Parexel International

AstraZeneca AB

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A Phase 2b, Randomised, Double-Blind, Active-Controlled, Multi-Centre Study to Evaluate the Efficacy, Safety and Tolerability of Oral AZD9977 and Dapagliflozin Treatment in Patients with Heart Failure and Chronic Kidney Disease

Statistical Analysis Plan

Final: 3.0

Parexel Project Number: 250951

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	25 May 2021	Not applicable – first version.
2.0	01 October 2021	SAP amended with: Changes made in the protocol amendment version 5.0. Changes from old to new standards. New analysis included for safety assessments. Details added for ABPM and KDQOL-36 endpoints.
3.0	03 February 2022	SAP amended with: Changes made in the protocol amendment version 6.0 and 7.0. Details added for Cohort 1 and Cohort 2 output. Details added for eGFR calculation formula.

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ACTH	Adrenocorticotropic hormone
ADMA	Asymmetric dimethylarginine
AE	Adverse event
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CI	Confidence interval
CKD	Chronic Kidney Disease
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
DAE	AEs leading to discontinuation
DBL	Database Lock
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DRM	Data Review Meeting
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EOT	End Of Treatment
ERT	eResearch Technology
ESV	End Systolic Volume
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug administration
FPG	Fasting Plasma Glucose

Abbreviation / Acronym	Definition / Expansion
GDF-15	Growth differentiation factor-15
GeoCV	Geometric coefficient of variation
GeoMean	Geometric Mean
HF	Heart Failure
HR	Heart Rate
hsTnT	High sensitivity troponin T
IB	Investigator's Brochure
ICAM	Intercellular adhesion molecule
ICF	Informed Consent Form
ICH	International Council for Harmonization
IMP	Investigational Medicinal Product
IPD	Important Protocol Deviation
K^+	Potassium
L-Arg	L-arginine
LAVI	Left Atrial Volume Index
LLOQ	Lower Limit of Quantification
LOCF	Last observation carried forward
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LV-GLS	Left Ventricular Global Longitudinal Strain
LVM	Left Ventricle Mass
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for repeated measurements
MR	Mineralocorticoid Receptor
MRA	Mineralocorticoid Receptor Antagonists
NA	Not available
Na^+	Sodium

Abbreviation / Acronym	Definition / Expansion
NGAL	Neutrophil gelatinase-associated lipocalin
NK	Not known
NT-proBNP	N-Terminal Natriuretic Peptide
PCS	Potentially Clinically Significant
PD	Protocol Deviation
PIIIP3	Procollagen type III N-terminal propeptide
PK	Pharmacokinetics
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
RBC	Red Blood Cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard Deviation
SDMA	Symmetric dimethylarginine
SE	Standard Error
SGLT2	Sodium-Glucose co-Transporter-2
SGLT2i	Sodium-Glucose co-Transporter-2 Inhibitors
SoA	Schedule of Activities
SOC	System Organ Class
SS	Safety Set
SToI	Safety Topics of Interest
ST2	Suppression of tumourigenicity 2 (biomarker)
T2DM	Type 2 Diabetes Mellitus
TAPSE	Tricuspid Annular Plane Systolic Excursion

Abbreviation / Acronym	Definition / Expansion
TFLs	Tables, Figures and Listings
TR Vmax	Tricuspid regurgitation maximal velocity
UACR	Urinary Albumin to Creatinine Ratio
WHO-DD	World Health Organization - Drug Dictionary

1 INTRODUCTION

Chronic heart failure (HF) continues to be a major cause of mortality, hospitalisations and suboptimal quality of life. Even with the best possible treatment, the 5-year survival rate for HF patients is worse than for most cancers. Moreover, the prevalence of chronic HF continues to increase globally. An estimated 38 million people are affected worldwide, with over 1 million hospitalisations annually in both the United States and Europe. The annual global economic burden in 2012 was estimated to be $108 billion and will increase dramatically as the population ages.

Although mineralocorticoid receptor antagonists (MRAs) are an important standard therapy for HF, they are currently contraindicated in patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 and are highly underused in patients with eGFR <60 mL/min/1.73 m^2 due to risk of hyperkalaemia.

AZD9977 is a selective mineralocorticoid receptor (MR) modulator, with a differentiated mode of action compared with the currently prescribed MR antagonists (e.g. spironolactone/eplerenone).

The mechanism of action for AZD9977 and dapagliflozin are different and outcome of treatment is expected to be additive since the main biological effects of AZD9977 would be to block MR driven oxidative stress, inflammation and fibrosis and dapagliflozin to inhibit sodium-glucose co-transporter-2 (SGLT2) driven metabolic dysfunction, volume overload and endothelial cell dysfunction.

The overall clinical evidence suggests that the combination of AZD9977 and dapagliflozin would have clinical benefit and an acceptable safety profile in patients with HF and that further development is warranted. Hence, a global, randomised, Phase 2b study is planned to evaluate the efficacy and safety of AZD9977 and dapagliflozin in patients with HF and CKD.

The purpose of the study is to establish a dose-response for effect on urinary albumin to creatinine ratio (UACR) and assess the safety of AZD9977 given in combination with dapagliflozin 10 mg once daily, considering serum potassium (K^+) and safety topics of interest (hyperkalaemia, hypotension and deteriorating renal function) in addition to general safety.

This statistical analysis plan (SAP) documents the variables to be analysed and the statistical methods of the planned analyses and outlines the statistical programming specifications for the tables, figures, and listings (TFLs). Any deviations after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in an SAP addendum, and discussed in the Clinical Study Report (CSR). Any changes to this SAP prior to database lock will be described in a new version of the SAP.

The following analyses will be reported in the "Dose/Exposure-Response Analysis Report" and are therefore outside of the scope of this SAP:

- Dose/exposure of AZD9977 and dapagliflozin relative to safety and pharmacodynamic variables (e.g. serum K^+, eGFR, aldosterone). A formal explanation of the dose response analysis is presented in the “Dose/exposure-response analysis plan for AZD9977 and dapagliflozin in patients with heart failure and chronic kidney disease (CKD).” attached to the SAP.

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

- Clinical Study Protocol (CSP), Version 7.0 (February 02, 2022)

- eCRF, Version 3.0 (July 14, 2021) that will be updated to Version 4.0 according to the changes introduced in the CSP 7.0.

The content of this SAP is compatible with the International Council for Harmonization (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to evaluate the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on UACR.

2.2 Secondary Objective

The secondary objective of the study is to assess the dose-response relationship of dapagliflozin (10 mg) alone and 3 doses of AZD9977 (15, 50, or 150 mg) combined with dapagliflozin (10 mg) on UACR.

2.3 Safety Objectives

The safety objectives of the study are:

- To assess the general safety and tolerability of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone
- To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on serum K^+ and eGFR

2.4 Exploratory Objectives

The exploratory objectives of the study are:

- To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on serum N-terminal natriuretic peptide (NT-proBNP) levels
- To assess plasma exposure of AZD9977 and dapagliflozin
- To explore the relationships between AZD9977 and dapagliflozin dose/exposure and safety/pharmacodynamic variables
- To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on blood uric acid, blood urea nitrogen (BUN), fasting plasma glucose, haematocrit, renin, adrenocorticotropic hormone (ACTH), cortisol and copeptin levels
- To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone, on mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), red blood cell (RBC) distribution width, erythrocyte count
- To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone, on urine sodium (Na^+), K^+, uric acid, urea, osmolality, glucose, creatinine, and cortisol
- To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone, on cardiovascular biomarkers in blood

- **Optional**: To collect and store serum, plasma, and urine samples for future exploratory biomarker research related to PK, pharmacodynamics, safety, and tolerability of AZD9977 or dapagliflozin; or related to cardiorenal diseases
- **Optional:** To collect and store blood samples for genetic research (according to each country's local and ethical procedures)

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2b, multi centre, randomised, double blind, active controlled parallel group, study to assess the efficacy, safety and tolerability of AZD9977 and dapagliflozin administered for 12 weeks in patients with HF (LVEF below 60%) and chronic kidney disease (CKD) (eGFR ≥ 20 and ≤ 60 mL/min/1.73 m^2), with at least 20% of patients with eGFR ≥ 20 to < 30 mL/min/1.73 m^2 and a maximum of 35% of patients with eGFR ≥ 45 mL/min/1.73 m^2.

The study is designed to evaluate the effect of AZD9977 in combination with dapagliflozin compared to dapagliflozin alone on UACR. The secondary objective is to assess the dose-response relationship of dapagliflozin (10 mg) alone and 3 doses of AZD9977 (15, 50, or 150 mg) combined with dapagliflozin (10 mg) on UACR.

The study will be conducted at approximately 150 to 250 sites in approximately 20 countries including the North America, Asia-Pacific and European countries.

Approximately 500 participants will be randomly assigned to study intervention (125 participants per group) such that approximately 476 evaluable participants (119 per group) complete the study.

Participants will be stratified according to T2DM (yes/no) and eGFR (≥20 to <30 mL/min /1.73 m^2; or ≥30 to <45 mL/min/1.73 m^2; or ≥45 mL/min/1.73 m^2) based on the latest eGFR assessment prior to the start of the study treatment (eGFR assessment at pre-randomisation Visit 2).

For each participant, the total duration of participation will be approximately 22 to 24 weeks, including a 1-week screening period, followed by up to 7-week run-in period followed by a 12-week treatment period (including 6 visits), the end of treatment (EOT) visit, and a 4-week safety follow-up after last dose (including 1 visit). An optional pre-screening visit may be scheduled. Week and day for pre-screening visit will be at the discretion of the investigator.

After screening, eligible participants currently on treatment with a SGLT2i other than dapagliflozin should stop taking the SGLT2i and start on dapagliflozin 10 mg.
Participants on dapagliflozin treatment will continue on treatment but the medication will be provided. Participants will then undergo a 4 to 5-week run-in period to ensure washout of forbidden medications and stable doses of allowed background medications.

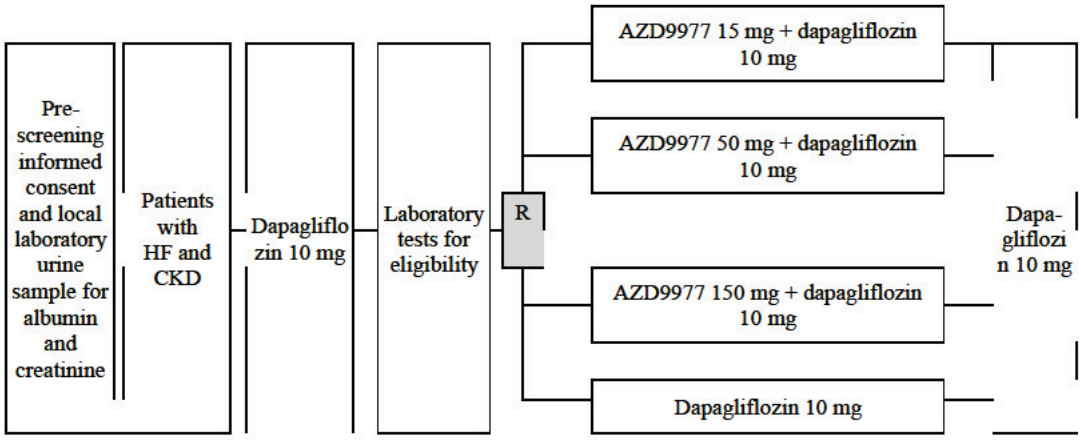
For participants eligible after screening, and not on treatment with a SGLT2i, treatment with dapagliflozin 10 mg will be initiated. Participants will then undergo a 6 to 7-week run-in period to ensure washout of forbidden medications and stable doses of allowed background medications.

During the treatment period, participants will be randomly assigned in a 1:1:1:1 ratio to receive once daily administration of one of the 4 study treatments as described below. To ensure blinding, the study treatment will be administered in the form of 3 oral capsules and 1 oral tablet in the following combinations:

Study Treatment	Capsule 1	Capsule 2	Capsule 3	Tablet
AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 15 mg	Placebo	Placebo	Dapagliflozin 10 mg
AZD9977 50 mg + Dapagliflozin 10 mg	Placebo	AZD9977 50 mg	Placebo	Dapagliflozin 10 mg
AZD9977 150 mg + Dapagliflozin 10 mg	Placebo	AZD9977 50 mg	AZD9977 100 mg	Dapagliflozin 10 mg
Dapagliflozin 10 mg alone	Placebo	Placebo	Placebo	Dapagliflozin 10 mg

A representation of the study design is provided in Figure 1 Study Design, and the schedule of activities (SoA) is provided in Appendix A: Schedule of Activities.

Figure 1 Study Design



	Pre-screening	Screening	Start Run-in [b]	Pre-Randomisation	Baseline	Treatment period (12 weeks)						EOT/ ET	Safety follow-up (4 weeks)
Visit	**Optional**	1a	1b	2	3	4	5	6	7	8	9	10	11
Weeks	[a]	(-8 to -7) [c] -6 to -5	(-7 to -6) [c] -5 to -4	-1	1		2	3	4	7	10	13	17
Day	[a]	-56 to -49) [c] -42 to -35	(-49 to -42) [c] -35 to -28	-10 to -3	1	3	8	15	22	43	64	85	113

CKD=chronic kidney disease; EOT=end of treatment; ET=early termination; HF=heart failure; R=randomisation
Note: Visits at Week 7 and Week 13 (Visits 8 and 10) correspond to visits after completion of 6 weeks and 12 weeks of study treatment, respectively.
[a] Week and day for pre-screening will be at the discretion of the investigator.
[b] Duration of run-in period for patients on treatment with a SGLT2i: 4 to 5 weeks

Duration of run-in period for patients not on treatment with a SGLT2i: 6 to 7 weeks

[c] Applies to SGLT2i naïve patients

An interim analysis will be performed when 300 patients have been treated for 12 weeks, unless the planned date of the interim analysis is too close to the expected data base lock date, for the complete study. The purpose of the interim analysis is to have the possibility to trigger Phase 3 activities; therefore, there will be no alpha spent. An Interim Unblinded Data Review Committee will be set up to review data from the pre-planned interim analysis and make decisions on future clinical development.

An Unblinded Safety Data Review Committee will be set up for this study for ongoing safety monitoring.

3.2 Endpoints and Associated Variables

3.2.1 Primary/Secondary Endpoint

The primary/secondary endpoint of the study is the percent change from baseline in UACR at the end of 12 weeks of study treatment (Visit 10). It is used as a primary endpoint to evaluate the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on UACR, and as a secondary endpoint to assess the dose-response relationship of dapagliflozin (10 mg) alone and 3 doses of AZD9977 (15, 50, or 150 mg) combined with dapagliflozin (10 mg) on UACR.

3.2.2 Safety Endpoints

The safety endpoints of the study are:

- Adverse Event (AE)/Serious Adverse Event (SAE) reporting
- Vital signs (BP, pulse rate)
- Clinical laboratory tests (clinical chemistry, haematology, and urinalysis)
- Digital 12-lead safety ECG assessments
- Safety topics of interest (hyperkalaemia, hypotension and deteriorating renal function)
- Absolute value, change, and percentage change from baseline in serum K^+ and eGFR over time

3.2.3 Exploratory Endpoints

- Percentage change from baseline in serum NT-proBNP over time
- Plasma concentrations of AZD9977 and dapagliflozin
- Dose/exposure of AZD9977 and dapagliflozin relative to safety and pharmacodynamic variables (e.g., serum/plasma K^+, eGFR, aldosterone)
- Change and percentage change from baseline in blood uric acid, BUN, fasting plasma glucose (FPG), haematocrit, renin, ACTH, cortisol and copeptin levels over time
- Change and percentage change from baseline in blood MCV, MCHC, RBC distribution width, erythrocyte count over time
- Change and percentage change from baseline in urine Na^+, K^+, uric acid, urea, osmolality, glucose, creatinine, and cortisol levels over time

- Evaluation of changes in blood biomarkers (including but not limited to hsTnT, PIIIP3, GDF-15, ST2, ADMA, SDMA, L-Arg, ICAM, NGAL) over time
- Biomarker assessment in serum, plasma, and urine samples
- Evaluation of changes in blood biomarkers (including but not limited to hsTnT, PIIIP3, GDF-15, ST2, ADMA, SDMA, L-Arg, ICAM, NGAL) over time

Exploratory research into genes/genetic variation that may influence response to treatment

3.2.4 Analysis of Cohort 1

The following summaries will be reported separately for Cohort 1:

- Demographics characteristics
- Baseline characteristics
- Disease characteristics
- Vital signs
- Prior and concomitant medications
- Adverse Events

4 STATISTICAL METHODS

4.1 Data Quality Assurance

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

4.2 General Presentation Considerations

Continuous data, if not otherwise specified, will be summarized in terms of number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum.

For log-normal variables, descriptive statistics will include n, mean, SD, median, minimum, maximum, geometric mean (GeoMean) and geometric coefficient of variation (GeoCV).

The minimum and maximum values will be reported to the same number of decimal places as the individual values. The mean, median, SD, Q1 and Q3 will be reported to one more decimal place than the raw data recorded in the database and the same level of precision will be used for standard error (SE), and confidence intervals (CI). In general, the maximum number of decimal places reported shall be three for any summary statistic.

Derived variables will be reported to one decimal.

Rounding should be the last operation in the treatment of data. There should be no rounding of intermediate results during the calculation of any derived value. Zeros at the end of a number should be retained.

Categorical variables will be summarized using frequencies and percentages. Unless otherwise noted, the denominator for the calculation of percentages will be the total number of participants within the respective analysis set and treatment group, as applicable.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using the number of participants within a treatment as denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

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

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

'Baseline' is defined as the last available pre-treatment assessment when not otherwise specified.
Baseline for UACR will be the value from Pre-randomization. The value is defined as the geometric mean of 3 UACR values derived from first morning void urine samples collected on 3 consecutive days (ideally day of visit and preceding 2 days).

'End of Study' is defined as the last available post-treatment assessment.

'Treatment Day' will be calculated relative to the date of randomisation i.e.

$$Treatment\ Day = Assessment\ Date - Randomization\ Date + 1.$$

Change from baseline will be defined as the value post-dosing minus the baseline defined, for each timepoint.

Percent change from baseline will be calculated as:

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

All other requirements and specifications for programming and presentation of TFLs will be specified in the TFL shells document.

4.3 Software

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

All TLFs will be presented in individual files (.rtf) and also one portable document format (PDF and .docx) book-marked document containing all Tables and Figures (14.x outputs) combined and, distinct PDF book-marked files for each of the 16.2.x subsections, i.e., one for all 16.2.1.x outputs, one for all 16.2.2.x ones, etc.

4.4 Handling of Missing Data

In general, other than for the below described, or where otherwise specified in the particular analysis, missing data will not be imputed and will be treated as missing.

However, laboratory assessment values of urine albumin and urine creatinine of the form of "<x" (i.e., below the lower limit of quantification [LLOQ]) will be imputed as x/2 and of the form ">x" (i.e., above the upper limit of quantification [ULOQ]) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.

For the urine albumin and urine creatinine electrolyte, which are used to calculate the UACR, the corresponding LLOQ and ULOQ are:

Urine albumin:

- LLOQ (SI units): 3.0 mg/L

- ULOQ (SI units): 12800.0 mg/L

Urine creatinine:

- LLOQ (SI units): 0.100 mmol/L

- ULOQ (SI units): 11264.000 mmol/L

Established conversion factors will be used when conversion of measurement units is necessary.

Partial or missing dates

Any AEs with incomplete start and end dates will be treated as follows:

- AEs with completely unknown start dates will be imputed with the date of first dosing, unless the imputed end date is known and prior to first dosing; in that case the start date will be imputed as the date of Screening.
- AEs with partially known start and end dates will be treated as follows:
    - If only the day is missing, then the day will be imputed with the first day of the month, unless the month and year in which the AE started is a month and year in which IMP was administered, then the day will be imputed with the first day on which IMP was administered in that month. If in the case of start date this results in a start date after the imputed end date, then the day will be imputed with the first day of the month.
    - If only the month is missing and the year is a year in which IMP was administered, then the month will be imputed with the first month in which IMP was administered. If in the case of start date this results in a start date after the imputed end date of the AE, then the month will be imputed with JAN. If the known year part is not a year in which IMP was administered, then the month will also be imputed with JAN.
    - If both the day and month is missing and the year is a year in which IMP was administered, then the day and month will be imputed with the day and month of dosing. If in the case of start date this results in a start date after imputed end date, then the day and month will be imputed with 01JAN. If the year is not a year in which IMP was administered, then the day and month will also be imputed with 01JAN.
    - If only the year is missing, then the year will be imputed with the year of dosing.

4.5 Populations for Analyses

The following populations are defined.

Table 1 Populations for Analyses

Population/Analysis Set	Description
Enrolled	All participants who sign the main ICF
Cohort 1 (randomized patients)	All participants randomized according to CSP versions 1.0 to 5.0
Cohort 2 (randomized patients)	All participants randomized according to CSP version 7.0
Full Analysis Set (FAS)	All participants who are randomised and either receive or do not 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 Set (PPS)	A subset of the FAS consisting of all participants who 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 set (SS)	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 to the treated dose, not the randomisation dose. If a participant received study drug from the wrong kit for only part of the treatment duration, they will be analysed according to their randomisation dose. The SS will be used for all safety analyses.
Pharmacokinetic set (PK)	All participants in the SS who have at least one quantifiable AZD9977 and/or dapagliflozin plasma concentration measurement after study start. The Pharmacokinetic Analysis set will be used for all pharmacokinetic assessments.
Pharmacodynamic set (PD)	All participants in the SS who have at least one quantifiable PD measurement after study start. The Pharmacodynamic Analysis set will be used for all pharmacodynamic assessments.

Upon database release, protocol deviation and the analyses population will be produced for review. An analysis set classification meeting will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to unblinding and will be documented and approved by the sponsor.

A summary of the number and percentage of participants in each analysis set will be provided by treatment group and overall. Exclusions from each analysis population will also be summarised overall and by reason.

By-participant listings of participants excluded from each analysis set and the data excluded from the FAS, the PPS, the SS, the PK and the PD will be provided.

4.6 Study Participants

4.6.1 Disposition of Participants

A clear accounting of the disposition of all participants who enter the study will be provided, from screening to study completion.

The following summaries will be provided:

- Number of subjects screened (including screen failures), number of subjects who were not randomized, and number of participants randomised and randomised not treated (including reason), number of participants started study treatment, as well as the number and percentage of subjects completed treatment and discontinued study treatment overall and by reason (including due to Coronavirus Disease 2019 [COVID-19] pandemic), completed the study and withdrawn from the study by treatment group and overall.
- Number and percentage of subjects completed treatment and the study as well as the number and percentage of subjects discontinued and withdrawn from the study due to global/country situation. Number and percentage of participants recruited per region, country, and centre, by treatment group and overall, by population (SCR, FAS, PPS and SS).
- Number and percentage of Global/country situation (COVID 19) study disruption based on FAS.

A summary of stratification factors at randomization by treatment group and overall. The stratification factors are T2DM (Yes, No) and eGFR (≥20 to <30 mL/min/1.73 m^2; or ≥30 to <45 mL/min/1.73 m^2; or ≥45 mL/min/1.73 m^2) based on the latest eGFR assessment prior to the start of study treatment (eGFR assessment at Pre-randomization Visit 2). This summary will be provided for FAS.

By-participant listings of disposition details for discontinued participants, participants completing the study, participants affected by COVID-19 pandemic including the details will be provided. Discontinued participants are those that were not followed up to the last visit expected by the protocol, irrespective of reason and including participants who died prior to the last visit.

Additionally, a by-participant listing of the randomisation scheme and codes and the various batched of investigational products will be provided.

4.6.2 Protocol Deviations

Important protocol deviations (IPD) are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of important protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by important protocol deviations.

This estimation will be performed on a Blinded Data Review Meeting (BDRM) shortly before database lock/ unblinding. Results and population assignments will be summarized in a BDRM report which will be signed off by all relevant scientific experts.

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

The IPD include the following:

- Inclusion/exclusion criteria deviations.
- Dosing deviations (eg, incorrect treatment received).
- Time window deviations for safety and/or PK assessments.
- Subjects receiving prohibited concomitant medications that are expected to influence the measurement of the primary endpoint.
- Subjects with at least one pandemic related important protocol deviation
- Other procedural and study conduct deviations recorded by the sites on a CSP deviation log.

The important protocol deviations will be summarised by treatment and overall on the FAS.

Important protocol deviations related to global/country situation (COVID-19) will be summarised separately by treatment and overall on the FAS. The following by-participant listings will be provided:

- Important protocol deviations
- Subjects affected by the COVID-19 pandemic

4.7 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the FAS, by treatment group, and overall.

A summary of participants demographics at baseline will be provided for the following variables:

Demographics characteristics:

- Age (years)
- Age Group (years) [21 - < 65 years, 65 - < 85 years, ≥ 85 years]
- Sex
- Race
- Ethnicity
- Country

A summary of participants characteristics at baseline will be provided for the following groups of variables:

Baseline characteristics:

- Height (cm)
- Weight (kg)
- Weight Group (kg) [<40, ≥40-< 75, ≥75-<90, ≥90-<120, ≥120]

- Body Mass Index (BMI) (kg/m^2)
- BMI Group (kg/m^2) [Underweight (<18.5), Normal weight (≥18.5 - <25.0), Overweight (≥25.0 - <30.0), Obese (≥30.0 to <35, ≥35 to <40 and ≥40)]

  Note: Body mass index less than 40 kg/m^2 is an inclusion criterion in the study.

Disease characteristics:

- T2DM status [yes/no]
- eGFR (mL/min/1.73m^2)
- eGFR Group [<30 mL/min/1.73 m^2, ≥30 to <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2]
- NT-proBNP ≥300 pg/mL for patients with sinus rhythm and ≥600 pg/mL for patients with atrial fibrillation/flutter at screening or in medical history.
- HbA1C (%)
- LVEF (%)
- Clinical Chemistry parameters: Serum K^+(mEq/L), Serum Na^+ (mEq/L), serum Creatinine (mg/dL), SBP (mmHg) and DBP (mmHg)
- Haemoglobin (g/dl)
- UACR (mg/mmol)
- Nicotine use at screening (Current, Former, Never)
- Alcohol use at screening (Current, Former, Never)
- Number of patients in each of the 2nd and 3rd class of the NYHA functional classification

By-participant listings of demographics and participants characteristics at baseline will be provided for the randomised subjects.

4.7.1 Medical, Surgical History and Concomitant illnesses

Medical history and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later.

Separate summaries will be provided for medical history and for surgical history. Each summary table will present the number and percentage of participants with any medical history conditions/surgical events by system organ class (SOC) and preferred term (PT) by treatment and overall for the FAS.

Medical and surgical history and concomitant illness will be listed by subject including treatment, description of the disease/procedure, MedDRA SOC, MedDRA PT, start date and stop date (or ongoing if applicable) based on the FAS.

Participants with multiple unique terms will be counted once per each unique PT and unique SOC. A participant can have one or more PTs reported under a given SOC. Each summary will be sorted by international order for System Organ Class and in alphabetical order for Preferred Term.

4.8 Prior and Concomitant Medications

Medications (other than study drug) will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD).

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the enrolment will be classified as Prior only. If a medication starts before the date of enrolment and stops on or after the date of enrolment, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of enrolment

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

All medications will be listed by patient for the enrolled set and will include the following information: reported name, anatomical therapeutic chemical (ATC), the route of administration, dosing frequency, total daily dose, study day of medication, duration of medication and therapy reason.

A summary of prior medications received and concomitant medications, by ATC level 3 code and PT by treatment and overall, on FAS will be reported.

Concomitant medications will be summarised by treatment group and overall, as:

- All concomitant medication taken during the study
- Disallowed concomitant medication taken during the study

The duration of medication will be calculated as:

$$Duration\ (days) = (end\ date - start\ date) + 1$$

The duration will be presented in days in the listing depending on the applicability to the emerging data. For medications with partial or completely missing start date and/or end date, the duration will not be calculated.

4.9 Treatment Exposure/Compliance

Treatment compliance will be assessed separately for the 3 doses of AZD9977 (15, 50 and 150 mg) combined with dapagliflozin (10 mg) and for dapagliflozin (10 mg) alone. Compliance (as a percentage) will be calculated as follows:

$$Compliance\ (\%) = \frac{Number\ of\ capsules/tablets\ taken}{Number\ of\ capsules/tablets\ planned}$$

The number of capsules/tablets planned is equal to the treatment duration (days)*number of planned capsules/tablets per day (3 capsules and 1 tablet daily). All tablets/capsules, including the placebo capsules, are to be counted. For subjects who withdraw prematurely from the study drug, compliance will be calculated up to the time of last dose.

The compliance will be summarized descriptively by treatment group and overall, on FAS. In addition, percent of compliance will be categorized into three groups, less than 80%, 80% to 120% and greater than 120%, and the categories will be summarized by treatment group and overall. In addition, listings for exposure and compliance of the investigational product will be also presented.

4.10 Efficacy evaluation

The analysis of all efficacy endpoints, unless otherwise specified will be performed on the FAS.

4.10.1 Primary/Secondary Endpoint

The primary efficacy endpoint for this study is the percent change from baseline in UACR at the end of 12 weeks of study treatment (Visit 10).

Central laboratory urine samples for the determination of albumin and creatinine and calculation of UACR will be collected at the timepoints described in the SoA (Appendix A: Schedule of Activities).

Participants will collect 1st 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).

The UACR from each urine sample will be calculated as follows:

$$UACR\ (mg/mmol) = 10 \times \frac{Urine\ Albumin\ (mg/dL)}{Urine\ Creatinine\ (mmol/L)}$$

At each visit, the geometric mean of the triplicate UACR values will be computed and used for the analysis of UACR. In case of missing values for UACR the geometric mean will be calculated considering the number of the available measurements. Baseline for UACR will be defined as the geometric mean of 3 consecutive days prior to the first dose of study treatment (ideally day of visit and preceding 2 days). Only samples collected prior to the first dose of study medication will be used.

As UACR is assumed to follow a log-normal distribution, it will be log transformed for statistical analysis purposes obtaining the ratio of geometric means.

Percent change from baseline in UACR at $Visit_k$, $k\ in\ \{7,\ 8,\ 9,\ 10\}$ will be calculated as:

$$100 \times \left(\frac{GeoMean(UACR_{Visit_k})}{GeoMean(UACR_{Baseline})} - 1 \right)$$

4.10.1.1 Analysis of the primary efficacy endpoint

Patients randomised according to CSP versions 1.0 to 5.0 (before dropping placebo and AZD9977 150 mg monotherapy arms) will be considered as part of Cohort 1, while patients randomised subsequently will be included in Cohort 2. The primary analysis for the four treatment groups maintained in Cohort 2 will combine data from both cohorts, while the accrued data from discontinued treatment groups will be analysed descriptively.

The change from baseline of the log transformed UACR at the end of 12 weeks of study treatment (Visit 10) will be analysed by a mixed-effects model for repeated measures (MMRM) at Visits 7, 8, 9, and 10. The analysis model will include treatment and visit as fixed effect, the log transformed baseline UACR and the stratifying factors (T2DM [yes/no] and eGFR [≥ 20 to <30 mL/min/1.73 m^2; or ≥30 to <45 mL/min/1.73 m^2; or ≥45 mL/min/1.73 m^2] as well as the Cohort variable (1 or 2) as covariates. Moreover, treatment × visit interaction will also be included in the model.

1. The model will involve the following four steps:
   a) Log-transformation of the UACR:

      First, the UACR at baseline and the UACR at post-baseline visits (7, 8, 9, and 10) will be log-transformed. The log-transformed UACR at baseline will then be subtracted from the log-transformed at post-baseline visits to calculate the change of UACR in log units.
   b) Execution of the model:

      The model will include the change in UACR in log units as a dependent variable and the log-transformed UACR at baseline as covariate, as well as the other independent variables described at the beginning of this section.
   c) Back-transformation of the results from the model:

      The results from the execution of the model will be back transformed to the original scale after an exponentiation of the means to obtain the percent change from baseline of the treatments. The LS mean difference and its CI between each treatment and dapagliflozin alone will also be back-transformed to yield the percent difference between two treatments with its 95% CI at Visit 10 expressed in percentage.
   d) The statistics for the percent change from baseline, percent difference between treatments and percentage 95% CI (%) will be calculated as follows:

      - percent change from baseline = (exp(estimate)-1)*100 where estimate is the LS mean
      - percent difference between treatments= (exp(estimate)-1)*100 where estimate is the LS mean difference
      - 95% CI lower and upper (%): (exp(lower)-1)*100; (exp(upper)-1)*100.

An unstructured covariance structure will be used for the within-participant errors. The denominator degrees of freedom will be calculated according to the Kenward-Roger method. If the estimating algorithms do not converge, the following steps will be taken to simplify the model until convergence is achieved:

> Try in order these four covariance structures: Toeplitz, the first-order autoregressive, compound symmetry and independent structure. Stop as soon as convergence is achieved.

The following comparison will be performed by the execution of a MMRM:

1. Overall comparison of the percentage changes from baseline in UACR at week 12 across all 4 treatment groups
2. Each of the 3 doses of AZD9977 in combination with dapagliflozin 10 mg versus dapagliflozin 10 mg in the following order:
    1. AZD9977 150 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg
    2. AZD9977 50 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg
    3. AZD9977 15 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg

The following graph will be provided:

- Mean percentage change from baseline for UACR by visit, separately for each treatment group

All available UACR values from all visits will be used regardless of any intercurrent events. Missing values will not be imputed. In this analysis it is thus assumed that any missing UACR values are missing at random (MAR).

4.10.1.2 Sensitivity Analysis of primary efficacy endpoint

The analysis described in Section 4.10.1.1 will be repeated for the PPS.

4.10.1.3 Analysis of the secondary efficacy endpoint - Dose-Response Analysis

The dose-response analysis will be conducted according to the "Dose/exposure-response analysis plan for AZD9977 and dapagliflozin in patients with heart failure and chronic kidney disease (CKD)."

4.10.1.4 Multi-centre Studies

No per centre (where the term 'centre' defines each investigator site) summaries or analyses will be made.

4.10.1.5 Multiple Comparisons/Multiplicity

The type I error will be controlled at a 2-sided α=0.05 level for multiplicity. Statistical significance will be assessed in the pre-specified order of the endpoints as specified below. The testing procedure will continue down the hierarchy if the preceding null hypothesis is rejected at a 2-sided α=0.05 level and will stop if the null hypothesis for the preceding endpoint is not rejected at a two-sided α=0.05 level.

1. Overall comparison of the percentage changes from baseline in UACR at week 12 across all 4 treatment groups (global null hypothesis)

2. Each of the 3 doses of AZD9977 in combination with dapagliflozin 10 mg versus dapagliflozin 10 mg in the following order:

    a. AZD9977 150 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg
    b. AZD9977 50 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg
    c. AZD9977 15 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg

4.10.1.6 Interim Analyses

An interim analysis will be performed when 300 patients have been treated for 12 weeks, unless the planned date of the interim analysis is too close to the expected data base lock date, for the complete study. The purpose of the interim analysis is to have the possibility to trigger Phase 3 activities; therefore, there will be no alpha spent. The conduct of the study will not be impacted by the results of the interim analysis. Descriptive summaries and the analysis methods for the outputs required for the interim analysis will follow the methodology outlined in this SAP. The outputs deliverables and the procedures for the provision and communication of the planned interim analysis will be provided in an Interim Unblinded Data Review Committee Charter.

4.10.1.7 Examination of Subgroups

Descriptive statistics of the primary efficacy variable by treatment group and subgroup (by T2DM [Yes versus No] and by eGFR [<30 mL/min/1.73 m^2; or ≥30 to <45 mL/min/1.73 m^2; or ≥45 mL/min/1.73 m^2]) will also be produced. A forest plot by T2DM status and eGFR categories will be also presented.

4.10.1.8 Japan specific analysis

A subset of the planned outputs will be repeated for participants from Japan, as required for interaction with the Japanese Regulatory Agency. The outputs will be identified in the tables, listings, and figures (TLF) mock shells.

4.10.2 Analysis of exploratory efficacy endpoints

4.10.2.1 Percent change from baseline in UACR

UACR will be summarized by treatment group and visit in terms of absolute values, and percentage changes from baseline.

A by-participant listing of the UACR data will be provided. Statistical analyses similar to those described for the primary analysis will be provided.

4.10.2.2 NT-proBNP

A summary of the NT-proBNP at baseline and at different visits as well as the percentage change from baseline will be provided by treatment group and time point.

Similar analyses described for the UACR at section 4.10.1.1 and 4.10.2.1 will be conducted for NT-proBNP.

4.11 Safety Evaluation

All safety summaries and analyses will be based upon the SS.

Safety summaries will be presented by treatment group and by eGFR categories (<30 mL/min /1.73 m^2; or ≥30 to <45 mL/min/1.73 m^2; or ≥45 mL/min/1.73 m^2), where appropriate. Individual safety and tolerability data will be provided in data listings.

Where applicable, data will be summarised for the observed value, and for the corresponding change from baseline. Change from baseline will be calculated as the differences between the post-dose value at each time point and the value prior to administration of the study medication.

4.11.1 Extent of Exposure

The duration of exposure (days) will be summarized by treatment group separately for AZD9977 in combination with dapagliflozin and dapagliflozin alone. This will be derived as follows:

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

Treatment duration (days) will be summarized by treatment group for the SS, using descriptive statistics. A by-subject listing of drug administration data will be provided. Dates and times will be listed for each subject and treatment duration.

4.11.2 Adverse Events

All AEs will be recorded from the time of randomisation and SAEs will be recorded from the time of signing the full ICF for the study (Visit 1a). No AE or SAE information will be collected after just signing of the optional pre-screening ICF. Recording of all AEs will continue until the end of the participant's safety follow-up period.

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

When not otherwise specified only AEs occurring with an onset date, or worsening, on or after first dose of investigational medical product (IMP) and within 28 days after last dose of IMP will be summarized.

The following rules will be used to determine whether or not an AE has taken place on-treatment:

1. An AE with an onset date and time on or after the date and time of first dose up to and including 5 days following the date and time of last dose of study treatment will be considered on-treatment
2. An AE with an incomplete start date and whose end date is not prior to the time of dosing on Day 1 will be considered to have taken place on-treatment unless the non-missing components of the incomplete start date indicate that the start date falls outside the time from dosing on Day 1 to last dose plus 5 days

The following variables will be collected for each AE:

- Adverse event diagnosis/description (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 medicinal product AZD9977 and/or the investigational product Dapagliflozin (yes or no)
- Action taken with regard to investigational products (AZD9977 and/or Dapagliflozin)
- Adverse event caused subject's withdrawal from the study (yes or no)
- Outcome

Unless otherwise specified, all summaries will be provided by treatment group for the SS.

The number and percentage of AEs will be presented by SOC and/or PT and for each eGFR category.

In the case that, within a visit, a patient has more than one episode of the same PT with different levels of intensity, action taken, outcome causality or seriousness, then the maximum intensity level, action taken (i.e. withdrawn) and outcome (i.e. fatal), causality level (i.e. related), or seriousness level (i.e. serious), respectively will be used. The following ordering will be used to define maximum intensity level, action taken, outcome causality level, or seriousness level:

- Intensity: Mild < Moderate < Severe
- Causality: No < Yes
- Seriousness: No < Yes
- Action taken: Unknown < Not applicable < Dose not changed < Drug interrupted < Drug withdrawn
- Outcome: Unknown < Recovered/resolved < Recovered/resolved with sequelae < Recovering/resolving < Not recovered/not resolved < Fatal

Summaries of the incidence of AEs will present the number and percentage of participants reporting at least one event in the corresponding AE category. Participants with multiple events in the same AE category will be counted once in that category. Participants with events in more than 1 category will be counted once in each of those categories.

Summaries of the occurrence of AEs will present the number of reported events within the corresponding AE category. Multiple events in the same AE category will be counted multiple times in that category. Multiple events belonging to more than 1 AE category will be counted multiple times in each of those categories.

An overview of AEs will present for each treatment group the number and percentage of patients with

- Any AEs
- Any SAEs
- Any SAE with outcome of death
- Any AEs leading to discontinuation of IMP
- Any AEs leading to withdrawal from study

An additional overview of AEs will be presented for each eGFR category.

The number and percentage of subjects who experience one or more AEs will be tabulated by each treatment group and by:

- SOC and PT
- SOC, PT and baseline eGFR category.
- SOC and PT with outcome of death
- SOC and PT and with discontinuation of investigational product
- SOC and PT and with discontinuation of investigational product by baseline eGFR categories
- SOC and PT and with possibly related adverse events

- SOC and PT and with other action taken
- SOC and PT and seriousness
- Serious AEs by SOC and PT
- Serious AEs by SOC and PT and baseline eGFR categories
- SOC and PT and outcome
- SOC and PT and maximum reported intensity
- SOC and PT and time from first dose to first onset of adverse event (0-21 days, 22-43 days, 44- 65 days, 66-85 days, >85 days.
- PT and most common AEs (>5% of participants in any treatment group) Note: This will be sorted by decreasing frequency of PT based on all participant in the SS.
- Number of SAEs by SOC and PT with outcome of death.
- Number of AEs by PT and timing of event i.e., time from first IMP dose to first AE onset (0-21 days, 22-43 days, 44- 65 days, 66-85 days, >85 days.).

In addition, a table including the key participant information will be provided for the following:

- Participants reporting SAEs with an outcome of death
- Participants reporting SAEs
- Participants reporting AEs leading to IMP discontinuation

An AE listing for the SS will cover details for each individual AE. A separate AE listing will be provided for participants enrolled but not randomised and participants not exposed to IMP.

4.11.3 Safety Topics of Interest

Hyperkalaemia, hypotension and deteriorating renal function are considered safety topics of interest in this study. The analyses below will be done for the overall population as well as each eGFR category (<30 mL/min/1.73m^2; ≥30 to <45mL/min/1.73m^2; and ≥45 mL/min/1.73m^2).

Hyperkalaemia

Hyperkalaemia will be evaluated by the analysis of serum/plasma K^+ levels (absolute values, change and percentage change from baseline in K^+, values meeting protocol-mandated discontinuation criteria for hyperkalaemia) and analysis of pre-defined AE preferred terms related to hyperkalaemia.

Hyperkalaemia will be presented as:

Hyperkalaemia related safety topics of interest

- Number (%) of patients with on-treatment local serum/plasma K^+ level > 5.5 mmol/L (confirmed by another local serum/plasma K^+ level) *
- Number (%) of patients with local on-treatment serum/plasma K^+ level > 5.5 mmol/L and central lab serum K^+ >5.5 mmol/L **
- Number (%) of patients with local on-treatment serum/plasma K^+ level > 6 mmol/L (confirmed by another local serum/plasma K^+ level) *

- Number (%) of patients with local on-treatment serum/plasma K^+ level > 6 mmol/L and central lab serum K^+ >6 mmol/L **
- Number (%) of patients who met the protocol mandated hyperkalaemia discontinuation criteria in the study:
  - Number (%) of patients with local on-treatment serum/plasma K^+ level > 5.5 to ≤ 6 mmol/L confirmed by another local or central serum/plasma K^+ level > 6.0 mml/L*
  - Number (%) of patients with local on treatment serum/plasma K^+ level > 6.0 mmol/L confirmed by another local or central serum/plasma K^+ level > 6.0 mmol/L*
- Number (%) of patients who discontinued due to meeting the protocol mandated hyperkalaemia discontinuation criteria in the study†

*Confirmation has to be the next consecutive lab sample which is ⩽ 7 days of the original lab sample. If time is available, 7 days is 168 hours from date and time of original lab. If time is missing, then 7 days is study day of original lab sample plus 7.

Additional analysis will include K^+ lab values confirmed at the next consecutive lab sample regardless of time from initial lab sample.

**Local and central lab to be on same day.

†Based on the end of treatment CRF page

Hyperkalaemia monitoring over time

- Absolute value, change and percentage change from baseline in serum K^+ level (central labs) by visit and treatment.

Hypotension

Symptomatic hypotension/decreased blood pressure will be evaluated by the analysis of BP measurements and the analysis of pre-defined AE preferred terms related to hypotension, as well as discontinuations due to hypotension. Hypotension will be presented as Number (%) of patients with:

- SBP<90 mmHg
- DBP <60 mmHg
- SBP<90 mmHg or DBP <60 mmHg*
- SBP<90 mmHg and DBP <60 mmHg*
- SBP<90 mmHg and decrease from baseline of >10mmHg*
- DBP<60 mmHg and decrease from baseline of >10mmHg*

* Recorded within the same measurement (or at a maximum within the same hour).

All the BP outliers will be presented based on the on-treatment definition.

An overall summary table of frequencies of AE, SAEs, DAEs, and a summary table by PT will be provided based on a pre-defined list of preferred terms included in the Appendix C: List of preferred terms. The summary will be provided for all the AE with an onset date, or worsening, on or after first dose of investigational medical product (IMP) and within 28 days after last dose of IMP and for the on-treatment definition included in section 4.11.2 overall and by eGFR categories.

The number and percentage of cases will be tabulated by each treatment group.

Deteriorating renal function

Deteriorating renal function will be evaluated by analysis of serum creatinine and eGFR values (percent change from baseline in eGFR, absolute values and change from baseline, values meeting protocol-defined discontinuation criteria for deteriorating renal function) and analysis of pre-defined AE preferred terms related to deteriorating renal function.

Deteriorating renal function will be presented as:

Deteriorating renal function related safety topics of interest

- Number (%) of patients with a decrease in eGFR of ≥25%, ≥30%, ≥40% and ≥57% from baseline at any visit during the randomized treatment period (based on central lab values). These decreases would need to be confirmed by another central eGFR measure. Summary will be based on the on-treatment definition included in section 4.11.2
- Number (%) of patients who met the protocol mandated renal discontinuation criteria in the study:
  - At any visit during the randomized treatment period eGFR >50% decline from baseline and/or decrease to an absolute value <15 ml/min/1.73 m^2 confirmed with eGFR >50% decline from baseline and/or decrease to an absolute value <15 ml/min/1.73 m^2 (based on central lab values).

Confirmation has to be the next consecutive central lab sample which is ≤ 14 days of the original central lab sample.

Additional analysis will include eGFR lab values confirmed at the next consecutive central lab sample regardless of time from initial lab sample.

- Number (%) of patients with >25% residual decrease in eGFR at safety follow-up visit compared to baseline
- Number (%) of patients who discontinued due to meeting the protocol mandated renal discontinuation criteria in the study†

†Based on the end of treatment CRF page

Deteriorating renal function monitoring over time

- Absolute value, change and percentage change from baseline in eGFR (central labs) by visit and treatment

SToI analysis of PTs as described in Appendix **C: List of preferred terms**C: List of preferred terms. This would include an overall summary table of frequencies of AE, SAEs, DAEs, and a summary table by PT based on a pre-defined list of preferred terms

The summary will be provided for all the AE with an onset date, or worsening, on or after first dose of investigational medical product (IMP) and within 28 days after last dose of IMP and based on the on-treatment definition when otherwise specified. A summary based by eGFR categories will be also presented.

The incidence of hyperkalaemia, hypotension and deteriorating renal function will be summarized by treatment group.

4.11.4 Clinical Laboratory Evaluation

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

The following laboratory variables will be measured.

Table 2 Laboratory Safety Variables

Haematology/Haemostasis (whole blood) [a]	**Clinical Chemistry (serum or plasma)** [a]
White blood cell (WBC) count	Na^{+} [b]
Red blood cell (RBC) count	K^{+} [b,c]
Haemoglobin (Hb)	Blood urea nitrogen (BUN)
Haematocrit (HCT)	Serum creatinine [b,d]
Neutrophils absolute count[f]	Uric acid[f]
Lymphocytes absolute count[f]	Albumin
Monocytes absolute count[f]	Calcium
Eosinophils absolute count[f]	Phosphate
Basophils absolute count[f]	Alkaline phosphatase (ALP)
Platelets	Alanine aminotransferase (ALT)
International normalised ratio (INR)[e]	Aspartate aminotransferase (AST)
MCV[f]	Total bilirubin (TBL)
MCHC[f]	Glutamate dehydrogenase (GLDH) [f]
RBC distribution width[f]	Creatine kinase (CK) [f]
HbA1c	Bicarbonate (HCO_3^-)[f]
Urinalysis (urine) [a]	Chloride (Cl^-)[f]
Protein	Magnesium (Mg^+)
Glucose	Glucose
Blood	Total cholesterol, direct HDL-C, triglycerides, LDL-C[g], VLDL-C[g] (fasting, see Section 5.3.1) [f]
Leukocyte esterase	**Other assessments**
Specific gravity [f]	Cystatin C [d, h]

Haematology/Haemostasis (whole blood) [a]	Clinical Chemistry (serum or plasma) [a]
pH [f]	RT-PCR test for SARS-CoV-2 (optional, at pre-randomisation visit)
Microscopic examination of the sediment if blood or leukocyte esterase are positive on dipstick [f]	Follicle stimulating hormone (FSH) (for confirmation of postmenopausal status of women <50 years old only [women who are permanently sterilised are exempted], at screening)

[a] Local laboratory at screening and pre-randomization (if applicable per SoA) and central laboratory at subsequent visits, unless specified otherwise.
[b] At the local laboratories, electrolytes (Na^+ and K^+) and creatinine may be measured in plasma samples instead of serum samples depending on their capability.
[c] Central laboratory measurements for K^+ levels will be with serum and plasma samples.
[d] eGFR (mL/min/1.73 m^2) will be calculated using the BSA adjusted CKD-EPI formula and including both serum creatinine and serum cystatin C for central laboratory assessments, and with serum/plasma creatinine alone for local laboratory assessments. Extended formulas adopted for eGFR calculation are provided in Appendix B.
[e] The post-randomisation INR measurements may be done at a local laboratory if the necessary material provided by the central laboratory is not available; and the measurements may be omitted if the local laboratory is not capable of doing the measurements. Refer to Laboratory Manual for details.
[f] These tests are not required at screening or pre-randomization.
[g] Per Friedewald equation
[h] Central laboratory for all cystatin C measurements.

Laboratory parameters will be presented for each treatment group and/or visit.

The outlier laboratory values based on predefined criteria will be presented by treatment as defined in Table 3. A laboratory value will be considered abnormal if it meets the predefined criteria for the abnormality, except where the baseline value met the criteria for the abnormality and the new value is less extreme than the baseline value. Only the most severe value per participant will be accounted for.

Table 3 Laboratory abnormalities by predefined criteria

Blood Chemistry	
ALP Number of subjects with any on-treatment value >1.5x ULN >3x ULN	Total bilirubin Number of subjects with any on-treatment value >1.5x ULN >2x ULN
ALT Number of subjects with any on-treatment value >3x ULN >5x ULN >10x ULN >20x ULN	Na^+ (mmol/L) Number of subjects with any on-treatment value <120 <130 >150

Blood Chemistry	
AST Number of subjects with any on-treatment value >3x ULN >5x ULN >10x ULN >20x ULN	K^+ (mmol/L) Number of subjects with any on-treatment value ≤2.5
ALT or AST Number of subjects with any on-treatment value >3x ULN >5x ULN >10x ULN >20x ULN	
Haematocrit	
Haematocrit (Vol) Number of subjects with any on-treatment value <0.20 >0.55 >0.60	Hemoglobin (g/L) Number of subjects with any on-treatment value <60 >180 >200

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

For haematology and chemistry, a shift table will present the baseline assessment against the minimum and the maximum on-treatment category.

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

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

The following summaries will be also provided:

- Baseline versus maximum value on-treatment in each urinalysis laboratory parameter by treatment group (shift table)
- Maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's Law criteria
- Treatment emergent haematology abnormalities and chemistry abnormalities by predefined criteria
- A summary of individual participant data for participants with Potential Hy's Law

By-participant listings of all laboratory data for the SS will be provided including participant identifier, treatment, age, sex, race, visit, category for lab test, lab test or examination name, result, standard units, reference range indicator. All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings.

The on-treatment definition is described in section 4.11.2.

4.11.5 Electrocardiogram

Single 12-lead ECG will be obtained after the patient has been resting in a supine position for at least 10 minutes, at the visits outlined in the SoA (Appendix A: Schedule of Activities).

A digital ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc 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. Digital ECGs will be collected, cleaned, and stored by eResearch Technology (ERT).

Potentially clinically significant (PCS) ECG values will be identified based on the predefined criteria displayed in Table 6

Table 4 PCS ECG predefined criteria

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

ms = milliseconds, bpm = beats per minute: NA= not applicable. Note, no standard criteria are established for treatment emergent increases or decreases in RR intervals or heart rates, or for treatment emergent decreases in PR, QRS or QT/QTc intervals.

*Cut-off values for categorical analyses as recommended by ICH E14 (Note, more than one category for high range increases in QT/QTc values).

Note, lower and upper RR interval limits and low and high RR interval reference ranges (all in ms), represent respectively the upper and lower heart rate limits and high and low heart rate reference ranges (all in bpm).

The following summaries will be provided:

- A summary of the ECG variables and change from baseline in each ECG variable by treatment group and time point
- A summary of ECG assessment (normal/abnormal clinically significant/abnormal not clinically significant), baseline versus last observation on-treatment.
- A summary of the number and percentage of subjects reporting PCS ECG values outside predefined criteria, by ECG parameter, treatment and visit

By-participant listings of ECG results and findings will be provided based on SS.

The on-treatment definition is described in section 4.11.2.

4.11.6 Vital Signs

Vital sign parameters will be presented for each treatment group based on SS.

Blood pressure and pulse rate will be assessed at the study site, as outlined in the SoA (Appendix A: Schedule of Activities), prior to blood collection for laboratory tests with the patient resting in a supine position using a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g., television, cell phones) and will consist of 1 pulse 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.

Notable changes from pre-dose at each post-dose time point for vital sign parameters will be identified. The predefined criteria for notable changes in vital signs values are displayed in Table 7

Table 5 PCS vital signs predefined criteria

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

BP = Blood pressure.

The following summaries will be presented:

- A summary of the observed values and change from baseline in each vital sign parameter by treatment group and time point.
- A summary of key participant information for participants reporting notable changes outside predefined criteria in each vital sign parameter
- A summary of the number and percentage of participants experiencing notable changes from baseline outside predefined criteria, by vital sign parameter and treatment group.

By-participant listings of vital signs results, and findings will be provided.

4.11.7 Physical Examinations

A by-participant listing of physical examinations will be provided including date of examination and confirmation of assessment performed (Yes/No).

4.11.8 Safety Unblinded Data Review Committee

A Safety Unblinded Data Review Committee will be set up for this study for ongoing safety monitoring. In addition to general safety/tolerability, the committee will focus on potential risks related to hyperkalaemia, hypotension and deteriorating renal function.

4.12 Other Analyses

4.12.1 Pharmacokinetics

Summary statistics for the PK concentrations will include number of observations, number of observations below the lower limit of quantification (LLOQ), geometric mean, GeoCV, arithmetic mean, arithmetic standard deviation, median, minimum, and maximum. Any concentrations that are not reportable or where no sample is available will be excluded from the summary tables. Three observations > LLOQ are required as a minimum for plasma concentrations at a specific time point to be summarised. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as not calculated. For PK concentration summaries, at a time point where less than or equal to 50% of the values are below LLOQ, values will be set to the LLOQ/2, and all descriptive statistics will be calculated.

Plasma concentrations of AZD9977 and dapagliflozin will be listed and summarised by treatment groups and visit, based on the PK Analysis Set. Plasma concentrations of AZD9977 and dapagliflozin will be measured throughout the study as described in Appendix A: Schedule of Activities.

The pre-dose plasma concentrations of AZD9977 and dapagliflozin will be summarised, separately, by descriptive statistics for each visit and each sample point for AZD9977-treated participants by treatment. To illustrate pre-dose plasma concentrations, a graph with boxplots will be generated, drawn against visit number (i.e. three boxplots corresponding to each of the visit with pre-dose PK collection; only pre-dose concentrations for Visit 7). One plot will be generated per each treatment group and analyte (two analytes: AZD9977 and dapagliflozin).

Separate summary statistics will be provided for each sampling time in the PK post-dose subgroup (Visit 7). Samples are to be taken 1 (±0.25), 2 (±0.25), 4 (±0.5), and 6 (±1) hours post-dose. Graphically, geometric-mean curves will be plotted against nominal time (±geometric standard deviation); two plots will be prepared per each analyte (AZD9977 and dapagliflozin): one on a linear scale and one on a semi-logarithmic scale. Pre-dose PK sample collected at Visit 7 will also be included in the summary statistics and when generating the curves.

A by-participant listing of drug concentration data of AZD9977 and Dapagliflozin will be provided for all randomised participants. Individual concentrations below the LLOQ will be reported as non-quantifiable (NQ) in the listings with the LLOQ defined. Individual plasma concentrations that are Not Reportable (NR) will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings.

4.12.2 Pharmacodynamics

The following summaries will be provided for the pharmacodynamic and biomarker variables by treatment group based on the PD set:

- Observed absolute values and change from baseline in plasma/serum uric acid, BUN, FPG, haematocrit, renin, ACTH, cortisol and copeptin levels by treatment group and time point.
- Observed absolute values and change from baseline in blood MCV, MCHC, RBC distribution width, erythrocyte count by treatment group and time point.
- Observed absolute values and change from baseline in urine Na^+, K^+, uric acid, urea, osmolality, glucose, creatinine, and cortisol levels by treatment group and time point.
- Observed absolute values and change from baseline in blood and urine biomarkers by treatment group and time point
- A by-participant listing of pharmacodynamic variables will be provided for all the randomised participants.

4.13 Determination of Sample Size

A total of 119 evaluable participants per arm will provide 80% power to detect a 30% placebo adjusted change from baseline in UACR at 12 weeks, assuming a standard deviation of 1.0 on the natural log-scale and α=0.05. To account for approximately 5% drop-out, approximately 500 participants will be randomly assigned to study intervention (125 participants per group) such that approximately 476 evaluable participants (119 per group) complete the study.

4.14 Changes in the Conduct of the Study or Planned Analysis

No changes in the Conduct of the study or Planned analysis are included in the SAP, however a clarification is needed:

The expression at 12 weeks in the protocol refers to the end of 12 weeks of study treatment and it should be considered equal to the start of week 13 i.e. 12 weeks (end of 12 weeks treatment) refers to week 13 (starting of week 13). To have consistency along the SAP the expression at Visit 10 was considered in the description of the efficacy evaluation (section 4.10). However, the expression at 12 weeks was maintained for the description of some endpoints accordingly to the protocol.

The first baseline eGFR category was reported in the shells as <30 to also include the patients with an eGFR between 20 and 30 based on the CSP and patient with an eGFR less than 20.

5 REFERENCES

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6 APPENDICES

Appendix A: Schedule of Activities

Procedure	Pre-screening	Screening	Start Run-in	Pre-randomisation	Baseline/ Randomisation	Treatment Period						EOT/ET [a]	Safety Follow-up	Notes
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**	
Informed consent	X	X												
Local laboratory urine samples for albumin and creatinine	X													Sample according to local clinical practice.
Inclusion and exclusion criteria		X	X		X									
Enrolment in RTSM		X												
Demography, height, smoking history, alcohol consumption		X												
Physical examination, weight		X			X (pre-dose)							X	X	For site visits only.
Medical/ surgical history		X			X									
Concomitant medication		X		X	X	X	X	X	X	X	X	X	X	

Procedure	Pre-screening	Screening	Start Run-in	Pre-randomisation	Baseline/ Randomisation	Treatment Period						EOT/ET [a]	Safety Follow-up	Notes
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**	
Adverse events		SAEs only		SAEs only	X	X	X	X	X	X	X	X	X	
Vital signs (blood pressure, pulse rate)		X			X (pre-dose)	X	X	X	X	X	X	X	X	Background treatment for hypertension should be individually optimised and stable for 3 weeks before randomisation (Visit 3); BP assessed for eligibility at Visit 3.
Digital 12-lead safety ECG		X [d]			X (pre-dose)	X		X		X		X		ECGs to be added as clinically indicated.
Local echocardio-graphy		X [d]												Needed to confirm eligibility if not assessed in past 12 months

Procedure	Pre-screening	Screening	Start Run-in	Pre-randomisation	Baseline/ Randomisation	Treatment Period						EOT/ET [a]	Safety Follow-up	Notes
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**	
Local laboratory blood samples for clinical chemistry and haematology		X [d]												
Local laboratory urine sample for albumin, creatinine, and urinalysis		X [d]												Spot urine sample
Local laboratory blood sample for NT-proBNP		X [d]												
Local laboratory blood sample for FSH measurement		X [d]												To confirm postmenopausal status of women (only women of non-child-bearing potential will be included in the study).
Local laboratory RT-PCR test for SARS-CoV-2				X [e]										Optional. If available at site.

Procedure	**Pre-screening**	**Screening**	**Start Run-in**	**Pre-randomisation**	**Baseline/ Randomisation**	**Treatment Period**						**EOT/ET** [a]	**Safety Follow-up**	**Notes**
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**	
Local laboratory serum/plasma samples for K^+ and Na^+				X [e]	X	X	X	X	X	X	X	X		Results needed for eligibility and to assess discontinuation criteria at each visit
Local laboratory serum/plasma samples for creatinine including eGFR calculation					X	X	X	X	X	X	X	X		
Central laboratory blood samples for clinical chemistry and haematology; and plasma sample for K^+ measurement					X (pre-dose)	X	X	X	X	X	X	X	X	

Procedure	**Pre-screening**	**Screening**	**Start Run-in**	**Pre-randomisation**	**Baseline/ Randomisation**	**Treatment Period**						**EOT/ET** [a]	**Safety Follow-up**	**Notes**
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**	
Central laboratory serum sample for creatinine for eGFR calculation				X [e]										
Central laboratory serum sample for cystatin C for eGFR calculation				X [e]	X (pre-dose)	X	X	X	X	X	X	X	X	
Central laboratory blood samples for HbA1c, cholesterol, and lipids					X (pre-dose)							X	X	After at least 8-hour fasting for lipids.
Central laboratory urinalysis					X (pre-dose)					X		X	X	

Procedure	Pre-screening	Screening	Start Run-in	Pre-randomisation	Baseline/ Randomisation	Treatment Period						EOT/ET [a]	Safety Follow-up	Notes
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**	
Central laboratory urine samples for albumin, creatinine (for UACR calculation), Na^+, K^+, uric acid, urea, osmolality, glucose, and cortisol [f]				X [e, f]			X		X	X	X	X	X	First morning void urine sample collected at home in provided vials over 3 consecutive days until the visit day.
Pharmaco-kinetics														
Predose sample for AZD9977 and dapagliflozin plasma concentrations							X		X			X		Collected before dose intake at site, or 1 day after last dose for the EOT/ET visit.
Optional postdose plasma samples for AZD9977 and dapagliflozin concentrations									X					Collected at 1 (±0.25), 2 (±0.25), 4 (±0.5), and 6 (±1) hours postdose.

Procedure	Pre-screening	Screening	Start Run-in	Pre-randomisation	Baseline/ Randomisation	Treatment Period						EOT/ET [a]	Safety Follow-up	Notes
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**	
Pharmaco-dynamics (Central laboratory)														
Blood samples for NT-proBNP, aldosterone, renin, ACTH, cortisol, copeptin, and FPG					X (pre-dose)		X		X			X	X	Collected at the same time of the day. After at least 8-hour fasting for FPG.
Exploratory measurements and biomarkers														
Serum/plasma samples for cardiovascular biomarkers					X (pre-dose)				X			X	X	Central laboratory.
Optional serum, plasma, and urine samples for exploratory assessment of biomarkers					X (pre-dose)				X			X		

Procedure	Pre-screening	Screening	Start Run-in	Pre-randomisation	Baseline/ Randomisation	Treatment Period						EOT/ET [a]	Safety Follow-up	Notes
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	* Applies to SGLT2i naïve patients
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**	
Optional genetic sample for Genomics Initiative exploratory analysis					X (pre-dose)									
Study treatments														
Randomisation in RTSM					X									
Dapagliflozin 10 mg			Daily-(morning) self-administration									Daily-(morning) self administration [a]		
Study treatment					Daily (morning) self-administration of the assigned study treatment									Taken at the site on visit days, after completing all predose procedures.
Drug dispensation			X		X				X	X	X	X		
Drug accountability					X	X	X	X	X	X	X	X	X	

ACTH=adrenocorticotropic hormone; BP=blood pressure; BUN=blood urea nitrogen; CKD=chronic kidney disease; CSP=Clinical Study Protocol; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EOT=end of treatment; ET=early termination; FPG=fasting plasma glucose; FSH=follicle stimulating hormone; HbA1c=glycated haemoglobin; HF=heart failure; K^+=potassium; Na^+=sodium; NT-proBNP=N-terminal natriuretic peptide; RT-PCR=reverse transcriptase polymerase chain reaction; RTSM=Randomisation and Trial Supply Management, SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; UACR=urinary albumin to creatinine ratio.

Note: Visits at Week 7 and Week 13 (Visits 8 and 10) correspond to visits after completion of 6 weeks and 12 weeks of study treatment, respectively.

[a] Patients will continue on open label dapagliflozin 10 mg after the EOT visit during the safety follow up period up to Visit 11. Patients who discontinue study treatment early may continue on open label dapagliflozin 10 mg after the ET visit during the safety follow up period up to Visit 11, as judged by the investigator. Patients who withdraw consent may perform an ET visit but the safety follow-up will not be performed

[b] If site visits are not possible due to local SARS-CoV-2 restrictions, home nursing visits may be considered after discussion with and approval by the Sponsor.

[c] Week and day for pre-screening will be at the discretion of the investigator.

[d] Results from the screening tests are needed to confirm eligibility before the run-in period can start.

[e] Results are needed to confirm eligibility before randomisation. Serum/plasma Na^+ will be assessed at Visit 2 only. The eGFR-based participant stratification will rely on central eGFR assessment at Visit 2.

Appendix B: eGFR calculation formulas

The participant's eGFR (mL/min/1.73 m^2) will be calculated based on the standard BSAadjusted CKDEPI formula using serum/plasma creatinine concentration alone (Levey et al 2009) as measured at a local laboratory and using both serum creatinine and serum cystatin C concentrations (Inker et al 2012) at a central laboratory. Note that for eGFR calculation based on creatinine levels, the calibrated methods provide equivalent results for plasma and serum sample types.

eGFR calculation using standard BSA-adjusted CKD-EPI formula using serum/plasma creatinine concentration (Levey et al 2009):

$$eGFR\ (mL/min/1.73m^2) = 141 \times min\ (SCr/\kappa,1)^{\alpha} \times max\ (SCr/\kappa,1)^{-1.209} \times 0.993^{Age} \times [1.018\ if\ female] \times [1.159\ if\ black]$$

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.
eGFR calculation using standard BSA-adjusted CKD-EPI formula using both serum creatinine and serum cystatin C concentrations (Inker et al 2012):

$$eGFR\ (mL/min/1.73m^2) = 135 \times min(SCr/\kappa, 1)^{\alpha} \times max(SCr/\kappa, 1)^{-0.601} \times min(Scys/0.8, 1)^{-0.375} \times max(Scys/0.8, 1)^{0.711} \times 0.995^{Age} \times 0.969\ [if\ female] \times 1.08\ [if\ black]$$

SCr (serum creatinine) = mg/dL, Scys (standardised serum cystatin C) = mg/L, κ = 0.7 (females) or 0.9 (males), α = -0.248 (females) or -0.207 (males), min(SCr/κ or 1) = indicates the minimum of SCr/κ or 1, max(SCr/κ or 1) = indicates the maximum of SCr/κ or 1, min(Scys/0.8, 1) = indicates the minimum of Scys/0.8 or 1, max(Scys/0.8, 1) = indicates the maximum of Scys/0.8 or 1, age = years

Appendix C: List of preferred terms defining the safety topics of interest

The PTs are based on MedDRA version 23.1 and these will be updated with the current MedDRA version for consistency.

Hypotension

- Hypotension
- Diastolic hypotension
- Orthostatic hypotension

Deteriorating renal function

- Acute kidney injury
- Acute phosphate nephropathy
- Anuria
- Azotaemia
- Continuous haemodiafiltration
- Dialysis
- Foetal renal impairment
- Haemodialysis
- Haemofiltration
- Neonatal anuria
- Nephropathy toxic
- Oliguria
- Peritoneal dialysis
- Prerenal failure
- Renal failure
- Renal failure neonatal
- Renal impairment
- Renal impairment neonatal
- Subacute kidney injury

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