Study Protocol; CSR = Clinical Study Report; GCP = Good Clinical Practice; IA = interim analysis; MRA = mineralocorticoid receptor agonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PK = pharmacokinetic; QTcF = QT interval corrected using Fridericia's formula; SGLT2 = sodium-glucose co-transporter 2; SoA = Schedule of Activities; SoC = standard of care; T2DM = type 2 diabetes mellitus; URC = Unblinded Review Committee.

Amendment 1 (03 Dec 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The original CSP was updated to provide overall clarification on study procedures based on investigator feedback. To align the study population with the target population in Phase 3, the lower eGFR limit was decreased to eGFR ≥ 20 mL/min/1.73 m^2, the upper limit of ≤ 60 mL/min/1.73 m^2 was removed, and the lower UACR limit was decreased to ≥ 150 mg/g. Local BNP testing after screening was removed from the CSP as the existing testing at the central laboratory will ensure more homogeneous results and some countries are unable to perform local BNP testing. Accordingly, local NT-proBNP was added as an option at the

screening visit. Home-based ABPM and heart rate monitoring was removed as only clinic-based monitoring is contributing to the database and participants were finding the home-based device too burdensome to wear during daily activities.

The start of Part A of the study was delayed due to the COVID-19 pandemic causing a greater overlap of Part A and Part B recruitment timelines globally than was originally planned. Therefore, the data contributing to the interim analyses (1.0 and 1.1) and the data to be reviewed was combined from Part A and Part B to reduce unnecessary exposure of participants to the study intervention.

The COVID-19 testing regimen was updated to facilitate enrolment and because testing as screening only is sufficient.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Title Page	Lower the eGFR limit to eGFR ≥ 20 mL/min/1.73 m^2, remove the upper eGFR limit of eGFR ≤ 60 mL/min/1.73 m^2.	To align the study population to the target population in Phase 3.	Substantial
Section 1.1 Synopsis	The synopsis was revised to align with revisions in the CSP sections.	Revisions were made for consistency.	Non-substantial
Section 1.2 Schema	Clarified that for Part A, all participants in IA1 are to be included in IA1.1. Updated number of participants for Part B in the schema and footnote and clarified that an administrative analysis will be done for IA2 with details provided in the SAP.	To reduce the number of participants randomised in Part B while maintaining more than 90% statistical power for the primary endpoint.	Substantial
Section 1.3 Schedule of Activities (Table 1)	Shortened visit window for screening.	To give more flexibility to shorten screening period if all test results are available.	Non-substantial
	Removed SARS-CoV-2 testing on Day 1.	Testing during screening is sufficient.	Non-substantial
	Clarified that echocardiography results must be available before randomisation.	To discontinue participant from the study prior to randomisation, if necessary.	Non-substantial
	Removed home-based monitoring of ABPM.	To decrease home-based digital monitoring burden.	Non-substantial
	Removed home-based heart rate monitoring.	To decrease home-based digital monitoring burden.	Non-substantial
	Added testing of exploratory PD samples to screening assessments.	To discontinue participant from study drug, if necessary.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Clarified that central BNP results must be reviewed by the investigator within 24 hours from receipt.		
	Optional local laboratory NT-proBNP testing added at the screening visit.	NT-proBNP is used to check Exclusion Criterion #4 if local BNP testing is not possible.	Non-substantial
	Clarified that vital signs must be performed, and results reviewed before randomisation.	To discontinue participant from the study prior to randomisation, if necessary.	Non-substantial
	Clarified that clinical chemistry and haematology results must be reviewed by the investigator within 48 hours from receipt of the result.	To discontinue participant from study drug, if necessary.	Non-substantial
	Clarified that participants will take their study intervention at home between clinic visits and as directed for visits with PK sampling.	To align with Section 6.4.	Non-substantial
Section 2.2 Background	Updated data from published study that investigated dapagliflozin in patients with CKD.	Study completed and published.	Non-substantial
Section 2.3 Benefit/Risk Assessment	Realigned text to reflect data contribution to interim analysis to include ALL data at a certain time point, not just Part A data.	To clarify what data will be reviewed by the sponsor during the interim analyses 1.0 and 1.1.	Non-substantial
Section 4.1 Overall Design	Lower the eGFR limit to eGFR $\geq$ 20 mL/min/1.73 m^2, remove the upper eGFR limit of eGFR $\leq$ 60 mL/min/1.73 m^2, and lower UACR limits to	To align the study population to the target population in Phase 3.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	≥ 150 mg/g and ≤ 5000 mg/g.		
	Realigned text to reflect that interim analyses 1.0 and 1.1 will include ALL data at a certain time point, not just Part A data and clarified what data will be reviewed by the sponsor.	To capture safety signal of fluid retention with zibotentan treatment sooner to be able to stop randomising participants to that treatment.	Non-substantial
	Updated number of participants to be included in Part B of the study.	To reduce the number of participants randomised in Part B while maintaining more than 90% statistical power for the primary endpoint.	Substantial
Section 4.3 Justification for Dose	Added CKD as indication for which dapagliflozin 10 mg is approved.	To align CSP with new information which became available.	Non-substantial
Section 5.1 Inclusion Criteria	Lower the eGFR limit for inclusion to eGFR ≥ 20 mL/min/1.73 m^2 and remove the upper eGFR limit of eGFR ≤ 60 mL/min/1.73 m^2. Lower UACR limit was decreased to ≥ 150 mg/g.	To align the study population to the target population in Phase 3.	Substantial
	Clarified that participants who have been deemed unable to tolerate ACEi or ARB therapy due to allergy or complications may be enrolled in the study.	To clarify that participants with medical contraindication for ACEi/ARB use can participate in the study.	Non-substantial
	Updated the period from which participants should refrain from using cytotoxic therapy, immunosuppressive	To align with Section 6.5.1 and to only exclude participants needing these therapies for inflammation in the kidneys.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	therapy or other immunotherapy prior to screening and clarified what participants treated with immune/cytotoxic therapy are excluded.		
	Clarified criteria regarding highly effective methods of contraception.	To clarify and define highly effective methods of contraception.	Non-substantial
Section 5.2 Exclusion Criteria	Deleted "anatomical causes of CKD".	To not exclude patients that are expected to benefit from the treatment. The definition of "anatomical causes" is unclear and leads to unnecessary exclusion.	Non-substantial
	Deleted history of epilepsy syndrome as exclusion criterion.	Participants with epilepsy syndrome will be allowed to participate in the study.	Substantial
	NT-proBNP added as an optional test that can be used instead of BNP to check eligibility.	Local BNP testing not possible in all countries.	Non-substantial
	Updated criteria regarding participants with hyponatremia.	Participants with Na^+ levels < 135 mmol should be excluded from the study at screening.	Non-substantial
	Updated criteria regarding participants with prolonged QT interval.	Participants with a prolonged QT interval at screening should not proceed to randomisation.	Non-substantial
	Updated criteria regarding open chest coronary artery bypass grafting or valvular repair/replacement.	Corrected typing error regarding the period within which participants should not had cardiac surgery prior to screening.	Non-substantial
	Updated criteria regarding participants with anaemia.	Participants with haemoglobin levels < 100 g/L or 10 g/dL should be excluded from the study at screening.	Non-substantial
	Removed chronic cystitis and/or recurrent urinary tract infections (3 or	Not a safety risk as per the Investigator's Brochure and can be justified by data from	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	more in the previous year) as exclusion criterion.	the DAPA-CKD study (NCT03036150).	
	Removed positive hepatitis B virus core antibody as exclusion criterion.	Remove a test which is inappropriate to exclude patients with active hepatitis.	Non-substantial
	Updated criteria regarding COVID-19 testing.	To reflect the sponsor position on accepting COVID-19 participants in clinical studies.	Non-substantial
	Added ejection fraction < 50% at screening as exclusion criterion.	To align with Section 8.1.3.3.	Substantial
	Added that a male participant in a sexually active relation with pregnant or breastfeeding partner should not be included in the study.	To give more clarity on this reproduction exclusion.	Substantial
Section 5.3.1 Meals and Dietary Restrictions	Added details regarding the light breakfast to be taken on the day of the short PK profile assessments.	To specify the source and content of the breakfast.	Non-substantial
Section 5.4 Screen Failures	Added that re-screened participants should re-sign informed consent.	To align with Appendix A A 3.	Non-substantial
	Clarified that one re-test for certain assessments will be allowed, if in the opinion of the investigator, values are close to the inclusion criteria.	Re-test is allowed due to high day-to-day variability of creatinine (eGFR) and UACR.	Non-substantial
Section 6.1.1 Investigational Products (Table 4)	Added details about zibotentan and dapagliflozin excipients.	To align with ICF.	Non-substantial
Section 6.1.2 Medical Devices	Updated description of devices to be used in the study.	To specify what devices will be used.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 6.4 Study Intervention Compliance	Clarified that participants will take their study intervention at the clinic on indicated visit days and at home on all other occasions.	To clarify and avoid confusion.	Non-substantial
Section 7.1 Discontinuation of Study Intervention	Updated the BNP study intervention discontinuation criteria to two separate bullet points.	To clarify and avoid confusion.	Non-substantial
	Added that at least 2.5% of increase in weight must be from total body water as measured by bioimpedance.	To clarify the site-specific instructions to be followed with the bioimpedance machine.	Non-substantial
Section 7.1.1 Ketoacidosis in Participants with T2DM	Added additional information on signs and symptoms regarding ketoacidosis in participants with T2DM.	To give the investigator a clinical guidance for identification of this rare condition.	Non-substantial
Section 8.1.3.1 Electronic Scale Measurement of Body Weight	Added that the provided digital scales will be used to monitor home-based body weight.	To specify what devices will be used.	Non-substantial
Section 8.1.3.3 Ambulatory Blood Pressure Monitoring	Removed home-based monitoring of ABPM.	To decrease home-based digital monitoring burden.	Non-substantial
Section 8.2.2 Vital Signs	Removed home-based ABPM and heart rate monitoring from CSP.	To decrease home-based digital monitoring burden.	Non-substantial
Section 8.2.3 Electrocardiograms	Added that 3 measurements will be taken per time point and that the average of the readings will be recorded in the eCRF.	To align with triplicate ECGs declared in ICF. Triplicate ECGs give a more robust result.	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments	Added local BNP or NT-proBNP testing to screening samples for parameters needed to confirm eligibility.	Local BNP testing not possible in all countries.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Removed blood gas and pH testing from central laboratory clinical chemistry panel.	Testing needs to be done on an arterial sample to be meaningful, therefore is not applicable.	Non-substantial
	Removed hepatitis B virus core antibodies testing from central laboratory clinical chemistry panel.	Remove a test which is inappropriate to exclude patients with active hepatitis.	Non-substantial
	Added footnote to Table 5.	To specify which SARS-CoV-2 tests are allowed.	Non-substantial
Section 8.3.8.1 Maternal Exposure	Removed text regarding the potential inclusion of women of childbearing potential in future studies with zibotentan.	The removed text is not relevant for the study protocol, women of childbearing potential are excluded from this study.	Non-substantial
Section 8.3.8.2 Paternal Exposure	Updated text regarding paternal exposure.	To align with the exclusion criterion and to avoid a potential risk due to paternal exposure.	Non-substantial
Section 8.5.1.2 Determination of Drug Concentration	Replaced Covance with Labcorp Bioanalytical Services LLC.	Updated Covance to Labcorp information to reflect organisational name change of vendor.	Non-substantial
Section 8.5.3.1 Collection of Samples	NT-proBNP added as an optional test that can be used instead of BNP to check eligibility.	Local BNP testing not possible in all countries.	Non-substantial
Section 9.2 Sample Size Determination	Updated sample size determination to state that a 1-sided type I error rate of 5% will have at least 91% power to detect a placebo-corrected UACR reduction of 40% or more. Updated sample size for Part B of the study.	To reduce the number of participants randomised in Part B while maintaining more than 90% statistical power for the primary endpoint.	Substantial
Section 9.4.3.1 Adverse Events	Clarified which AEs will be presented in summary tables.	To clarify how AEs will be presented.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 9.5 Interim Analyses	Updated text to reflect the number of interim analyses planned and data contribution to the interim analyses.	To clarify the number and timing of planned interim analyses.	Non-substantial
Section 10 Supporting Documentation and Operational Considerations Appendix F: F 4	Deleted the example of "home nursing" as this was never applicable to this CSP.	Only on-site visits will be allowed.	Non-substantial
Section 11 References	Added reference to publication referring to in Section 2.2.	To provide source for newly added information.	Non-substantial
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarised.	Non-substantial

ABPM = Ambulatory Blood Pressure Monitoring; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blockers; BNP = B-type natriuretic peptide; CKD = chronic kidney disease; COVID-19 = coronavirus disease 2019; CSP = Clinical Study Protocol; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; ICF = informed consent form; Na^+ = sodium; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UACR = urinary albumin to creatinine ratio.

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