Parexel International

AstraZeneca

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A Phase 2b Randomised, Double-Blind, Placebo-Controlled, Multi-Centre, Dose-Ranging Study of AZD5718 in Participants with Proteinuric Chronic Kidney Disease

Statistical Analysis Plan

Version: 3.0

Parexel Project Number: PXL248068

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	15 OCT 2020	Original document
2.0	26 APR 2022	Addition of Ambulatory Blood Pressure Monitoring (ABPM) analyses for day-time/night-time, and hourly ABPM Mixed Models for Repeated Measures. Sub-group and sensitivity analyses added. Appendix D added to include Multiple Imputation (MI) for ABPM data. Update to Appendix D to clarify that MI will be performed using hourly mean Systolic Blood Pressure (SBP) measurements. Statistical modelling for the hourly mean SBP will be based on the change of hourly mean SBP. Sensitivity analysis of the ABPM analysis for participants with treatment compliance ≥ 80% added. By-strata efficacy analysis added for urine albumin to creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR).
3.0	27 SEP 2022	Following early termination of study, planned analysis is updated to reflect analysis of interest for final clinical study report. Removal of AZD5718 pharmacokinetic (PK) analysis, Dapagliflozin PK analysis, biomarker analysis and ABPM sensitivity analysis. Addition of Changes from Planned Analysis section which outlines the differences between the study protocol and the statistical analysis plan following the study termination.

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition/Expansion
5-LO	5-lipoxygenase
ABPM	Ambulatory Blood Pressure Monitoring
ACR	Albumin to Creatinine Ratio
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
CCI	[redacted]
BMI	Body Mass Index
BMP	Blinding Maintenance Plan
BP	Blood Pressure
CI	Confidence interval
CKD	Chronic Kidney Disease
COVID-19	Coronavirus Disease of 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CST	Central Subfield Thickness
DBL	Database Lock
DBP	Diastolic Blood Pressure
DKD	Diabetic Kidney Disease
DM	Diabetes Mellitus
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
CCI	[redacted]
FAS	Full Analysis Set
FCS	Fully Conditional Specification
FLAP	5-Lipoxygenase Activating Protein
HR	Heart rate
CCI	[redacted]
CCI	[redacted]
IMP	Investigational Medicinal Product
IPD	Important protocol deviations
LOCF	last observation carried forward
CCI	[redacted]
MCP-Mod	Multiple Comparison Procedure – Modelling
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
CCI	[redacted]
PD	Pharmacodynamic
PEY	Participant Exposure Year
PK	Pharmacokinetic(s)
PP	Per-Protocol
CCI	[redacted]
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT2i	Sodium-Glucose Cotransporter 2 inhibitors

Abbreviation/Acronym	Definition/Expansion
SoA	Schedule of Activities
SOC	System Organ Class
T2DM	Type 2 Diabetes Mellitus
TELVC	Treatment-emergent laboratory and vitals change
UACR	Urine Albumin to Creatinine Ratio

1 INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem associated with significant morbidity and mortality; diabetes mellitus (DM) is the leading cause of end-stage renal disease. The pathophysiology of diabetic kidney disease (DKD) is multifactorial, with both haemodynamic effects contributing to glomerulofibrosis and inflammation emerging as major contributors to disease progression. CCI

While it is anticipated that sodium-glucose cotransporter 2 inhibitors (SGLT2i) will be a key component of standard of care for proteinuric CKD in the future, definitive evidence in non-diabetic CKD is anticipated, but not yet available, and current uptake in DKD is limited with fewer than 5% of participants on SGLT2i treatment.

This Phase 2b study will investigate if AZD5718, a FLAP inhibitor, can reduce albuminuria in participants with proteinuric CKD both on treatment with dapagliflozin as future standard of care and on current standard of care with minimal SGLT2i use. The dose-response relationship, and the safety and pharmacokinetic (PK) profile of AZD5718 will be evaluated. Following the early termination of the FLAIR study, details for changes to analysis are included in Section 4.14.

The results of the study will form the basis for the future clinical development programme for AZD5718. The primary endpoint for this study is based on anticipated future standard of care with all participants on the SGLT2i dapagliflozin. Efficacy, and safety on current standard of care with limited use of SGLT2i are secondary endpoints

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

- CCI
- CCI

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

- Safety laboratory data
- Electrocardiogram (ECG) data
- AZD5718 concentration in plasma
- E-Diary

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

- Study Protocol, Version 3.0 (25 JAN, 2021)
- eCRF, Version 2.0 (12 OCT, 2020)

2 STUDY OBJECTIVES

2.1 Primary Objective

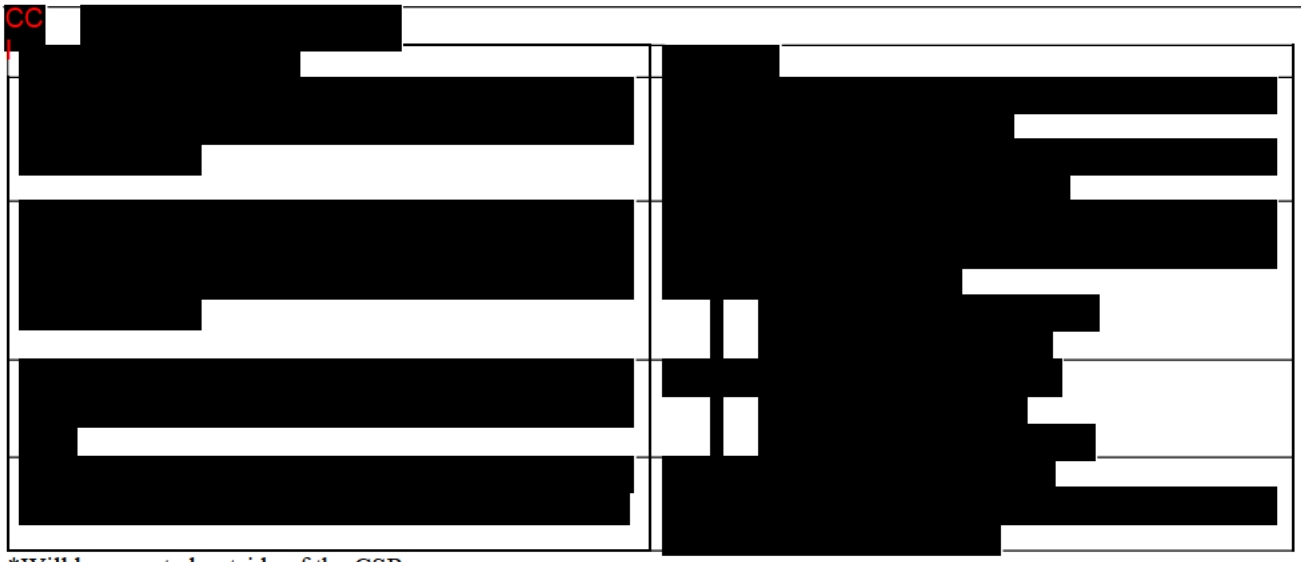
Primary Objective	Estimand Description
To evaluate the dose-response effect of AZD5718 on urine ACR at 20 weeks in participants with proteinuric CKD (on treatment with dapagliflozin as future standard of care from Weeks 12 to 20)	Reduction of urine ACR from baseline to Week 20 compared with placebo. 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 Per-Protocol population. The endpoint being assessed is the change in log-transformed urine ACR from baseline to Week 20. For the intercurrent event, if a participant discontinues treatment due to AE or lack of efficacy, or uses prohibited medication, the urine ACR data are treated as missing after the event and no imputation is performed. The summary measure being evaluated is the geometric mean reduction of urine ACR from baseline to Week 20.

Abbreviations: ACR = albumin to creatinine ratio; AE = adverse event; CKD = chronic kidney disease.

2.2 Secondary Objectives

Secondary Objectives	Endpoints
To evaluate the dose-response effect of AZD5718 on urine ACR at 12 weeks (on current standard of care)	Reduction of urine ACR from baseline to Week 12 compared with placebo. The clinical quantity of interest to be estimated is defined by the following three components: • Population Randomised participants who meet all eligibility criteria and have valid non-missing urine ACR records at baseline and at least one post-treatment visit. • Endpoint Change in log-transformed urine ACR from baseline to Week 12. • Summary measure Geometric mean reduction of urine ACR from baseline to Week 12 compared with placebo.
To evaluate the safety and tolerability of AZD5718 in participants with proteinuric CKD	• AEs/SAEs • Vital signs • Clinical chemistry/ haematology/urinalysis parameters • ECG assessments
To evaluate the effect of AZD5718 on ambulatory blood pressure in participants with proteinuric CKD	Change in 24-hour mean SBP from baseline to Week 12.
To assess the PK of AZD5718 after repeated oral dosing for 20 weeks in participants with proteinuric CKD	AZD5718 plasma concentrations [Note: following the termination of FLAIR study, the PK analyses will not be performed]
To assess the effect of AZD5718 on renal function in participants with proteinuric CKD with and without the addition of dapagliflozin	Change in eGFR from baseline to Week 12 and from Week 12 to Week 20.

Abbreviations: ACR = albumin to creatinine ratio; AE = adverse event; CKD = chronic kidney disease; ECG = electrocardiograms; eGFR = estimated glomerular filtration rate; PK = pharmacokinetic(s); SBP = systolic blood pressure; SAE = serious adverse event.



*Will be reported outside of the CSR.
Abbreviations: 5-LO = 5-lipoxygenase; ACR = albumin to creatinine ratio; CCI ; CKD = chronic kidney disease; CSR = clinical study report; CCI ; DKD = diabetic kidney disease; CCI ; CCI ; CCI ; CCI ; CCI ; CCI ; PK = pharmacokinetics; CCI .

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

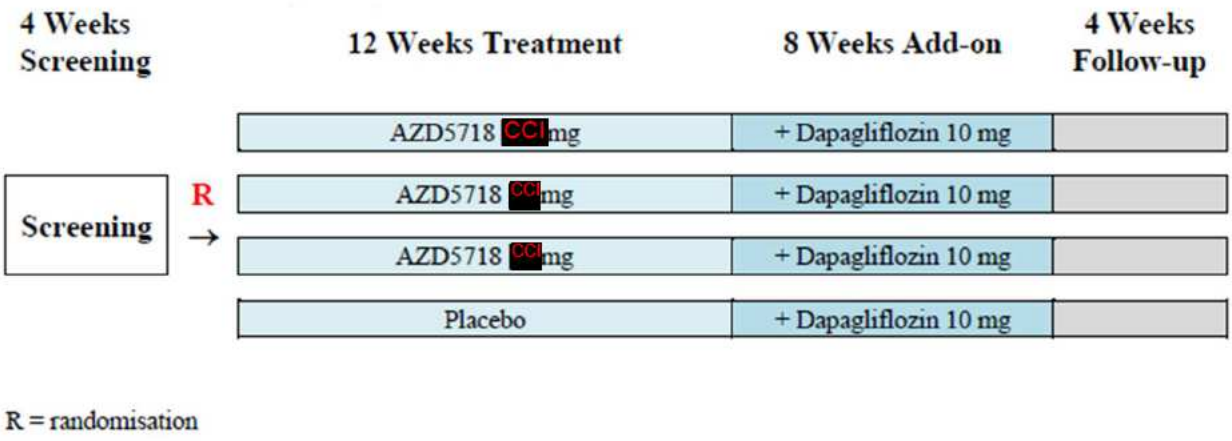
This study is a Phase 2b, randomised, double-blind, placebo-controlled, multi-centre, dose-ranging study to evaluate the efficacy, safety, and PK of AZD5718 in participants with proteinuric CKD. The study will be conducted in approximately 118 study centres across 12 countries.

Approximately 632 participants comprising of 67% DKD and 33% non-DKD participants will be randomised 1:1:1:1 to receive once daily oral doses of CCI mg AZD5718, CCI mg AZD5718, CCI mg AZD5718, or placebo, for the first 12 weeks with an add-on therapy of 8 weeks of dapagliflozin for all participants, to have 158 participants per group.

The study will include four periods as shown in Figure 1:

- Screening Period of up to 4 weeks
- Treatment Period 1 consisting of 12 weeks where participant receives study drug (AZD5718/placebo)
- Treatment Period 2 consisting of 8 weeks where participants receive study drug (AZD5718/placebo) in addition to a once daily oral dose of dapagliflozin CCI mg.
- Follow-up Period of up to 4 weeks.

Figure 1 Study Design



R = randomisation

The total duration of the study will be at least 28 weeks for each individual participant. Following early termination of the study, participants will have a total study duration of up to 28 weeks.

It is planned to have approximately 568 evaluable participants (142 per group) completing the study. Randomisation will be stratified by diabetes status (DKD and non-DKD) at the time of randomisation in order to ensure approximate balance between treatment groups within each sub-population. The strata are:

- Stratum 1: DKD participants without SGLT2i background outside Japan
- Stratum 2: DKD participants with SGLT2i background outside Japan
- Stratum 3: Non-DKD participants outside Japan
- Stratum 4: DKD participants without SGLT2i background in Japan
- Stratum 5: DKD participants with SGLT2i background in Japan
- Stratum 6: Non-DKD participants in Japan

The number of randomised DKD and non-DKD participants will be monitored in order to ensure that the non-DKD sub-population is 30% to 35% of the total participants randomised. At least 72 Japanese participants will be included.

The primary objective is to determine the efficacy of AZD5718 as assessed by change from baseline in urine albumin to creatinine ratio (ACR) at Week 20, when compared to placebo as defined in Section 4.9.2.

The study schedule of activities (SoA) is available in Appendix A.

An administrative interim analysis will be conducted when approximately 200 participants have completed the 20-week treatment period. For further details, see Section 4.9.1.5.

3.2 Endpoints

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

3.2.1 Efficacy Variables

3.2.1.1 Urine ACR

Urine ACR is a key marker for assessing kidney damage. Urine ACR is a ratio between measured albumin and measured creatinine, which estimates 24-hour urine albumin excretion. See the SoA in Appendix A for timing of collection.

Urine ACR will be calculated as:

$$Urine\ ACR\ (mg/g) = \frac{urine\ albumin\ (mg/dL)}{urine\ creatinine\ (g/dL)}$$

Spot urine samples are collected during the Screening Visit and at the remaining timepoints, participants are required to collect first morning void urine samples on 3 consecutive days. At each visit, the geometric mean of the triplicate ACRs will be computed centrally and used for all analysis of urine ACR.

Baseline urine ACR is taken to be the geometric mean of urine ACR geometric mean measurements taken at Visit 2 (Screening Visit 2) and Visit 3 (Study Day 1).

3.2.1.2 Estimated GFR

Estimated GFR is a marker for assessing kidney function. Estimated GFR is calculated based on serum creatinine values and will be calculated by the central laboratory using the CKD-EPI equation as follows:

$$eGFR\ (\mathrm{mL/min/1.73m^2}) = 141 \times \min(SCr/\kappa, 1)\,\alpha \times \max(SCr/\kappa, 1)^{-0.209} \times 0.993\ Age \times (1.018\ if\ female) \times (1.159\ if\ Black)$$

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.

3.2.1.3 Ambulatory Blood Pressure

24-hour ambulatory blood pressure monitoring (ABPM) will be performed at timepoints as specified in the SoA in Appendix A. During ABPM, systolic blood pressure (SBP), diastolic BP (DBP), heart rate (HR), and mean arterial pressure readings will be recorded over a period of 24 hours.

3.2.1.4 AZD5718 Plasma Concentrations

Venous blood samples will be collected for the measurement of plasma concentrations of AZD5718 as specified in the SoA in Appendix A. The actual date and time (24-hour clock time) of each sample and date and time (24-hour clock time) of previous dose taken will be recorded in the eCRF. Site may refer to e-Diary or home dosing diary for time of last dose taken by the participant prior to dosing in clinic, if available.

A sub-group of at least 80 participants (20 per dose group including placebo) will have four additional PK samples taken within 1-2 hours (h), 2-5 h, 5-8 h, and 8-12 h post-dose (one sample taken at each time window with the additional requirement of at least 1 h between 2 subsequent samples) for analysis of AZD5718. As indicated in the SoA in Appendix A, the additional samples will be taken at Visit 5 for only the sub-group of 80 participants, while pre-dose PK samples for analysis of AZD5718 will be collected from all study participants.

Samples for determination of AZD5718 (and dapagliflozin) concentration in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

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

3.2.2 Safety Variables

Safety will be assessed by descriptive analysis of adverse events (AEs) (including serious adverse events [SAEs]), vital signs, laboratory assessments, ECGs, and physical examinations.

3.2.2.1 Adverse Events/Serious Adverse Events

Adverse events are collected from time of first dose through to the Follow-Up Period. Serious adverse events will be collected from the time of signed informed consent through to the Follow-up Period.

3.2.2.2 Vital Signs

Vital signs will be performed at timepoints as specified in the SoA in Appendix A. Vital signs will include BP, HR, respiratory rate, pulse oximetry, and body temperature. Vital signs should be collected pre-dose on the days of study drug dosing and before blood draws.

3.2.2.3 Clinical Laboratory Parameters (Clinical Chemistry, Haematology, and Urinalysis)

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA in Appendix A. 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. Clinical chemistry, haematology, and urinalysis will be performed at the central laboratory, except for the pregnancy test at Visit 3 which will be done locally via urine dipstick. Any other tests performed by urine dipstick are also performed locally, shown in Table 1. The laboratory variables to be measured are presented in Table 1.

Table 1 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-White blood cell count	S/P-Sodium
B-Red blood cell count	S/P-Potassium
B-Haemoglobin	S/P-Urea
B-Haematocrit	S/P-Creatinine
B-Mean corpuscular volume	S/P-Creatine kinase
B-Mean corpuscular haemoglobin	S/P-Albumin
B-Mean corpuscular haemoglobin concentration	S/P-Calcium
B-Neutrophils absolute count	S/P-Phosphate
B-Lymphocytes absolute count	S/P-Glucose (fasting) (Non-fasting at Screening Visit 1)
B-Monocytes absolute count	S/P-Alkaline phosphatase
B-Eosinophils absolute count	S/P-Alanine aminotransferase
B-Basophils absolute count	S/P-Aspartate aminotransferase
B-Platelets	S/P-Total bilirubin
B-Reticulocytes absolute count	S/P-Follicle stimulating hormone^
	S/P-Luteinising hormone^
Coagulation	S/P-Thyroid stimulating hormone
B-International normalised ratio	S/P-Free triiodothyronine
B-Activated partial thromboplastin time	S/P-Creatinine (for eGFR quantification)
B-Fibrinogen	S/P-Chloride
	S/P-Bicarbonate
Urinalysis *	S/P-Magnesium
U-Glucose (dipstick)	S/P-Human chorionic gonadotropin hormone#
U-Albumin (quantification/semi-quantification)	S/P-Albumin
U-Glucose	S/P-Total Protein
U-Blood (dipstick)	
U-White blood cells	
U-human chorionic gonadotropin hormone@	
Other Clinical Safety Panels^ (serum or plasma)	
S/P-Hepatitis B surface Antigen (HBsAg)	
S/P-Hepatitis C virus antibody	

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

* If urinalysis abnormal Microscopy through central laboratory – including white blood cells, red blood cells, and casts.

^ Screening Visit 1 only.

@ Via urine dipsticks.

3.2.2.4 Electrocardiogram Assessments

Triplicate 12-lead ECGs will be performed at timepoints as specified in the SoA in Appendix A. The Investigator will make an overall evaluation of the ECG as normal or abnormal. If abnormal, it will be decided whether or not the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF.

3.2.2.5 Physical Examinations

Physical examination will be performed at timepoints as specified in the SoA in Appendix A and will include:

- A complete physical examination will be performed and include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities) and neurological systems. Weight and body mass index (BMI) will also be collected.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

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.

CCI

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[redacted]

[redacted]

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

All efficacy and safety variables will be summarised by study treatment group using descriptive statistics. For continuous variables, descriptive statistics will include the number of participants (n), mean, SD, median, minimum and maximum. For log-normal variables, descriptive statistics will include n, mean, SD, median, minimum, maximum, geometric mean (GeoMean), and coefficient of variation (CV). Categorical variables will be summarised using frequencies and percentages. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile, and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator, unless otherwise specified. 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".

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

Data will be summarised by-visit as applicable.

'Baseline' is defined as the last value obtained prior to the first dose of study medication, unless otherwise stated. 'End of Study' is defined as the last available post-treatment assessment. 'Study Day' will be calculated relative to the date of randomisation, ie:

If Assessment Date < Randomisation Date, then

$$Study\ Day = Assessment\ Date - Randomisation\ Date$$

If Assessment Date ≥ Randomisation Date then

$$Study\ Day = Assessment\ Date - Randomisation\ Date + 1$$

All visit-based summaries will use analysis visits. All post-randomisation scheduled and unscheduled visits (excluding Discontinuation Visit), will be mapped to an appropriate analysis visit as shown in Table 2.

Table 2 Analysis Visit Windows

eCRF Visit	Target Day	Protocol Visit Window	Actual assessment day	Analysis visit
Visit 3 (randomisation)	D1	D1	D1	Randomisation
Visit 4 (Wk 2)	D15	D12 to D18	D2 to D21	Week 2
Visit 5 (Wk 4)	D29	D26 to D32	D22 to D42	Week 4
Visit 6 (Wk 8)	D57	D54 to D60	D43 to D71	Week 8
Visit 7 (Wk 12)	D85	D82 to D88	D72 to D88	Week 12
Visit 8 (Wk 16)	D113	D110 to D116	D89 to D127	Week 16
Visit 9 (Wk 20)	D141	D138 to D144	D128 to D144	Week 20
Visit 10 (Wk 24)	D169	D164 to D174	D145 to D183	Follow-up

Abbreviations: D = day; eCRF = electronic Case Report Form; Wk = week.

For visit-based summaries, if there is more than one value per participant within a time window, then the closest value will be summarised, or the earliest in the event the values are equidistant from the nominal visit date. The listings will highlight the value for that participant that went into the summary table, wherever feasible.

The Coronavirus Disease of 2019 (COVID-19) pandemic was declared by the World Health Organisation on 11 March 2020. Due to this, some COVID-19 specific summaries will be presented to summarise the impact of the pandemic.

4.3 Software

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

4.4 Study Participants

4.4.1 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:

- A summary of the number of participants screened, screen failures, enrolled into the study, randomised, treated, completing Treatment Period 1, completing Treatment Period 2 and completing the study, by treatment group and overall. In addition, reasons for not being treated, not completing Treatment Period 1, not completing Treatment Period 2 and not completing the study will be summarised by treatment group and overall (Analysis set: All participants).
- A summary of the number of participants randomised per region, country and centre, by treatment group and overall (Analysis Population: Randomised participants).
- A summary of Interactive Voice Recognition System (IVRS) stratification factors ie, DKD status (DKD participants, non-DKD participants), SGLT2i history (with SGLT2i background, without SGLT2i background) and region (Japan, Rest of World) at randomisation by treatment group and overall (Analysis Population: Randomised participants).

By-participant listings of disposition details for discontinued participants and participants completing the study will be provided. In addition, a by-participant listing of the randomisation scheme and codes will be provided.

4.4.2 Protocol Deviations

Important protocol deviations (IPDs) 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 IPDs 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 IPDs.

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

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

- Deviation 1: Participants who did not meet the Inclusion criteria or met Exclusion criteria and received study treatment.
- Deviation 2: Participants assigned to treatment who received their assigned study treatment at an incorrect dose at one or more occasions.
- Deviation 3: Participant received prohibited medication during study treatment period.
- Deviation 4: Met study treatment discontinuation criteria but continued study treatment and potentially had major impact to participants' safety according to clinical judgement.

- Deviation 5: Missed visits, assessments, or treatments that, in the Investigator's opinion, were due to the COVID-19 global pandemic and there was a significant effect on EITHER completeness, accuracy, and/or reliability of the participant's data, OR the participant's rights, safety or well-being.
- Deviation 6: Data in CRF not consistent with source documents and/or discrepancies are not explained.

The number and percentage of participants with any IPD will be summarised for each IPD category based on the full analysis set (FAS). Participants with more than one deviation in the same IPD category will be counted once for that IPD category. Any participants who have deviations in more than one IPD category will be counted once in the overall summary.

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

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

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

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

4.5 Analysis Populations

The following summaries will be provided:

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

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

Table 3 Populations for Analysis

Analysis Populations	Description
Enrolled	All participants who sign the informed consent form.
Full Analysis Population	All participants who are randomised and receive any study drug. Participants are evaluated according to the treatment assigned at randomisation. The Full Analysis Population will be used for all analyses of demographic data, baseline characteristics and efficacy data.
Per Protocol Population	A subset of the Full Analysis Population consisting of all participants who receive the additional treatment with dapagliflozin post-Week 12 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 Population	All participants who are randomised and receive any study drug. 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 Safety Analysis set will be used for all safety analyses, unless otherwise specified.
Extended Safety Analysis Population	A subset of the Safety Analysis Population consisting of all participants who receive the additional treatment with dapagliflozin post-Week 12.
Ambulatory Blood Pressure Monitoring Population	All participants in the Full Analysis Population who have valid ambulatory blood pressure data for change from baseline analyses.

4.5.1 Analysis Sets

Analysis sets consist of two components: (1) analysis population (See Section 4.5), which specifies the participants included in an analysis; (2) data period, defining the time period during which data will be included in the analysis.

Analysis Set	Analysis Population	Data Period
Full Analysis Set	Full Analysis Population	Day 1 to the end of the follow-up period
Per-Protocol Set	Per-Protocol Population	Day 1 to the end of the follow-up period
Safety Analysis Set	Safety Analysis Population	Day 1 to the end of the follow-up period
Monotherapy Safety Analysis Set	Safety Analysis Population	Day 1 to the end of the first treatment period
Extended Safety Analysis Set	Extended Safety Analysis Population	Day 1 to the end of the follow-up period with flag to subset Week 12 to the end of the follow-up period

The Extended Safety Analysis Set includes participants who entered the second treatment period. The Week 12 flag is added to the Extended Safety Analysis Set to allow subsetting of participant data to be from Week 12 to end of study.

4.6 Demographic and Other Baseline Characteristics

Age will be calculated as the number of complete years between a participant's birth date and the date of informed consent.

Demographic and other baseline characteristics will be listed for all participants and summarised for the Full Analysis Population, as:

- Demographics
  - age (years),
  - age group (< 50, ≥ 50 to < 65, ≥ 65 to < 85, ≥ 85 years),
  - sex, race (if collected),
  - country,
  - ethnicity.
- Participant characteristics at baseline
  - height [cm],
  - weight [kg],
  - weight groups (< 40, ≥ 40 - < 75, ≥ 75 - < 90, ≥ 90 - < 120, and ≥ 120 kg),
  - body mass index (BMI),
  - BMI groups: Underweight (<18.5 kg/m^2), Normal weight (= 18.5 - < 25.0 kg/m^2), Overweight (= 25.0 - < 30.0 kg/m^2), Obese (≥ 30.0 kg/m^2).
- Baseline disease characteristics
  - Type 2 Diabetes Mellitus (T2DM) diagnosis (Y/N)
  - T2DM duration (years),
  - CKD stage (eGFR category): Stage 2 (60–89 mL/min)/Stage 3a (45–59 mL/min)/ Stage 3b (30–44 mL/min)/Stage 4 (15–29 mL/min)/Stage 5 (<15 mL/min),
  - eGFR (mL/min/1.73m^2),
  - albuminuria (defined as 200 -5000 mg albumin/g creatinine; count and percentage of participants meeting criteria),
  - SGLT2i history (background/no background),
  - primary renal diagnosis: Cystic kidney disease, Diabetic nephropathy, Ischaemic/Hypertensive nephropathy, Chronic glomerulonephritis, Renal artery stenosis, Chronic pyelonephritis (infectious), Chronic interstitial nephritis, Obstructive nephropathy, Unknown, Other (Specify),
  - Chronic glomerulonephritis type: IgA nephropathy, Focal segmental glomerulosclerosis (FSGS), Lupus nephritis, Membranous nephropathy, Minimal change, Other primary or secondary glomerulonephritis,
  - Angiotensin Converting Enzyme Inhibitors (ACEi)/ Angiotensin II Receptor Blockers (ARB) history (Y/N))
- A summary and a list of participants by site and country will be provided.

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

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

4.7 Concomitant Medication

Any medication or vaccine (including over-the-counter or prescription medications, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study will be recorded as concomitant. Medications starting after the completion/withdrawal date of study will be listed but will not be classified or summarised.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of enrollment. 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 enrollment. If there is clear evidence to suggest that the medication started prior to enrollment, the medication will be assumed to be both prior and concomitant, unless there is clear evidence to suggest that the medication stopped prior to enrollment. If there is clear evidence to suggest that the medication stopped prior to enrollment, the medication will be assumed to be prior only.

The frequency and percentage of participants receiving rescue medication during the treatment periods will be presented by treatment group. A by-participant listing will also be presented for all rescue medications taken during the treatment periods, by treatment group.

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

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

The type of medication in terms of common concomitant, anti-diabetic, and heart failure related medication will be derived from the CRF module assigned to the respective type of medication. A by-participant listing of concomitant medications at study entry and taken during treatment will be presented.

A by-participant listing of medications not started due to the COVID-19 pandemic will be presented.

4.8 Treatment Compliance

Treatment compliance will be assessed using two methods:

- Counting the number of AZD5718/placebo and dapagliflozin tablets dispensed to and taken by each participant, providing an overall percentage of treatment compliance for the study.
- Summarising instances of dose interruptions lasting 3 or more consecutive days.

Participants will be requested to return all unused study medication and empty packages to the clinic at each visit. The amount of dispensed and returned study medication will be recorded in the eCRF. The percentage treatment compliance will be calculated from the dose as:

$$\frac{Overall\ amount\ of\ dose\ actually\ taken}{Overall\ amount\ of\ dose\ planned} \times 100$$

Participants taking ≥ 80% and ≤ 120% of planned study medication are considered to be compliant. Overall study compliance percentage will be summarised as follows:

- Descriptive statistics will be summarised by the four treatment groups and overall.
- Percent compliance will be categorised according to the following three categories:
  - < 50% or ≥ 150% (significant drug non-compliance)
  - ≥ 50% and < 80% or > 120% and < 150% (moderate drug non-compliance)
  - ≥ 80%, ≤ 120% (drug compliance)

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

A separate compliance measure is to be defined as dose interruptions which last three or more days. This will indicate severe non-compliance.

A summary of the number of occurrences of drug interruptions lasting three or more consecutive days, by treatment group and treatment period. A by-participant listing of all participants who have at least one instance of a dose interruption of three or more consecutive days will be presented.

4.9 Efficacy Evaluation

4.9.1 Analysis and Data Conventions

This study is designed to test for superiority and assess the dose-response relationship. The null hypothesis for the treatment comparison will be that there is no difference between AZD5718 with dapagliflozin and placebo with dapagliflozin on urine ACR. The alternative hypothesis will be that there is a difference. Symbolically, this is expressed as follows:

H(0): μ(AZD5718+dapagliflozin) = μ(placebo + dapagliflozin)

H(1): μ(AZD5718+dapagliflozin) $\neq$ μ(placebo + dapagliflozin)

A 2-sided test with $\alpha = 0.1$ will be used to test this hypothesis.

4.9.1.1 Dose-response Testing

Not applicable for this study. See Section 4.14 for further details.

4.9.1.2 Multi-centre Studies

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

4.9.1.3 Adjustments for Covariates

The primary efficacy analysis will be adjusted for the following baseline covariates:

1. DKD status (stratification variable)
2. SGLT2i history (stratification variable)
3. Visit
4. Baseline measure of log (urine albumin to creatinine ratio [UACR])
5. Treatment-by-visit interaction
6. Baseline log (UACR)-by visit interaction

Strata with low counts (<5 participants in a stratum) will be pooled with adjacent strata.

4.9.1.4 Handling of Dropouts or Missing Data

Summary statistics will be based on non-missing values. For analyses of UACR, if a measurement is missing it will not be imputed. Missing safety data will generally not be imputed. However, safety assessment values (vital signs, laboratory assessments excluding urine albumin, urine creatinine and UACR) of the form of "< x" (ie, below the lower limit of quantification) or > x (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings. Measurements of urine creatinine, urine albumin and UACR which are displayed as "< x" or "> x" will be imputed by Covance Central Laboratory in order to effectively calculate the geometric mean.

Partial or missing dates

If the start date of the concomitant medication, medical history relating to T2DM diagnosis or AE is missing, the following rules will be applied:

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

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

- If the year is missing, the year should be imputed as the year that participant received the last dose of study treatment.
- If the year is available and the month and day are missing, then impute the month as December and the day as 31.
- If the year and month are available and the day is missing, impute the day as the last day of the month (eg, 28, 29, 30, or 31).
- It is not expected to have missing dates for unscheduled laboratory or ECG data. However, if there are missing dates, for any derivations, the dates should be imputed following the rules for concomitant medications and AEs.

4.9.1.5 Interim Analyses

An administrative interim analysis will be conducted when approximately 211 participants have completed the 20-week treatment period. See Section 4.12 and Appendix B for further details

4.9.1.6 Examination of Sub-groups

Sub-group analyses for the primary efficacy endpoint by SGLT2i background and by DKD status will be presented. Summaries of the primary efficacy variable by treatment group and sub-group will also be produced. No formal statistical analysis will be performed within these sub-group.

A forest plot will present the least-squares mean and 90% CI overall and for each sub-group individually. These will be taken from the primary analysis model.

4.9.2 Primary Efficacy Variable – *UACR*

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 per protocol population. The endpoint being assessed is the change in log-transformed urine ACR from baseline to Week 20. For the intercurrent event, if a participant discontinues treatment due to AE or lack of efficacy, or uses prohibited medication, the urine ACR data are treated as missing after the event and no imputation is performed. The summary measure being evaluated is the geometric mean reduction of urine ACR from baseline to Week 20.

4.9.2.1 Primary Analysis

The primary efficacy endpoint for this study is the reduction of urine ACR from baseline to Week 20 compared to placebo (on treatment with dapagliflozin as future standard of care). As urine ACR is assumed to follow a log-normal distribution, it will be log-transformed for statistical analysis purposes. The mean log changes in urine ACR at Week 20 ($\hat{Y}_1$, $\hat{Y}_2$, $\hat{Y}_3$, $\hat{Y}_4$) for each of the 3 AZD5718 doses and placebo will be estimated in a mixed model for repeated measures [MMRM] (Weeks 2, 4, 8, 12, 16, and 20). The values will be back transformed onto the original scale to give the geometric mean relative change from baseline at Week 20. 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 (urine ACR) and baseline log (urine ACR)-by-visit interaction. An unstructured covariance structure will be used for the within-participant errors. A homogeneity assessment between the DM and the non-DM sub-populations will be performed. Denominator degrees of freedom will be estimated using the Kenward-Roger approximation. If the MMRM model does not converge using an unstructured covariance structure, the heterogeneous Toeplitz covariance structure will be evaluated, followed by the heterogeneous autoregressive of first order, heterogeneous compound symmetry, and homogeneous compound symmetry covariance structures in the case of further non-convergence. If none of the models converge, the analysis will be altered to use an analysis of covariance (ANCOVA) with last observation carried forward (LOCF) imputation method implemented.

The point estimates from the model, including the 95% CIs and p-values will be presented. The point estimate and 95% CI for the geometric mean ratio will be converted to the percentage change as follows:

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

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

The primary analysis will be repeated by strata (DKD without SGLT2i background, DKD with SGLT2i background, non-DKD), with the analysis model will include the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, plus the continuous covariates of baseline log (urine ACR) and baseline log (urine ACR)-by-visit interaction.

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

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

4.9.3 Secondary Efficacy Variables

4.9.3.1 UACR at 12 Weeks

Urine ACR will be analysed to determine the dose-response effect of AZD5718 at 12 weeks (on current standard of care). The population of interest are randomised participants who meet all eligibility criteria and have valid non-missing urine ACR records at baseline and at least one post-treatment visit. The mean log change from baseline in urine ACR will be analysed using a mixed model for repeated measures. The summary measure being evaluated is the geometric mean reduction of urine ACR from baseline to Week 12. This will be evaluated using the same methods for the primary efficacy endpoint. The analysis will be repeated on the Per-Protocol Analysis Population.

The results of the model parameters (estimates, p-values, and 95% CIs) will be presented. The point estimate and 95% CI for the geometric mean ratio will be converted to the percentage change as follows:

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

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

The analysis will be repeated by strata (DKD without SGLT2i background, DKD with SGLT2i background, non-DKD), with the analysis model will include the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, plus the continuous covariates of baseline log (urine ACR) and baseline log (urine ACR)-by-visit interaction.

4.9.3.2 Estimated GFR

Estimated GFR will be analysed, comparing eGFR at baseline with that at 12 weeks, to determine whether there is any acute change with the introduction of AZD5718 to inform planning for a GFR slope analysis in Phase 3. This will be analysed using a by-visit ANCOVA, adjusting for DM stratification factor, treatment group and baseline eGFR. The FAS will be used for this analysis and eGFR will be evaluated on the original scale. The analysis will be repeated on the Per-Protocol Analysis Population.

The results of the by-visit ANCOVA will be presented by treatment group. A summary of change from baseline of eGFR results will be presented by treatment group and a by-participant listing provided of eGFR results at each visit. Plots of the least-squares mean by treatment group over time, and the mean eGFR over time up to follow-up visit will be presented.

An ANCOVA model will be produced for eGFR up to Week 20, analysed on the Per-Protocol Analysis set, similarly to that described above.

The analysis will also be repeated by strata (DKD without SGLT2i background, DKD with SGLT2i background, non-DKD), adjusting for treatment group and baseline eGFR.

4.9.3.3 Ambulatory Blood Pressure Monitoring

For drugs intended for chronic use, the US Food and Drug Administration (FDA) recommended use of ambulatory blood pressure monitoring (ABPM) to assess the sustained BP effect (FDA guidance on Assessment of Pressor Effects of Drugs, May 2018). The collection and the analysis of the ABPM data in this study is aimed to delineate differential BP effect of AZD5718 relative to placebo.

The device will be provided to the participants at the visits outlined in the SoA in Appendix A (Screening Visit 2 and Visit 6 [Week 8]). They will be instructed to perform the ABPM 24-hours before their next visit, ie, Visit 3 (Week 1) and Visit 7 (Week 12), respectively. The ABPM recording must have finished prior to dosing at each specified visit.

If the 24-hour ABPM assessment session provided at a visit is confirmed to not meet the validity criteria, the associated study visit may be rescheduled to allow for a repeat ABPM recording only if the rescheduled visit can be completed within the specified tolerance period for study visits, as described in the SoA in Appendix A. An assessment session is valid if there is a minimum of 20 hours of the recording with at least 70% of expected measurements being successful. If the repeated assessment session is not valid using the same validity criteria, no further repeats will be performed for that visit. This criterium for the validity of measurements will only be used on site to reschedule the ABPM assessment session. The inclusion criteria for the statistical analysis are separate and are described in the following paragraph.

Recordings will be done every 20 minutes during the day-time (06:01 to 22:00) and every 30 minutes during the night-time (22:01 to 06:00). These definitions of day-time and night-time are only to be used on site for collecting recordings; they will be defined differently for the purpose of statistical analyses.

For the purpose of inclusion in the statistical analyses, the session needs to satisfy two conditions:

1. There should be at least 50% of successful measurements in both day-time (06:01 to 22:00) and night-time (22:01 to 06:00). If both the scheduled and repeat assessment sessions have more than 50% of successful measurements in the respective timeframes, the assessment session with a higher overall percentage of successful measurements will be included in the analyses. In the unlikely event that both the scheduled and repeated assessment sessions have the same percentage of successful measurements (and both above 50%), the scheduled assessment session will be taken as the visit assessment.
2. There are not more than two consecutive hours with no available measurements in an ABPM assessment session.

Primary ABPM Analysis

The primary endpoint in the analysis is the change from baseline in 24-hour mean SBP at Week 12. Participants with missing mean 24-hour SBP at Week 12 will be excluded from the analysis.

In order to derive the mean SBP over various time periods, the hourly mean SBP is derived for each participant for each hour using the available data at the visit. This is the sum of the successful non-missing SBP measurements in the hour, divided by the number of non-missing SBP measurements in the respective hour. This derivation will be used to further derive the endpoints of interest.

The 24-hour mean SBP is derived as the sum of the non-missing hourly mean SBP measurements, divided by the number of hours with non-missing hourly mean SBP. Missing hourly mean SBP derivations will not be counted towards the 24-hour mean.

For the ABPM analysis, baseline for the 24-hour mean ABPM parameter (or mean day-time, mean night-time, mean hourly) is defined as the 24-hour mean value (or corresponding mean day-time value, mean night-time value, mean hourly value) during the Screening Visit 2.

The change from baseline in 24-hour mean SBP at Week 12 will be analysed using an ANCOVA model, with change from baseline in 24-hour mean SBP as the dependent variable, adjusting for DM stratification factor, treatment group (AZD5718 CCI mg, AZD5718 CCI mg, AZD5718 CCI mg, placebo), plus baseline 24-hour mean SBP and BMI as covariates. The ambulatory blood pressure monitoring population will be used for this analysis. The least squares (LS) mean difference between each of the AZD5718 doses and placebo (ie, placebo-corrected change from baseline in 24-hour mean SBP) will be derived from the model. The 2-sided 90% CI for these differences will be presented.

If the proportion of participants within a sub-group category is too small for effective analyses, sub-group categories can be collapsed or removed from the sub-group analyses, where appropriate.

The change from baseline in 24-hour mean DBP at Week 12 will be analysed similarly to the primary endpoint using an ANCOVA model. The 2-sided 90% CI for the difference between each of the AZD5718 doses and placebo will be derived from the model and presented.

Sensitivity ABPM Analysis – 24-hour Mean SBP

The proportion of missingness of ABPM data (the number of participants who did not meet either of the statistical validity criteria at baseline and Week 12) will be summarised by treatment group and by key baseline characteristics (age group, race, BMI group, and randomisation strata).

Secondary ABPM Analysis

The secondary ABPM endpoints are change from baseline in mean day-time and mean night-time ABPM metrics (SBP and DBP), these will be evaluated similarly to the primary ABPM endpoint using ANCOVA models, presenting only the 90% CI between each of the AZD5718 doses and placebo. No formal hypothesis testing will be performed. Day-time is defined as 09:00 to 21:00, night-time is defined as 01:00 to 06:00.

The mean day-time SBP will be derived as the sum of the hourly mean SBP from 09:00 to 21:00 divided by the total number of hours with non-missing data. The mean night-time SBP will be derived as the sum of the hourly mean SBP from 01:00 to 06:00 divided by the total number of hours with non-missing data. The same derivations will be performed for DBP. Summary statistics will be presented for mean day-time and night-time values.

By-participant listing for ambulatory blood pressure monitoring values and derivations will be presented by treatment group and visit.

4.10 Safety Evaluation

All safety summaries and analyses will be based upon the Safety analysis set as defined in Section 4.5, unless otherwise specified. Safety summaries will be presented by treatment group and with a pooled AZD5718 group, where appropriate.

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.

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

Outputs presented on the Extended Safety Analysis Set will include the Week 12 flag to subset for data in the second treatment period. These outputs may be repeated without the Week 12 flag if deemed appropriate by the study team, thereby including all data for participants who continued into the second treatment period only.

4.10.1 Extent of Exposure

The extent of exposure (days) will be derived as follows for AZD5718 and for dapagliflozin:

$$Duration\ of\ exposure[AZD5718]\ (days) = Date\ of\ last\ dose[AZD5718] - Date\ of\ first\ dose[AZD5718] + 1$$

$$Dur.\ of\ exp.\ to\ dapagliflozin\ (days) = Date\ of\ last\ dose[dapagliflozin] - Date\ of\ first\ dose[dapagliflozin] + 1$$

The following extent of exposure summaries will be provided separately for AZD5718 and for dapagliflozin:

- A summary of the duration of exposure to treatment (days) and cumulative exposure over time (≥ 1 day, ≥ 28 days, ≥ 57 days, ≥ 85 days, ≥ 120 days), by treatment group.
- Total exposure to study treatment (days) = (min(last dose date, death date) - first dose date +1) / (365.25)
- Time on study – defined as the time in days from the start date of treatment to the date of last study assessment or the date of withdrawal.

A summary of duration of exposure to treatment (days) will also be presented for the Monotherapy Safety Analysis Set and the Extended Safety Analysis Set with Week 12 flag.

The following summaries will be produced for the Safety Analysis Set, by treatment group:

- Number of and reasons for dose interruptions

4.10.2 Adverse Events

Adverse events will be coded using MedDRA version 23.0 or later.

An AE (classified by preferred term) started during the treatment period will be considered a treatment-emergent adverse event if it was not present prior to the first dose of randomised treatment. An AE that starts more than 7 days after the last dose of study medication will not be counted as a treatment-emergent AE. AEs which worsen after the start of treatment will not be included as a treatment-emergent AE but will be recorded.

Adverse events (and also separately SAEs) will be summarised by study treatment group in incidence summaries by MedDRA SOC and PT. Adverse events will be assigned to the period where they start and will be summarised for the Safety Analysis Set, with selected outputs summarized for the Monotherapy Safety Analysis Set and Extended Safety Analysis Set with Week 12 flag. Serious adverse event collection will begin after the participant signs the informed consent document, and all AE collection will begin after the participant has received the first dose of the study drug. The SAE/AE collection will last until the end of the participant's follow-up period.

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

- Prior treatment: The SAE occurred before the first administration of study drug. Only applicable for SAEs.
- On treatment: The AE occurred on or after the first administration until 7 days after last dose of AZD5718 and/or dapagliflozin.
- Off treatment: The AE occurred more than 7 days after the last dose of study drug.

The number, percentage and percentage per participant exposure year (PEY) of participants reporting treatment-emergent AEs in each treatment group will be tabulated by SOC and PT; by SOC; by SOC, PT, and relationship to study medication as assessed by the Investigator. If more than one event occurs with the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarisation by severity and by relationship to the study medication.

The event rate per 100 PEY is defined as:

$$\left(\frac{number\ of\ subjects\ with\ AE}{sum\ of\ days\ at\ risk\ for\ AE\ in\ treatment\ period + 7\ days}\right) \times 365.25 \times 100$$

The denominator is calculated per participant then summed. The distribution of treatment-emergent AEs by severity and relationship to study medication will be summarized by treatment group.

A summary of AEs in any category will be presented by treatment. The incidence of common (≥5% of participants in any treatment group) treatment-emergent AEs, common treatment-emergent serious AEs, and AEs leading to discontinuation of study medication will be summarized by SOC, PT and treatment group, sorted in decreasing overall (across treatments) frequency. Treatment-emergent AEs with outcome of deaths will also be presented. In addition, all fatal SAEs (ie, events that caused death) will be summarized. For each participant and each AE, the worst intensity recorded will be attributed and used in the by-intensity summaries. Similarly, the worst causality will be attributed and used in the by-causality summaries. Multiple occurrences of a treatment-emergent AE in the same participant will only be counted once overall. Non-serious treatment-emergent AEs occurring in more than 5% of participants will be presented by treatment.

The number and percentage of participants reporting AEs by treatment group, SOC and PT will also be presented for the Monotherapy Safety Analysis Set and the Extended Safety Analysis Set with Week 12 flag.

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

4.10.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

The following summaries will be provided:

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

The number and percentage of participants reporting a treatment-emergent AE leading to death, and SAEs by treatment group, SOC and PT will also be presented for the Monotherapy Safety Analysis Set and the Extended Safety Analysis Set with Week 12 flag.

4.10.4 Clinical Laboratory Evaluation

The following summaries will be provided:

- A summary of the observed absolute values and change from baseline in each haematology and clinical chemistry laboratory parameter by treatment group and time point.
- A summary of baseline versus maximum observation on treatment in each laboratory parameter by treatment group (shift table)
- A summary of baseline versus minimum observation on treatment in each laboratory parameter by treatment group (shift table)
- A summary of key participant information for participants reporting changes outside reference ranges in each laboratory parameter
- A summary of the number and percentage of participants reporting changes outside reference ranges in each laboratory parameter
- A plot of alanine aminotransferase (ALT) versus total bilirubin, expressed as multiples of upper limit of normal (ULN)
- A plot of aspartate aminotransferase (AST) versus total bilirubin, expressed as multiples of ULN
- A plot of liver biochemistry over time, for participants with potential Drug Induced Liver Injury (ie, ALT/AST $\geq$ 3 x ULN and total bilirubin (BILI) $\geq$ 2 x ULN, and in which the elevation in transaminases precede or coincide with (that is, on the same day as) the elevation in BILI or ALT/AST $\geq$ 5 x ULN)
- A summary of the number and percentage of participants reporting maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's Law criteria
- A summary of individual participant data for participants with Potential Hy's Law ie, participants with combined ALT or AST, and bilirubin elevations
- A summary of treatment-emergent laboratory changes will be presented for the Safety Analysis Set, the Monotherapy Safety Analysis Set (Treatment Period 1) and the Extended Safety Analysis Set with Week 12 flag (Treatment Period 2).

Treatment-emergent laboratory and vitals change (TELVC) limits of interest for this study are provided in Appendix C for the laboratory parameters, and in Table 5 for vital signs.

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

4.10.5 Vital Signs, Physical Findings and Other Observations Related to Safety

ECG measurements will be evaluated by the clinician at each visit described in the SoA in Appendix A as either normal or abnormal. Number and percentage of participants with normal and abnormal ECG readings by visit will be presented by treatment group. Abnormal ECG results and reasons entered into the CRF will be listed by participant and by visit.

Potentially clinically significant (PCS) ECG values will be identified from Third Party Vendor data collected. The predefined criteria (based on severity) for PCS ECG values are displayed in Table 4.

Table 4 Potentially Clinically Significant 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*		

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

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 5.

Table 5 Vital Sign Notable Change Predefined Criteria

Vital sign		Observed value	Notable change from baseline
Systolic BP (mmHg)	High	≥ 140	Increase of ≥ 20

	Low	< 90	Decrease of ≥ 20
Diastolic BP (mmHg)	High	≥ 90	Increase of ≥ 10
	Low	< 60	Decrease of ≥ 10
Pulse Rate (bpm)	High	≥ 110	Increase of ≥ 20
	Low	< 50	Decrease of ≥ 20
Pulse Oximetry	High	N/A	N/A
	Low	< 90%	Decrease of ≥ 5%

BP = blood pressure.

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

The following summaries will be provided:

- A summary of the observed absolute 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.
- A summary of the observed absolute values and change from baseline in each ECG parameter by treatment group and time point. Both pre- and post-investigational medicinal product (IMP) measurements will be presented at each time point.
- A summary of the number and percentage of participants with QTcF intervals exceeding predefined upper limits (as stated in Table 4).
- A summary of ECG assessment (normal/abnormal [clinically significant, not clinically significant]), baseline versus last observation on treatment. Post-IMP measurement at last observation on treatment will be used.
- A summary of key participant information for participants reporting PCS ECG values outside predefined criteria by treatment group and visit.
- A summary of the number and percentage of participants reporting PCS ECG values outside predefined criteria, by ECG parameter and treatment group.

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

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.

4.10.6 Safety Monitoring

This is not applicable for this study.

4.11 Other Analyses

4.11.1 Pharmacokinetics

Following the early termination of the FLAIR study, it was confirmed that all PK analysis (AZD5718 and Dapagliflozin) is no longer required for Final Analysis.

4.11.2 Retinal Sub-Study

The retinal study to be performed on eligible DKD study participants will provide descriptive summaries of BCVA and OCT, as described in Section 3.2.3.1. Summary statistics and change from

baseline will be presented by visit for each treatment group. The baseline assessment is taken during screening.

Cataract assessments will be presented by visit for each treatment group.

By-participant listings of CCI and CCI measurements will be presented by treatment group and visit for DKD participants only.

4.12 Interim Analysis

An administrative interim analysis will be performed for this study when approximately 211 participants have reached Week 20. A separate review committee of AstraZeneca representatives will review the unblinded interim outputs. The design and the conduct of the study will not be impacted by the results observed at the interim. The main study team will remain blinded for the duration of the study.

The blinding maintenance plan (BMP) will document study roles which have access and will receive unblinding study data. Unblinded data will be received for the interim analysis and following unblinding for DBL. A separate unblinded study team will be implemented at Parexel to run and deliver unblinded outputs to a separate independent unblinded team at AstraZeneca. Further detail of the logistics of the interim within AstraZeneca are included in the interim analysis charter, which will be stored in the AstraZeneca eTMF.

The interim analysis will be performed on clean data, such that the data for the participants included in the interim analysis will be cleaned and fully coded, where appropriate. The outputs for the interim analysis will be a subset of the outputs for the primary analysis. These will be clearly marked in the mock shells. Further details are provided in Appendix B.

4.12.1 Early Termination of Study

Following the results observed at the interim analysis, it was confirmed by sponsor to terminate the study due to lack of efficacy. There were no safety concerns related to the study. All participants who were on-going in the study were allocated early termination visits. The main study team remained blinded to treatment allocation for the final analysis. Details of changes to planned analysis from those outlined in the protocol are highlighted in Section 4.14. This includes the removal of MCP-Mod analysis, and all PK analysis from the final analysis.

4.13 Determination of Sample Size

For the primary endpoint, a total of 142 evaluable participants per group will provide CCI power to detect a placebo-adjusted CCI reduction in urine ACR from baseline between AZD5718 CCI mg and placebo group with CCI, assuming a SD of CCI on the natural log-scale. It will also assure at least CCI power to detect the same urine ACR reduction and the significance of dose-response over multiple dose-response models in the DKD sub-population. To account for approximately CCI discontinuation, 158 participants per group will be enrolled.

The sample size was calculated using nQuery (version 8.2.0.0) and validated using EAST (version 6.4.1).

4.14 Changes in the Conduct of the Study or Planned Analysis

Following the results from the interim analysis, it was decided to terminate the study early and reduce the scope of analysis. This decision led to the removal of the MCP-Mod analysis as outlined in the protocol, and the previously described sensitivity analysis for the ABPM analysis. The statistical analysis plan has been updated to include only the analysis which will be performed following database lock.

Pharmacokinetic analyses of AZD5718 and dapagliflozin were also removed from the final analysis. The statistical analysis plan has been updated to reflect this.

Due to the early termination of the study, the total number of randomised participants is 613 with 340 participants completing treatment. Therefore, efficacy analyses should be evaluated with caution due to lack of power.

The total study duration, as highlighted in Section 3.1, will vary following study termination, up to a maximum of 28 weeks.

5 REFERENCES

FDA, 2018

FDA Guidance: Assessment of Pressor Effects of Drugs, May 2018.

6 APPENDIX

Appendix A: Schedule of Activities

Table 6 Schedule of Activities

Study Period	Screening		Treatment Period 1				Treatment Period 2			Discontinuation	Follow-up
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**
Study Day	**-32 to -3**		**1**	**15±3**	**29±3**	**57±3**	**85±3**	**113±3**	**141±3**		**169±5**
Study Week	**-4 to 0**		**1**	**2**	**4**	**8**	**12**	**16**	**20**		**24**
Informed consent (main)	X										
Informed consent (optional) for genetic and biomarker research	X										
Verify eligibility criteria	X	X	X				X[a]				
Demography	X										
Full physical examination including height, weight and BMI	X[b]		X		X		X		X	X	X
Physical examination (abbreviated)				X		X					
Medical history	X										
Serum hCG, FSH and LH[c]	X										
Pregnancy test[c]			X								
Drug and alcohol screen	X										
Hepatitis B and C screening	X										
Spot urine for ACR	X										
Safety laboratory assessments (Clinical chemistry, haematology, coagulation, urinalysis)[d]	X		X[e]	X	X	X	X	X	X[e]	X[e]	X
12-lead ECG	X		X	X	X	X	X	X	X	X	X
Vital signs[f]	X		X	X	X	X	X	X	X	X	X
Randomisation			X								
Retinal study (**optional DKD sub-group only**)[g]	X						X				
HbA1c[h]	X								X		
Calculation of eGFR	X		X	X	X	X	X	X	X	X	X
Blood sample for cystatin-C	X		X	X	X	X	X	X	X	X	X

Study Period	Screening		Treatment Period 1				Treatment Period 2			Discontinuation	Follow-up
Visit Number	1	2	3	4	5	6	7	8	9		10
Study Day	-32 to -3		1	15±3	29±3	57±3	85±3	113±3	141±3		169±5
Study Week	-4 to 0		1	2	4	8	12	16	20		24
Pharmacokinetics plasma sample for AZD5718				X (pre-dose)	X[i] (pre-dose)	X (pre-dose)	X (pre-dose)	X (pre-dose)	X (pre-dose)	X (pre-dose)	
Pharmacokinetics plasma sample for dapagliflozin								X (pre-dose)	X (pre-dose)		
CCI		X	X		X		X		X		
CCI			X		X		X	X	X	X	
Plasma, serum, and urine for future use (optional)[j, h]			X		X		X		X	X	
Blood sample for genomic initiative (optional)[j]			X								
Dispense supply of containers for urine samples	X	X	X	X	X	X	X	X	X		
E-Diary, dispensation and completion of diary[k]			X	X	X	X	X	X	X	X	X
Reminder to collect first morning void urine samples, 3 days before visit[l]	X	X	X	X	X	X	X	X	X	X	
Urine samples for ACR[h, m]		X	X	X	X	X	X	X	X	X	X
24-hour ABPM, provision and completion		X[n]	X[o]			X[n]	X[o]				
Study drug dispensation[p]			X		X	X	X	X			
Study drug returned[p,q,r]					X	X	X	X	X	X	
Study drug intake in study centre			X	X	X	X	X	X	X	X	
Assessment of AEs/SAEs	Only SAEs		X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X

a Any participant with urine ACR < 30 mg/g at Week 12 will be excluded from Treatment Period 2. The eligibility check to enter Treatment Period 2 will be done at Visit 7 (Week 12) using the last available urine ACR result, calculated as the geometric mean of the replicated measurements using 3 sequential first morning urine voids.

b Full physical examination will be completed at the indicated visits, with the exception that height will only be recorded at Screening Visit 1.

c Serum hCG, FSH, and LH tests, and a urine dipstick pregnancy test are required for all women.

d Except for Screening Visit 1, participants should be requested to be in a fasting state (except water) for at least 8 hours prior to sample collection and samples should be collected in the morning.

e To include thyroid function tests (TSH, fT4 and fT3).

f All vital signs (blood pressure, heart rate, respiratory rate, body temperature and pulse oximetry) will be measured with the participant in a supine position having rested for at least 10 minutes before each reading and should be taken before any blood draws. Vital signs should be collected pre-dose on the days of study drug dosing.

g Optional, to be conducted only at study centres with the appropriate facility to conduct the assessment. There is no requirement for all participants at centres undertaking the sub-study to participate.

h To be collected prior to study drug administration.

h Containers to be dispensed at any study visit as required.

i At specific PK sampling sites, for a sub-group of at least 80 participants (20 per dose group including placebo), 4 additional PK samples will be collected at this visit within 1-2 h, 2-5 h, 5-8 h, and 8-12 h post-dose. Pre-dose samples will be collected for all participants. Each PK sample must be separated by at least 1 h.

j Only if consent is obtained. The blood sample for Genomic Initiative will be obtained from the participants at Visit 3 prior to study drug administration (at or after randomisation). If for any reason the sample is not drawn at Visit 3, it may be taken at any visit window until the last study visit. Only 1 sample should be collected per participant.

k Participants will be requested to download an e-Diary application on their smartphones starting from Visit 3, in order to set study reminders and capture drug accountability throughout the treatment period, at sites where applicable. If needed, participants may be provided with a smartphone in order to use the application. Participants will be trained on how to use the application/device and the site will help the participants to login into the application for the first time. Data will be available to the site/Sponsor in real time. The participants who received a smartphone to use the e-Diary will return the smartphones at the last visit. Prior to deleting the e-Diary application from their personal smartphone, or returning a site provided smartphone, the participants will be requested to complete a satisfaction survey through the application (this survey is only applicable for e-Diary). When completion of an e-Diary is not applicable, participant will be requested to complete a paper dosing diary.

l Phone call will occur after results from Screening Visit 1 are available and the participant is confirmed eligible in order to remind the participant to collect the first morning void urine samples and schedule the Screening Visit 2. If scheduled Visit 3 (Week 1) or Visit 7 (Week 12) will need to be delayed due to the need to repeat ABPM recording there is no need to repeat collection of the 3 urine samples.

m Participants to collect first morning void urine samples on 3 consecutive dates (ideally day of visit and each of the preceding 2 days [refrigerated overnight] which are returned on the day of visit). This collection may be repeated once during the course of screening.

n Participants will be provided an ABPM cuff at Screening Visit 2 and Visit 6 (Week 8) and instructed to perform ABPM 24-hours before their next visit ie, Visit 3 (Week 1) and Visit 7 (Week 12), respectively. Site will be asked to call the participant the day prior to next visit as a reminder to complete assessments. The participant may also visit the site for ABPM cuff placement 1 day before their next visit of scheduled assessment (i.e., Visit 3 [Week 1] and Visit 7 [Week 12], respectively)

o Sites should ensure that the validity criterion described in Section 8.2.5 (CSP) is met prior to completing any other assessments at the visit. If the validity criterion is not met, the associated study visit may be rescheduled to allow for a repeat ABPM recording only if the rescheduled visit can be completed within the specified tolerance period for study visits:

- Visit 3: up to 72 hours following the originally scheduled visit for Visit 3 but no more than 32 days from Screening Visit 1.
- Visit 7: ±72 hours from Day 85.

If a repeat ABPM session is not possible, the study visit should proceed as indicated. In addition, the visit should also continue if the ABPM session does not meet the validity criterion after the repeat session.

p Study drugs refer to AZD5718/placebo during Treatment Period 1 and AZD5718/placebo + dapagliflozin during Treatment Period 2.

q Site should follow-up directly with the participant via phone to remind the participant.

r Participants to return all study drug dispensed at previous visits and only use the newly dispensed study drug. Participants should be reminded not to take study drug on the days of a study visit until instructed by the study site.

NOTE: All laboratory assessments are to be performed in central laboratories, except for tests completed using dipsticks and drug and alcohol screen tests which will be done locally. Laboratory kits used locally will be provided by the central laboratory.

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

Abbreviations: ABPM = ambulatory blood pressure monitoring; ACR = albumin to creatinine ratio; AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CKD = chronic kidney disease; CSP = clinical study protocol; DKD = diabetic kidney disease; ECG = electrocardiogram; e-Diary = electronic Diary; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; fT3=free triiodothyronine; fT4=free thyroxine; h = hour, HbA1c = glycated haemoglobin; hCG = human chorionic gonadotropin; LH = luteinising hormone; CCI [redacted]; PK = pharmacokinetic(s); SAEs = serious adverse events; TSH=thyroid stimulating hormone.

Appendix B: Interim Analysis Plan

This section stipulates definitions of analysis sets, key efficacy endpoints and statistical methods for the interim analysis.

The administrative interim analysis is planned when about 200 participants have completed their 20-week treatment. The purpose of the interim analysis is to trigger the activities related to the Phase 3 program, it will not impact the design and the conduct of FLAIR.

B.1. Analysis Sets

Analysis Set	Analysis Population	Data Period
Interim Safety	The cohort of the first 240 participants who had been randomised and took at least one dose of study medication.	Day 1 to the end of the end of Treatment Period 2 (ie, Week 20)
Interim Per Protocol	The participants in the interim Safety set who completed the first 12-week treatment, eligible to enter the second treatment period and receive the additional treatment with dapagliflozin post-Week 12. Participants should have no important protocol deviations which are identified as requiring exclusion from Per-Protocol analysis set.	Day 1 to the end of the end of Treatment Period 2 (ie, Week 20)

Note: 240 participants randomised accounts for expected drop-out to ensure approximately 200 participants complete Week 20.

B.2. Efficacy Analysis

The efficacy variable to be summarized are UACR and eGFR. The key endpoint is the UACR reduction from baseline to Week 20. It will be analysed by means of the MMRM approach as described in Section 4.9.2.1 using the Interim Per Protocol Analysis Set. The Least Squares estimate of the placebo-adjusted UACR reduction and its SE will be used to construct the decision plot. The following decision criteria and actions will be considered.

Interim Outcome	UACR reduction from baseline to Week 20	Action recommended
Go	Estimate in Green Zone	Move forward to Phase 3 ID, trigger further investment and activities to enable start of Phase 3
No Action	GO criteria not met	No trigger of further investment and activities to enable start of future studies.

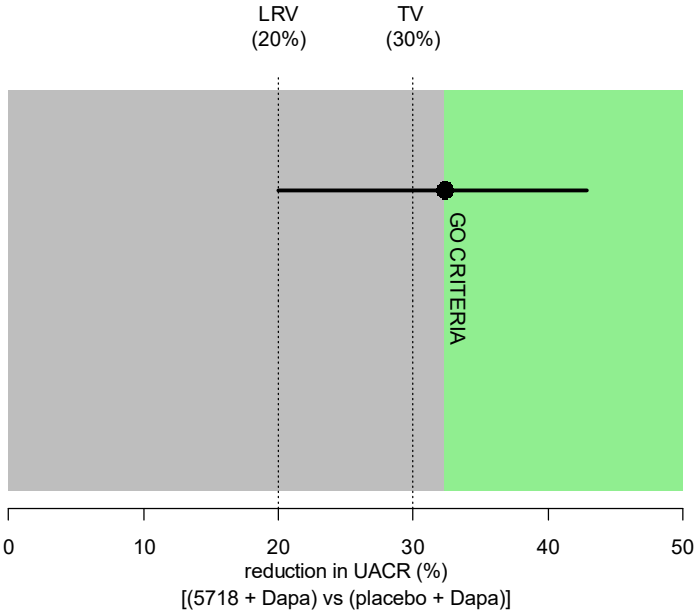
The GO thresholds in terms of the placebo-adjusted UACR reduction are calculated as

$$GO = \max\left(e^{(\log(LRV)+q_{0.8}\sigma)} * 100 - 100, e^{(\log(TV)-q_{0.9}\sigma)} * 100 - 100\right)\%,$$

Where

σ = the standard error of the estimate,
$q_{0.8} = \Phi^{-1}(0.8)$ ie, the 0.8-level quantile of the normal distribution,
$q_{0.9} = \Phi^{-1}(0.9)$ ie, the 0.9-level quantile of the normal distribution,
TV = 0.357 representing a Target Value (TV) of 30%,
LRV = 0.223 representing a Lower Reference Value (LRV) of 20%.

A decision plot will be created for UACR reduction for the placebo-adjusted estimates of AZD5718 CCI, CCI and CCI mg at week 20. A schematic example of a decision plot for UACR reduction at week 20 for the AZD5718 is illustrated below.



Abbreviations: LRV = Lower Reference Value; TV = Target Value; UACR = urine albumin to creatinine ratio.

Initiation of future studies requires at least one dose to have GO for the placebo-adjusted UACR reduction at week 20 and the response of the other doses pointing in the right direction.

Reference:

Paul Frewer, Pat Mitchell Claire Watkins and James Matcham, Decision-making in early clinical drug development, Pharmaceutical Statistics 2016, 15 255–263

B.3. Safety Analysis

Safety analysis will be based on the Interim Safety Analysis set. Selected safety outputs will be presented by treatment group and overall.

The number, percentage and percentage per participant exposure year (PEY) of participants reporting TEAEs in each treatment group will be tabulated by SOC and PT, by SOC. A summary of adverse events in any category will be presented by treatment. The incidence of common (≥ 5% of participants in any treatment group) treatment-emergent AEs, common treatment-emergent serious AEs, and AEs leading to discontinuation of study medication will be summarized by SOC, PT and treatment group, sorted in decreasing overall (across treatments) frequency. Moreover, treatment-emergent AEs leading to hospitalization will also be presented.

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

Summary statistics of laboratory data (as described in Section 4.10.4) will be presented. Participants with laboratory values which are highlighted as abnormal will be listed. Summary statistics of vital signs data may be collected.

Appendix C: Treatment-Emergent Laboratory and Vital Signs Criteria limits

The treatment-emergent laboratory and vitals change (TELVC) limits of interest for this study are as follows:

Laboratory Parameter	Range	TELVC limits
Creatinine		≥ 1.5 x Baseline Serum Creatinine ≥ 2 x Baseline Serum Creatinine
Sodium		< 120 mmol/L < 130 mmol/L > 150 mmol/L
Potassium		≤ 2.5 mmol/L ≥ 6.0 mmol/L
Creatine Kinase		> 5 x ULN > 10 x ULN

Appendix D: Exclusion from Per-Protocol Analysis

Participants will be excluded from Per-Protocol analysis if they present with an important protocol deviation (IPD) which is deemed to severely impact the validity of the analysis. The IPDs identified as leading to exclusion from the Per-Protocol analysis set are outlined in the protocol deviation specification. All protocol deviations are reviewed by the study team and IPDs are reviewed on a case-by-case basis.

During the study, prior to the interim analysis and interim database lock, it was documented that one site in Poland (site 5702) did not have sufficient source documentation or medical validation for anomalous laboratory assessments. The data from the site could impact data integrity of the interim and final analyses if included in the Per-Protocol analysis set. A specific IPD was created and documented as:

- Data entered in the eCRF that are transcribed from source documents not being consistent with the source documents and /or the discrepancies are not explained /and /or medical records not available.

Participants from the site in Poland were allocated this IPD and are thereby excluded from the Per-Protocol analysis set. Their data will remain in the Full Analysis Set, in line with the Intention-to-Treat principles.

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