| **Clinical Study Protocol** | |
|---|---|
| Study Intervention | AZD5718 |
| Study Code | D7551C00001 |
| Version | 3.0 |
| Date | 25 Jan 2021 |

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

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**Regulatory Agency Identifier Number(s):**

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

**Protocol Number:**

Amendment Number: 2

Study Intervention: AZD5718

Study Phase: 2b

**Short Title:** Dose Response Effect, Efficacy, and Safety of AZD5718 in Reducing Albuminuria in Participants with Proteinuric Chronic Kidney Disease

**Study Physician Name and Contact Information will be provided separately**

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# PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Version 3.0, Amendment 2 | 25-Jan-2021 |
| Version 2.0, Amendment 1 | 05-Aug-2020 |
| Version 1.0 | 29-May-2020 |

The Protocol Amendment Summary of Changes Table for the current amendment (Amendment 2) is provided below, and for previous amendment, is in Appendix H.

### Amendment 2 (25-January-2021)

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

### Overall Rationale for the Amendment

The Global Clinical Study Protocol (CSP), Final 2.0, dated 05 Aug 2020, is updated following a review by the several regulatory authorities and Ethics Committees (ECs). Updates have been made in accordance with the requested clarifications.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis, 1.3 Schedule of Activities, and 4.1 Overall Design | Clarification that any participant with urine albumin to creatinine ratio (ACR) < 30 mg/g at Week 12 will be excluded from Treatment Period 2. | Process clarification |
| 1.3 Schedule of Activities and Section 8.1.1.1 Urinary Albumin Creatinine Ratio | The following clarification was added regarding urine sampling in the event of delayed Visits 3 and 7: ***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.*** | Process clarification. |
| 1.3 Schedule of Activities and Section 8.2.5 Ambulatory Blood Pressure Monitoring | In Section 8.2.5, the following clarification was added regarding Ambulatory Blood Pressure Monitoring (ABPM): ***The participant may also visit the site for APBM cuff placement 1 day before their next assessment visit, as scheduled in the SoA (Table 1).*** ***The site should check the validity of the ABPM session at the beginning of the scheduled visit prior to completion of any other study assessments. An ABPM session may be repeated once if the following validity criterion has not been met:*** | Process clarification. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | • ***A minimum 20 h recording with at least 70% of expected measurements being successful***<br>***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, as described in the SoA (Table 1).***<br>***If a repeat ABPM session is not possible, the study visit should proceed as indicated. In addition, the visit should also continue if ABPM session does not meet validity criterion after the repeat session.***<br>A corresponding update was made to the footnotes in Table 1 in Section 1.3 Schedule of Activities:<br>***n*** *Participants will be provided an ABPM cuff* ***at Screening Visit 2 and Visit 6 (Week 8)*** ~~*at the indicated visit*~~ *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 APBM cuff placement 1 day before their next visit of scheduled assessment (ie, Visit 3 [Week 1] and Visit 7 [Week 12] respectively).***<br>***o Sites should ensure that the validity criterion described in Section 8.2.5 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:***<br>• ***Visit 3: up to 72 hours following the originally scheduled visit for Visit 3 but no more than 32 days from Screening Visit 1***<br>• ***Visit 7: ± 72 hours from Day 85***<br>***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.*** | |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.2 Background | The text in this section was updated as follows:<br>Sodium glucose cotransporter 2 inhibitors have been shown to slow down CKD progression by lowering glomerular pressure **in patients with CKD, with or without Type 2 Diabetes Mellitus (T2DM)** (Wanner et al, 2016, **Heerspink et al, 2020[b]**). ~~However, additional long-term studies are required to assess whether SGLT2i should be added to the current standard of care for CKD patients, with or without Type 2 Diabetes Mellitus (T2DM) (Kelly et al, 2019).~~<br>……<br>While it is anticipated that SGLT2i will be a key component of standard of care for proteinuric CKD in the future, **based on data from DAPA-CKD (Heerspink et al, 2020[b]), this** ~~definitive evidence in non-diabetic CKD~~ is not yet ~~available, and~~ **a licensed indication.** | Updated with new information from a published article. |
| 2.3.2 Dapagliflozin | The text in this section was updated as follows:<br>Dapagliflozin is authorised for treatment of T2DM, ~~and~~ T1DM, and heart failure **with reduced ejection fraction**, and **is** under development for treatment in patients with CKD and heart failure with preserved ejection fraction. | Clarification provided about the approved indications for dapagliflozin. |
| 4.2.3 Rationale for Study Population | A correction was made to the range of values used to define albuminuria (text added in bold):<br>*The study population with CKD (eGFR 20 – 75 mL/min/1.73m$^2$) and albuminuria (200 – 5000 mg **albumin**/g **creatinine**) enables assessment of the clinical efficacy and safety as well as supporting dose selection in a population at risk for progression to renal failure (Go et al, 2018).* | Correction made per the referenced article. |
| Section 5.1 Inclusion Criteria | Inclusion criterion 1 was updated as: For participants **who haven't reached the age of maturity according to local regulations in their country** ~~aged 18 to < 20 years and enrolled in Japan~~, a written informed consent should be obtained from the participant and his or her legally acceptable representative. | Inclusion criterion 1 was updated to accommodate local regulations in several countries. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 5.1 Inclusion Criteria | Inclusion criterion 5 was updated as:<br>Female participants must be of non-childbearing potential and must have been surgically sterilised (ie, bilateral oophorectomy, **and/or,** ~~,~~complete hysterectomy, **and/**or bilateral ~~tube ligation)~~, **salpingectomy; tubal ligation is not sufficient)** or be postmenopausal **(amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and** assessed by serum **follicle stimulating hormone [**FSH**]** and **luteinising hormone [**LH**]** levels at Screening Visit 1). | Inclusion criterion 5 was updated to provide more details on the eligibility of female study participants with regard to their child-bearing potential. |
| Section 5.1 Inclusion Criteria | The following text was added to inclusion criterion 6:<br>**Approved/Certified measurements in Japan are as below:**<br>**Vasectomy, tubal occlusion, intrauterine device (provided coils are copper banded), levonorgestrel intrauterine system (eg, Mirena®). These measurements are acceptable forms of highly effective birth control in Japan. Not Approved/Certified measurements in Japan are as below: Cerazette® (desogestrel) pills , medroxyprogesterone injections (eg, Depo-Provera®), etonogestrel implants (eg, Implanon®, Norplan®), normal and low dose combined oral pills, norelgestromin/ethinylestradiol transdermal system (eg, Evra® Patch), intravaginal device (eg, NuvaRing®).** | Inclusion criterion 6 was updated to accommodate Japanese Pharmaceuticals and Medical Devices Agency (PMDA) regulations. |
| Section 5.2 Exclusion Criteria | Exclusion criterion 10 was edited to clarify the exclusion of participants who received treatment with any concomitant medications known to be associated with Torsades de Pointes or potent inducers/inhibitors of cytochrome P450 3A4 within 4 weeks of Visit 3 (Randomization). | Process clarification. |
| Section 5.2 Exclusion Criteria | Exclusion criterion 15 was added to exclude participants who had a known hypersensitivity to dapagliflozin or any of the excipients of the product. | Since hypersensitivity to AZD5718 and its excipients is already part of the clinical study protocol, it was clarified that sensitivity to dapagliflozin should also be considered for study eligibility. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 5.2 Exclusion Criteria | Exclusion criterion 23 was added to the study as follows: **Participants working night shifts, and who cannot avoid strenuous manual labour during the study.** | Added per FDA recommendation to ensure feasibility of a minimum 20 h ambulatory blood pressure monitoring. |
| Section 7.1 Discontinuation of Study Drugs | Clarification was provided regarding participants who chose to discontinue either AZD5718 or dapagliflozin, or chose to discontinue ***both*** AZD5718 and dapagliflozin prior to the end of Treatment Period 2, as follows:<br>• *Participants who choose to discontinue either AZD5718 or dapagliflozin ~~or both drugs together~~ prior to the end of Treatment Period 2 are expected to continue in the study on **the** remaining study therapy **and are expected to complete the study assessments according to the schedule of study procedures for the remainder of the study.***<br>• ***Participants who choose to discontinue both AZD5718 and dapagliflozin prior to the end of Treatment Period 2 are expected to complete the study assessments** according to the schedule of study procedures for the remainder of the study**.*** | Process clarification for IMP discontinuation as indicated previously by an Ethics Committee. |
| Section 7.1, Discontinuation of Study Drugs | More specific language was added to qualify an unexpected acute decline in eGFR (ie, > 15% decrease in eGFR from the Screening Visit values) which would prompt participant evaluation. Instruction was added for the Investigator and the Study Physician to consider discontinuation of the IMP in participants with a > 30% decrease in eGFR from the Screening Visit values. | Process clarification for IMP discontinuation in the event of unexpected acute decline in kidney function, as indicated previously by a regulatory agency. |
| 7.4 Study Termination | A new subsection (7.4 Study Termination) was created, and a statement was added under it regarding the criteria for study termination as follows "***AstraZeneca may terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD5718***".<br><br>For clarity and continuity, the statement "*Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.*" was moved under the newly created Section 7.4 from its previous location in Section 7.3. | Added study termination criteria for clarity as indicated previously by an Ethics Committee. |
| Throughout | Minor editorial, typographical and document formatting revisions | Minor, therefore, have not been summarised. |

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

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

**Short Title:** Dose Response Effect, Efficacy, and Safety of AZD5718 in Reducing Albuminuria in Participants with Proteinuric Chronic Kidney Disease

**Rationale:**

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 glomerular fibrosis and inflammation emerging as major contributors to disease progression. 5-lipoxygenase activating protein (FLAP) is part of the 5-lipoxygenase (5-LO) pathway that generates biologically active lipid mediators, leukotrienes. CCI [redacted] 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 patients on SGLT2i treatment. The primary endpoint for this study is based on anticipated future standard of care with all participants on the SGLT2i dapagliflozin. Efficacy, safety, and pharmacokinetics (PK) on current standard of care with limited use of SGLT2i are secondary endpoints. 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 PK profile of AZD5718 will also be evaluated in these participants. The result of the study will form the basis for the future clinical development programme for AZD5718.

**Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| Primary | |
| To evaluate the dose response effect of AZD5718 on urine ACR at 20 weeks in participants with | Reduction of urine ACR from baseline to Week 20 compared with placebo. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| proteinuric CKD (on treatment with dapagliflozin as future standard of care from Weeks 12 to 20) | 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. |
| Secondary | |
| 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.<br>The clinical quantity of interest to be estimated is defined by the following 3 components:<br>• Population<br>Randomised participants who meet all eligibility criteria and have valid non-missing urine ACR records at baseline and at least one post-treatment visit.<br>• Endpoint<br>Change in log-transformed urine ACR from baseline to Week 12.<br>• Summary measure<br>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<br>• Vital signs<br>• Clinical chemistry/haematology/coagulation/urinalysis parameters<br>• 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 |

| Objectives | Estimand Description/Endpoints |
|---|---|
| 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 |
| CCI | |
| | |
| | |
| | |
| | |

Abbreviations: 5-LO = 5-lipoxygenase; ACR = albumin to creatinine ratio; AEs = adverse events; CCI ; CKD = chronic kidney disease; CSR = clinical study report; CCI DKD = diabetic kidney disease; CCI ECG = electrocardiograms; eGFR = estimated glomerular filtration rate; CCI ; CCI ; CCI ; CCI ; PK = pharmacokinetics; CCI ; SAEs = serious adverse events; SBP = systolic blood pressure

[a] Will be reported outside of the CSR

## Overall Design

This 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 plan is to have approximately 568 evaluable participants (142 per group) completing the study.

**Disclosure Statement**: This is a double-blinded placebo-controlled treatment study with 4 arms.

**Number of Participants:**

Approximately 632 participants will be enrolled to achieve 568 evaluable participants (142 per group).

**Intervention Groups and Duration:**

The study will include 4 intervention groups: CCI mg AZD5718, CCI mg AZD5718, CCI mg AZD5718, and placebo for the first 12 weeks followed by the addition of dapagliflozin to all participants from Week 12 to 20.

The study will include 4 periods:

- Screening Period of up to 4 weeks
- Treatment Period 1 consisting of 12 weeks where the participants will receive a once daily oral dose of the assigned dose of study drug to be taken with approximately 200 mL water in the morning with no restrictions on food intake.
- Treatment Period 2 consisting of 8 weeks where the participants will receive a treatment of once daily oral dose of dapagliflozin 10 mg in addition to the assigned dose of study drug. Only participants still taking their assigned treatment from Treatment Period 1 will progress to Treatment Period 2. Any participant with urine albumin to creatinine ratio (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.
- Follow-up Period of up to 4 weeks.

The study will include a total of 10 visits which includes 2 visits during the Screening Period, 5 visits during the Treatment Period 1, 2 visits during the Treatment Period 2, and 1 visit during the Follow-up Period.

The expected total study duration, including the Screening Period, for each participant will be at least 28 weeks.

**Data Monitoring Committee:** Not applicable

**Statistical Methods**

The primary efficacy variable is the change from baseline in urine ACR at 20 weeks compared to placebo. Primary analyses will be based on the per protocol population where participants are evaluated according to the randomised treatment assignment. Urine ACR will be log-transformed and analysed using mixed model repeated measures method. 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.

The change from baseline in urine ACR at 12 and 20 weeks will be analysed using the Multiple Comparison Procedure Modelling approach. Multiple candidate dose response models will be assessed. The best fitting model based on Akaike's Information Criteria will be used as a reference for dose selection.

Efficacy on current standard of care will be based on the Full Analysis population up to Week 12. The change in urine ACR from baseline to Week 12 will be log-transformed and be analysed similarly as the primary variable.

Estimated glomerular filtration rate (eGFR) 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 an eGFR slope analysis in Phase 3. This will be analysed using a by-visit analysis of covariance (ANCOVA), adjusting for DM stratification factor, treatment group and baseline eGFR. The Full Analysis population will be used for this analysis and eGFR will be evaluated on the original scale, if appropriate.

The principal endpoint for ambulatory blood pressure (BP) is the change from baseline in 24-hour mean systolic BP (SBP) at Week 12. It will be analysed using an ANCOVA model with terms for treatment and stratification factor plus the baseline 24-hour mean SBP and body mass index (BMI) as covariates.

The secondary efficacy variable is the change from baseline of eGFR at Week 12 and from Week 12 to Week 20. It will be analysed using by-visit ANCOVA with terms for treatment, stratification factor and baseline eGFR.

Safety analysis will be based on the Safety Analysis population where participants are evaluated according to the actual treatment received. Serious adverse event (SAE) collection will begin after the participant signs the informed consent document, and all adverse event (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. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term. Specific AEs will be counted once for each participant for calculating rates, but will be presented in total in participant listings. In addition, if the same AE occurs multiple times within a particular participant, the highest severity and level of causality will be reported. All treatment emergent AEs will be summarised overall and by deaths and SAEs. Treatment discontinuations due to AEs will be provided. For AEs, Treatment Periods 1 and 2 will be analysed separately, and then overall.

Clinical laboratory safety tests including serum chemistry, haematology, coagulation, and urinalysis parameters will be summarised using descriptive statistics at each time point by treatment group. Change from baseline to each post baseline time point in these data will also be summarised, where appropriate. A shift table will be provided for these clinical laboratory parameters as well, where possible.

Vital sign results and electrocardiograms will be summarised using descriptive statistics at each time point by treatment group.

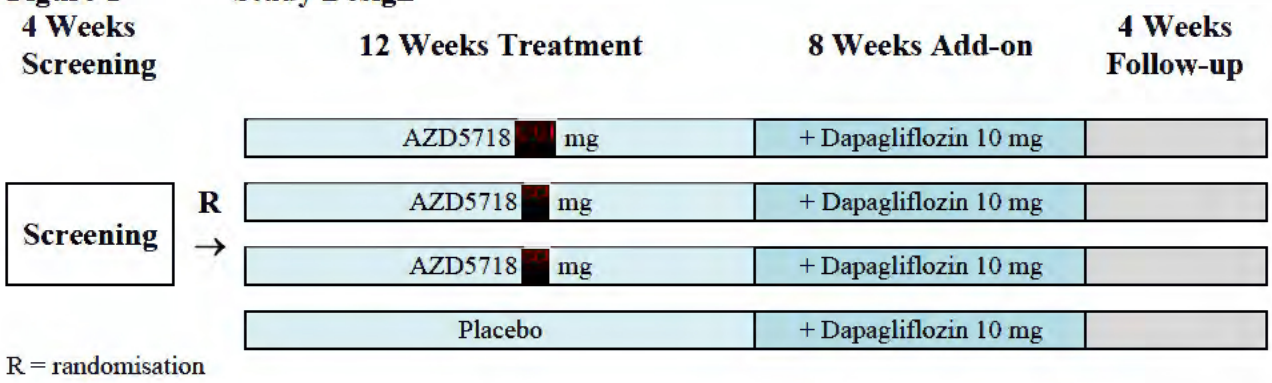
AZD5718 plasma concentration data will be summarised by descriptive statistics for each visit and each sample collection time point for each dose cohort.

CCI [redacted] will be summarised by treatment group and will be reported outside of the clinical study report.

**Interim analysis:** An administrative interim analysis will be conducted when approximately 200 participants have completed the 20-week treatment period.

## 1.2 Schema

**Figure 1 Study Design**




R = randomisation

## 1.3 Schedule of Activities

### Table 1 Schedule of Activities

| Study Period | Screening | | Treatment Period 1 | | | | | Treatment Period 2 | | Discontinuation | Follow-up | Details in CSP Section or Appendix |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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 | | | | | | | | | | | Section 5.1 |
| Informed consent (optional) for genetic and biomarker research | X | | | | | | | | | | | Section 5.1 |
| Verify eligibility criteria | X | X | X | | | | X[a] | | | | | Sections 5.1 and 5.2 |
| Demography | X | | | | | | | | | | | Section 5.1 |
| Full physical examination including height, weight, and BMI | X[b] | | X | | X | | X | | X | X | X | Section 8.2.1 |
| Physical examination (abbreviated) | | | | X | | X | | | | | | Section 8.2.1 |
| Medical history | X | | | | | | | | | | | Section 5.1 |
| Serum hCG, FSH, and LH[c] | X | | | | | | | | | | | Section 5.1 |
| Pregnancy test[c] | | | X | | | | | | | | | Section 5.2 |
| Drug and alcohol screen | X | | | | | | | | | | | Section 5.2 |
| Hepatitis B and C screening | X | | | | | | | | | | | Section 5.2 |
| Spot urine for ACR | X | | | | | | | | | | | Section 5.1 |
| Safety laboratory assessments (Clinical chemistry, haematology, coagulation, urinalysis)[d] | X | | X[e] | X | X | X | X | X | X[e] | X[e] | X | Section 8.2.4 |

| **Study Period** | **Screening** | | **Treatment Period 1** | | | | | **Treatment Period 2** | | **Discontinuation** | **Follow-up** | **Details in CSP Section or Appendix** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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** | |
| 12-lead ECG | X | | X | X | X | X | X | X | X | X | X | Section 8.2.3 |
| Vital signs[f] | X | | X | X | X | X | X | X | X | X | X | Section 8.2.2 |
| Randomisation | | | X | | | | | | | | | Section 6.3 |
| Retinal sub study (**optional, DKD sub-group only**)[g] | X | | | | | | X | | | | | Section 8.1.3 |
| HbA1c[h] | X | | | | | | | | X | | | Section 8.2.6 |
| Calculation of eGFR | X | | X | X | X | X | X | X | X | X | X | Section 8.1.2.1 |
| Blood sample for cystatin-C | X | | X | X | X | X | X | X | X | X | X | Section 8.5.3 |
| 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) | | Section 8.5.1 |
| Pharmacokinetics plasma sample for dapagliflozin | | | | | | | | X (pre-dose) | X (pre-dose) | | | Section 8.5.1 |
| CCI [redacted] | | X | X | | X | | X | | X | | | Section 8.6 |
| CCI [redacted] | | | X | | X | | X | X | X | X | | Section 8.5.3 |
| Plasma, serum, and urine for future use (optional)[j, h] | | | X | | X | | X | | X | X | | Section 8.6.2 |
| Blood sample for Genomics Initiative (optional)[j] | | | X | | | | | | | | | Section 8.7 and Appendix D |

| Study Period | Screening | | Treatment Period 1 | | | | | Treatment Period 2 | | Discontinuation | Follow-up | Details in CSP Section or Appendix |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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** | |
| Dispense supply of containers for urine samples | X | X | X | X | X | X | X | X | X | | | Section 8.1.1.1 |
| E-Diary, dispensation and completion of diary[k] | | | X | X | X | X | X | X | X | X | X | Section 6.4 |
| Reminder to collect first morning void urine samples, 3 days before visit[l] | X | X | X | X | X | X | X | X | X | X | | Section 8.1.1.1 |
| Urine samples for ACR[h, m] | | X | X | X | X | X | X | X | X | X | X | Section 8.1.1.1 |
| 24-hour ABPM, provision and completion | | X[n] | X[o] | | | X[n] | X[o] | | | | | Section 8.2.5 |
| Study drug dispensation[p] | | | X | | X | X | X | X | | | | Section 6.4 |
| Study drug returned[pq,r] | | | | | X | X | X | X | X | X | | Section 6.4 |
| Study drug intake in study centre | | | X | X | X | X | X | X | X | | | Section 6.4 |
| Assessment of AEs/SAEs | Only SAEs | | X | X | X | X | X | X | X | X | X | Section 8.3 |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | Section 6.5 |

Abbreviations: ABPM = ambulatory blood pressure monitoring; ACR = albumin to creatinine ratio; AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; 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; HbA1c = glycated haemoglobin; hCG = human chorionic gonadotropin; LH = luteinising hormone; CCI [redacted]; PK = pharmacokinetics; SAEs = serious adverse events; TSH = thyroid stimulating hormone

[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 taken 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 is in a supine position having rested for at least 10 minutes before each reading and should be taken before any bloods draws. Vital signs should be collected pre-dose on the days of study drug dosing.

[g] Optional, to be conducted only at study centres who agree to participate and have 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.

[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 Visit 5 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 Genomics 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 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). Where 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 participants 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 days (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 APBM cuff placement 1 day before their next visit of scheduled assessment (ie, Visit 3 [Week 1] and Visit 7 [Week 12] respectively).

[o] Sites should ensure that the validity criterion described in Section 8.2.5 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 drug refers 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.

# 2 INTRODUCTION

## 2.1 Study Rationale

The current Phase 2b study is being conducted to assess functional improvement, as defined by change in urine albumin excretion, in participants with proteinuric CKD when dosed with AZD5718. Additionally, the dose response relationship, and the safety and PK profile of AZD5718 will be evaluated in these participants. Furthermore, the additive effect of the SGLT2i dapagliflozin taken together with AZD5718 on albuminuria will be assessed in an 8-week extension period where participants will be treated with AZD5718/placebo and dapagliflozin.

## 2.2 Background

Chronic kidney disease is a worldwide public health problem associated with significant morbidity and mortality; DM is the leading cause of end-stage renal disease (Mills et al, 2015, Koye et al, 2018). The pathophysiology of DKD is multifactorial, with both haemodynamic effects contributing to glomerular fibrosis and inflammation emerging as major contributors to disease progression (Hickey and Martin 2018). Angiotensin converting enzyme inhibitors and ARBs have been standard of care for treatment of CKD for decades, but these drug classes have been shown to confer incomplete protection (Ku et al, 2018). Sodium-glucose cotransporter-2 inhibitors have been shown to slow down CKD progression by lowering glomerular pressure in patients with CKD, with or without Type 2 Diabetes Mellitus (T2DM) (Wanner et al, 2016, Heerspink et al, 2020[b]).

Five-lipoxygenase activating protein (FLAP) is part of the 5-LO pathway that generates biologically active lipid mediators called leukotrienes. The 5-LO pathway is expressed by white blood cells and has a primary role in host defence. Five-lipoxygenase activating protein is located within nuclear membranes and facilitates transfer of substrate (arachidonic acid) from membrane phospholipids to 5-LO for the generation of CCI [redacted]

CCI [redacted] Inflammation has been recognised as a key component of diabetic nephropathy and increased expression of the 5-LO and FLAP genes in the tubulointerstitial compartment in patients with CKD indicating the potential for an increased inflammatory leukotriene drive (ERCB cohort renal transcriptomics data in collaboration with University of Michigan, Yasuda et al, 2006). CCI [redacted] and CCI [redacted] can cause endothelial dysfunction, increasing glomerular permeability to albumin. This may explain the reduced urinary albumin excretion seen in a number of experimental models with leukotriene inhibition including in-house data on aged monkeys with metabolic syndrome treated with a FLAP inhibitor similar to AZD5718. Short term treatment with a FLAP inhibitor reduced proteinuria associated with glomerulonephritis in

human subjects (Gausch et al, 1999). CCI [redacted] are also vasoconstrictive reducing renal perfusion which can be improved by leukotriene antagonists.

AZD5718, previously identified as AZ13702997, is a reversible FLAP inhibitor. Inhibition of FLAP activity will attenuate production of pro-inflammatory and vasoactive leukotrienes by leukocytes (eg, neutrophils) and is hypothesised to reduce albuminuria in the CKD population with and without DM.

While it is anticipated that SGLT2i will be a key component of standard of care for proteinuric CKD in the future, based on data from DAPA-CKD (Heerspink et al, 2020[b]), this is not yet a licensed indication. Current uptake in DKD is limited with fewer than 5% of patients on SGLT2i treatment. The primary endpoint for this study is based on anticipated future standard of care with all participants on the SGLT2i dapagliflozin. Efficacy, safety, and PK on current standard of care with limited use of SGLT2i are secondary endpoints.

Dapagliflozin is a highly potent, selective, and reversible inhibitor of SGLT2 that improves glycaemic control in patients with DM and provides cardio-renal benefits in patients with T2DM and without DM. Dapagliflozin is currently approved in 100 countries for the treatment of T2DM as an adjunct to diet and exercise and in some countries for the treatment of T1DM as an adjunct to insulin, when insulin does not provide adequate glycaemic control. Dapagliflozin is commercially available as 5 mg and 10 mg tablet formulations.

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 PK profile of AZD5718 will also be evaluated in these participants. The result of the study will form the basis for the future clinical development programme for AZD5718.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD5718 and dapagliflozin are provided in the respective IBs.

## 2.3 Benefit/Risk Assessment

### 2.3.1 AZD5718

As of 31 March 2020, 4 clinical studies with AZD5718 in healthy volunteers are complete (D7550C00001, D7550C00002, D7550C00004, and D7550C00005), 3 studies in healthy volunteers are ongoing (D7550C00007, D7550C00008, and D7550C00009), and 1 study is ongoing in participants with CAD (D7550C00003). AZD5718 has been administered to healthy volunteers (in completed studies) in single doses up to CCI mg, and in repeated doses up to CCI mg for 10 days. AZD5718 has been administered to 122 healthy volunteers (in completed studies) in single doses up to CCI mg, and in repeated doses up to CCI mg for 10

days.

The safety and tolerability of AZD5718 in fasting and fed male healthy volunteers following single and multiple ascending doses have been evaluated in the single-multiple ascending dose (SMAD; D7550C00001), Japanese SMAD (JSMAD; D7550C00004), combined drug-drug interaction/bioavailability (DDI/BA; D7550C00002) and BA (D7550C00005) studies.

AZD5718 has been well tolerated in male healthy volunteers. No clinically meaningful differences for changes over time in clinical laboratory tests, vital signs or electrocardiograms (ECGs) were observed between healthy volunteers who received AZD5718 and those who received placebo. There were no deaths or SAEs and all healthy volunteers completed the studies. The most common AE in healthy volunteers receiving AZD5718 across the SMAD (D7550C00001), DDI/BA (D7550C00002) and BA (D7550C00005) studies was headache; the most common AE in Study D7550C00004 was contact dermatitis (reported in Japanese healthy volunteers receiving both placebo and AZD5718). No safety concerns were raised during the studies.

More detailed information about the known and expected benefits and potential risks of AZD5718 may be found in the Investigator's Brochure (IB).

### 2.3.2 Dapagliflozin

The safety profile of dapagliflozin has been evaluated in clinical development programmes for T2DM, T1DM, and heart failure. This includes more than 15000 participants treated with dapagliflozin for T2DM, more than 1000 participants treated with dapagliflozin for Type 1 Diabetes Mellitus (T1DM) and more than 2000 participants treated with dapagliflozin for heart failure. Overall, treatment with dapagliflozin 5 mg was similar to treatment with dapagliflozin 10 mg in both T1DM and T2DM. The safety profile of dapagliflozin was overall consistent across the studied indications. Dapagliflozin is authorised for treatment of T2DM, T1DM, and heart failure with reduced ejection fraction, and is under development for treatment in patients with CKD and heart failure with preserved ejection fraction.

The most commonly reported AEs associated with the use of dapagliflozin include genital infections, urinary tract infections, back pain, and polyuria. In addition, rash has been identified as an AE of unknown frequency in marketed use of dapagliflozin.

**Diabetic Ketoacidosis**

In the cardiovascular outcomes study, DECLARE, 8574 participants received dapagliflozin (FORXIGA) 10 mg and 8569 participants received placebo for a median exposure time of 48 months. Events of diabetic ketoacidosis (DKA) were reported in 27 participants in the dapagliflozin 10 mg group and 12 participants in the placebo group.

The events occurred evenly distributed over the study period. Of the 27 participants with DKA

events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a T2DM population.

More detailed information about the known and expected benefits and potential risks of dapagliflozin may be found in the IB.

### 2.3.3 Other Risks

See Appendix F for details on background information, risks and mitigations plans, and impact of coronavirus disease-2019 (COVID-19) on the current study.

# 3 OBJECTIVES AND ENDPOINTS

**Table 2 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| Primary | |
| 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.<br>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. |
| Secondary | |
| 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.<br>The clinical quantity of interest to be estimated is defined by the following 3 components:<br>• Population<br>Randomised participants who meet all eligibility criteria and have valid non-missing urine ACR records at baseline and at least one post-treatment visit.<br>• Endpoint<br>Change in log-transformed urine ACR from baseline to Week 12.<br>• Summary measure<br>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<br>• Vital signs<br>• Clinical chemistry/haematology/coagulation/urinalysis parameters<br>• ECG assessments |

| Objectives | Estimand Description/Endpoints |
|---|---|
| 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 |
| 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 |
| CCI | |
| | |
| | |
| | |
| | |

Abbreviations: 5-LO = 5-lipoxygenase; ACR = albumin to creatinine ratio; AEs = adverse events; CCI ; CKD = chronic kidney disease; CSR = clinical study report; CCI ; DKD = diabetic kidney disease; CCI ; ECG = electrocardiograms; eGFR = estimated glomerular filtration rate; CCI ; CCI ; CCI ; CCI ; CCI ; PK = pharmacokinetics; CCI ; SAEs = serious adverse events SBP = systolic blood pressure

[a] Will be reported outside of the CSR

# 4 STUDY DESIGN

## 4.1 Overall Design

This 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. Furthermore, the additive effect of the SGLT2i dapagliflozin taken together with AZD5718 on albuminuria will be assessed in an 8-week extension period where participants will be treated with AZD5718/placebo and dapagliflozin.

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 10 mg dapagliflozin for all participants, to have 158 participants per group. The plan is to have approximately 568 evaluable participants (142 per group) completing the study.

The study will include 4 periods:

- Screening Period of up to 4 weeks.
- Treatment Period 1 of 12weeks where the participants will receive a once daily oral dose of the assigned dose of study drug to be taken with approximately 200 mL water in the morning with no restrictions on food intake.
- Treatment Period 2 of 8 weeks where the participants will receive a treatment of once daily oral dose of dapagliflozin 10 mg in addition to the assigned dose of study drug. Only participants still taking their assigned treatment from Treatment Period 1 will progress to Treatment Period 2. Any participant with urine albumin to creatinine ratio (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.
- Follow-up Period of up to 4 weeks.

The study will include a total of 10 visits which includes 2 visits during the Screening Period, 5 visits during the Treatment Period 1, 2 visits during the Treatment Period 2, and 1 visit during the Follow-up Period.

The expected total study duration, including the Screening Period, for each participant will be at least 28 weeks.

The SoA to be conducted during the study is presented in Table 1 and a schematic

representation of the study is presented in Figure 1.

## 4.2 Scientific Rationale for Study Design

### 4.2.1 Rationale for Study Design

This study is randomised and double-blinded to prevent bias in treatment allocation and in the subjective assessment of effect of the study drug in the intended study population. A randomised, blinded, multi-centre, placebo-controlled study design is considered the best design to achieve the objectives of the study, from both safety and efficacy perspectives. Additionally, the study is designed to demonstrate efficacy versus placebo and thus, a placebo control arm in the study will enable placebo-corrected analysis of safety and efficacy.

### 4.2.2 Rationale for Study Endpoints

Change in urine albumin excretion during the Treatment Periods provides information about renal efficacy (predictive of meeting hard renal endpoints in Phase 3 clinical studies) both on anticipated future standard of care and current standard of care, and a sustained effect following study drug washout would suggest benefit to renal structure. The treatment duration allows a suitable assessment of safety following multiple dose administration and is of sufficient length to evaluate the effects of the study drug on urine albumin excretion (Levey et al, 2020).

The study also intends to evaluate the effect of AZD5718 on ambulatory BP in participants with proteinuric CKD in line with FDA recommendation to understand the temporal changes in BP and changes in risk. As elevated BP is known to increase the risk of stroke, heart attack, and death, the effect of any drug during the clinical development phase on BP can therefore be an important consideration in benefit-risk assessment. A 24-hour ambulatory blood pressure monitor (ABPM) is shown to provide precise estimates of BP changes to assess the effects of drug on BP and lack a pronounced placebo response (Garnett et al, 2020).

Additionally, this study will assess the PK of AZD5718 to support the dose selection for future development in this participant population. CCI [redacted] hese biomarkers may include, but are not limited to CCI [redacted] In addition, blood samples for potential current and future CCI [redacted] will be collected in participants who have given a separate consent for genetic research.

### 4.2.3 Rationale for Study Population

The study population with CKD (eGFR 20 - 75 mL/min/1.73m$^2$) and albuminuria (200 – 5000 mg albumin/g creatinine) enables assessment of the clinical efficacy and safety as

well as supporting dose selection in a population at risk for progression to renal failure (Go et al, 2018).

## 4.3 Justification for Dose

### 4.3.1 AZD5718

The AZD5718 doses selected for this study are based on the goal of characterising the dose response for urine ACR and evaluating safety in a proteinuric CKD participant population. The doses have been selected based on data from human volunteer studies with the aim of suppressing production of both CCI

Single doses of up to CCI mg AZD5718 and once daily repeated doses of CCI mg, CCI mg, CCI mg and CCI mg for 10 days have been well tolerated in healthy volunteers. In an ongoing Phase 2a study in coronary artery disease (CAD) participants with a recent myocardial infarction, doses of CCI mg and CCI mg are being evaluated.

A study in non-human primates with a similar compound to AZD5718 showed a beneficial and clinically relevant reduction in urine ACR at exposures aiming for an 80% reduction of CCI production in blood. Model predicted relationship between inhibition of *ex vivo* CCI production in blood and exposure in healthy subjects has shown that a CCI mg once daily dose at steady state gives > 80% inhibition during the whole dosing interval. A CCI mg dose is predicted to result in a 30% reduction by the end of the dosing interval and the CCI mg dose is between the lowest and the highest dose evaluated.

### 4.3.2 Dapagliflozin

A once daily dose of 10 mg dapagliflozin has been established as having the optimal effect on albuminuria in DKD (Heerspink et al, 2020[a]).

## 4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the Follow-up Visit as shown in the Schedule of Activities (SoA; Table 1).

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

# 5 STUDY POPULATION

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

## 5.1 Inclusion Criteria

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

**Age**

1 Participants must be ≥ 18 years of age inclusive, at the time of signing the informed consent.

For participants who haven't reached the age of maturity according to local regulations in their country, a written informed consent should be obtained from the participant and his or her legally acceptable representative.

**Type of Participant and Disease Characteristics**

2 Participants with proteinuric CKD defined as

- eGFR 20 – 75 mL/min/1.73m$^2$ based on chronic kidney disease epidemiology collaboration (CKD-EPI) equation at Screening Visit 1 **and**
- albuminuria defined as 200 -5000 mg albumin/g creatinine based on the geometric mean of the replicated measurements using 3 sequential first morning void urine at Visit 2.

  **and**
- with diagnosis of T2DM (for **DKD sub-group only**).

**Weight**

3 Body weight within 50-150 kg and BMI within the range 18 to 45 kg/m$^2$ (inclusive).

**Sex**

4 Male or female

5 Female participants must be of non-childbearing potential and must have been surgically sterilised (ie, bilateral oophorectomy, and/or complete hysterectomy, and/or bilateral salpingectomy; tubal ligation is not sufficient) or be postmenopausal (amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and assessed by serum follicle stimulating hormone [FSH] and luteinising hormone [LH] levels at Screening Visit 1). All female participants must have a negative serum pregnancy test at Screening Visit 1 and negative urine pregnancy test at Visit 3 (Day 1) prior to study drug administration.

6 Male participants must be surgically sterile or agree to use highly effective contraceptives. Non-sterilised male participants who are sexually active with a female partner of childbearing potential must use a male condom with spermicide from Day 1 to 3 months after the last dose of the study drug. It is strongly recommended for the female partner of a male participant to also use a highly effective method of contraception throughout this period.
Note: In case a male condom with spermicide is not available in a country or region, non-sterilised male participants who are sexually active with a female partner of childbearing potential must use a male condom without spermicide and the female partner should use a highly effective contraceptive method.

Note: Highly effective birth control methods for female partners of male participants include: total sexual abstinence (true abstinence in line with the preferred and usual lifestyle choice of the participant), vasectomised partner, tubal occlusion, intrauterine device (provided coils are copper banded), levonorgestrel intrauterine system (eg, Mirena®), medroxyprogesterone injections (eg, Depo-Provera®), etonogestrel implants (eg, Implanon®, Norplan®), normal and low dose combined oral pills, norelgestromin/ethinylestradiol transdermal system (eg Evra® Patch), intravaginal device (eg, NuvaRing®), and Cerazette® (desogestrel) pills.

**Approved/Certified measurements in Japan are as below:**

Vasectomy, tubal occlusion, intrauterine device (provided coils are copper banded), levonorgestrel intrauterine system (eg, Mirena®).

These measurements are acceptable forms of highly effective birth control in Japan.

**Not Approved/Certified measurements in Japan are as below:**

Cerazette® (desogestrel) pills, medroxyprogesterone injections (eg, Depo-Provera®), etonogestrel implants (eg, Implanon®, Norplan®), normal and low dose combined oral pills, norelgestromin/ethinylestradiol transdermal system (eg, Evra® Patch), intravaginal device (eg, NuvaRing®).

**Informed Consent**

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

8 CCI [redacted].

**Other Criteria**

9 Participants should have a stable BP meeting all of the following criteria:

(a) BP ≤ 150/100 mmHg at Screening Visit 1 and Visit 3.

(b) Stable dose of angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 4 weeks prior to Screening Visit 1 with ACEi and ARB dosing according to local guidelines. Participants who have been deemed unable to tolerate ACEi or ARB therapy due to allergy or complications may be enrolled.

10 For participants on any additional antihypertensive medication (including diuretic therapy), the doses must be stable for at least 4 weeks prior to Screening Visit 1.

11 If on SGLT2i or glucagon-like peptide-1 receptors agonists (GLP1-RA) treatment, the participants must have been on a stable dose for at least 4 weeks prior to randomisation

visit. No new additional SGLT2i or GLP1-RA therapy is permitted until the 8-week extension period.

12 If on treatment with other drugs with potential to influence albuminuria, eg non-steroidal anti-inflammatory drug (NSAID)s, the participants must have been on a stable dose for at least 4 weeks prior to Screening Visit 1.

13 Renin inhibitor or an aldosterone antagonist in combination with an ACEi or an ARB (dual renin angiotensin aldosterone system inhibitor therapy) is permitted and participants must have been on a stable dose for at least 4 weeks prior to Screening Visit 1.

## 5.2 Exclusion Criteria

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

**Medical Conditions**

1 Recent hepatitis, or positive screening test for hepatitis B (hepatitis B virus surface antigen) or hepatitis C (hepatitis C antibody).

2 Diagnosis of polycystic kidney disease or anatomical causes of CKD.

3 Diagnosis of T1DM.

4 Participants with severe hepatic impairment (Child-Pugh class C).

5 Abnormal laboratory findings at Screening Visit 1

(a) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN) or total bilirubin > 2 × ULN (unless due to Gilbert's disease) or evidence of chronic liver disease.

(b) Serum potassium > 5.5 mmol/L that cannot be adjusted to values ≤ 5.5 mmol/L by appropriate management.

6 Any of the following concomitant conditions or diseases at Screening Visit 1

(a) History of QT prolongation associated with other medications that required discontinuation of that medication.

(b) Congenital long QT syndrome.

(c) Acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass grafting within 6 months.

(d) High degree atrioventricular block II-III, sinus node dysfunction with significant sinus pause, untreated with pacemaker.

(e) Stroke within 3 months.

(f) Heart failure New York Heart Association classification III-IV.

(g) Anticipated dialysis or renal transplantation within 1 year.

(h) History of substance dependence or a positive screen for drugs or alcohol abuse, likely to impact participant safety or compliance with study procedures, at the

discretion of the Investigator. Alcohol and drug screening to be completed for all participants locally with laboratory kits provided by the central laboratory.

(i) Prior malignancy other than non-melanoma skin cancer or cervical cancer in situ treated with apparent success with curative therapy (response duration of > 5 years).

(j) Any other condition or clinically relevant abnormal findings in physical examination, laboratory results or ECG during screening period that, in the opinion of the Investigator, may compromise the safety of the participant in the study, reduce the participant's ability to participate in the study, or interfere with evaluation of the study drug.

7 Participant who had severe course of COVID-19 (extracorporeal membrane oxygenation, mechanically ventilated), and/or had a confirmed case of COVID-19 within 4 weeks of Screening Visit 1 (for further details See Appendix F).

**Prior/Concomitant Therapy**

8 Ongoing use of any biologic drug and/or small molecule targeting the immune system (for example, tumour necrosis factor blockers, anakinra, rituximab, abatacept, azathioprine, mycophenolate, cyclophosphamide, tocilizumab, corticosteroids other than topical or inhaled).

9 Any serum creatinine-altering drugs within 1 month prior to Screening Visit 1 including but not limited to amphotericin, cimetidine, clofibrate, dronedarone, ketoconazole, probenecid, ranolazine, trimethoprim, aminoglycosides, or cephalosporins.

10 Treatment with any concomitant medications known to be associated with Torsades de Pointes or potent inducers/inhibitors of cytochrome P450 3A4 within 4 weeks of Visit 3 (Randomization).

11 Treatment with zileuton, cilastatin (dipeptidase-1 [DPEP1] inhibitor), or leukotriene receptor antagonists (eg, montelukast) within 4 weeks of Screening Visit 1.

12 Treatment with simvastatin, lovastatin, and atorvastatin at doses > 40 mg per day within 1 month prior to Screening Visit 1.

**Prior/Concurrent Clinical Study Experience**

13 Concurrent enrolment in another clinical study involving an investigational treatment or drug or participation in a device study within 3 months prior to Screening Visit 1.

14 Participants with a known hypersensitivity to AZD5718 or any of the excipients of the product.

Participants with a known hypersensitivity to dapagliflozin or any of the excipients of the product.

**Other Exclusions**

15 Donation of blood or significant blood loss in excess of 500 mL within 3 months prior to Day 1 (or > 1200 mL in the year prior to Day 1).

16 Plasma donation within 60 days prior to Day 1.

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

18 Judgement by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

19 For women only - currently pregnant (a negative serum pregnancy test is required at Screening Visit 1 and urine pregnancy test at Day 1 [Visit 3]) or breast-feeding.

20 An employee, or close relative of an employee, of AstraZeneca, the Contract Research Organisation (CRO), or the study site, regardless of the employee's role.

21 Participants who are legally institutionalised.

22 Participants working night shifts, and who cannot avoid strenuous manual labour during the study.

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.

## 5.3 Lifestyle Considerations

### 5.3.1 Meals and Dietary Restrictions

1 Refrain from consumption of Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study drug until after the final dose.

2 Participant should only be requested to arrive at the clinic after fasting for at least 8 hours (no food or liquid [except for water] intake permitted) for all study visits except for Screening Visit 1.

### 5.3.2 Caffeine and Alcohol

1 Participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for at least 12 hours before each visit to study centre.

2 Participants will abstain from alcohol for at least 48 hours before each visit to study centre.

### 5.3.3 Activity

1 Participants will abstain from strenuous exercise for at least 24 hours before each blood collection for clinical laboratory tests.

### 5.3.4 Reproductive Restrictions

1 Male participants should agree to use highly effective method of contraception from Day 1 until 3 months after the final dose of the study drug.

### 5.3.5 Other Restrictions

1 Male participants will abstain from donating the sperm throughout the duration of the study and for 3 months after the final dose of the study drug.

2 Participants will abstain from donating blood or plasma throughout the duration of the study and for 3 months after the final dose of the study drug.

## 5.4 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

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

## 6.1 Study Intervention(s) Administered

### 6.1.1 Investigational Products

**Table 3 Investigational Products**

| Intervention name | AZD5718 | Dapagliflozin | Placebo[a] |
|---|---|---|---|
| Type | Drug | Drug | Drug |
| Dose formulation | Tablets | Tablets | Tablets |
| Unit dose strength(s) | CCI mg, CCI mg, and CCI mg | 10 mg | Not applicable |

| Intervention name | AZD5718 | Dapagliflozin | Placebo[a] |
|---|---|---|---|
| Dosage level(s) | CCI mg, CCI mg (CCI mg + CCI mg), and CCI mg, once daily | 10 mg, once daily | Once daily |
| Route of administration | Oral | Oral | Oral |
| Use | Experimental | Experimental | Placebo- comparator |
| IMP and NIMP | IMP | IMP | IMP |
| Sourcing | Provided centrally by the Sponsor | Provided centrally by the Sponsor | Provided centrally by the Sponsor |
| Packaging and labelling | Study drug will be provided in blisters that will be packed in a wallet. There will be 2 blisters packed in one wallet. Each wallet will be labelled in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language as required. | Study drug will be provided in bottle. Each bottle will contain 35 tablets and will be labelled in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language as required. | Study drug will be provided in blisters that will be packed in a wallet. There will be 2 blisters packed in one wallet. Each wallet will be labelled in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language as required. |

Abbreviations: GMP = Good Manufacturing Practice; IMP = Investigational medicinal product; NIMP = Non-investigational medicinal product

[a] As comparator to AZD5718 only.

## 6.2 Preparation/Handling/Storage/Accountability

1 The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drugs.

2 Only participants enrolled and randomised into the study may receive study drugs and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

3 The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drugs accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

## 6.3 Measures to Minimise Bias: Randomisation and Blinding

### 6.3.1 Methods for Assigning Treatment Groups

All participants will be centrally assigned to randomised study drug using Interactive Response Technology/Randomization and Trial Supply Management (IRT/RTSM). Before the study is initiated, the telephone number and call-in directions for the Interactive Voice Response System (IVRS) and/or the log-in information and directions for the Interactive Web Response System (IWRS) will be provided to each study centre. The IRT/RTSM will provide to the Investigator(s) or pharmacists, the kit identification number to be allocated to the participant at the dispensing visit.

Randomisation will be stratified by participants with and without DM at the time of randomisation in order to ensure approximate balance between treatment groups within each sub-population.

- 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%-35% of the total participants randomised. At least 72 Japanese participants will be included.

At randomisation, the IRT/RTSM will assign eligible participant a unique randomisation code and blinded study drug kit number(s). Specific information concerning the use of the IRT/RTSM will be provided in the separate user manual at each study centre.

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

Block randomisation using IRT/RTSM will be used to randomise participants in a 1:1:1:1 ratio

to receive AZD5718 ([redacted] mg), AZD5718 ([redacted] mg), AZD5718 ([redacted] mg), or placebo in Treatment Period 1 followed by add-on 10 mg of dapagliflozin to the randomised dose level in Treatment Period 2. Upon completion of the randomisation request form, the randomisation will be produced by Parexel Informatics using the AstraZeneca randomisation solution (AZRand).

### 6.3.2 Methods for Ensuring Blinding

The study will have a double-blind design. Placebo tablets will match appearance of each of 4 dosage levels: [redacted] mg AZD5718, [redacted] mg AZD5718, [redacted] mg AZD5718 and placebo.

No member of the study team at AstraZeneca, or representative, personnel at study centres, or any CRO handling data will have access to the randomisation scheme prior to unblinding for the primary analysis, with the exception of the Parexel Informatics personnel generating the randomisation scheme as well as AstraZeneca Supply Chain, and the CRO companies conducting PK sample analyses, providing the IRT/RTSM and carrying out the packaging and labelling of the study drug. This documentation will be kept in a secure location until the end of the study. Separate personnel with no other involvement in the study will be unblinded for the interim analysis.

### 6.3.3 Methods for Unblinding

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

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to the blinded study drug and that potentially require expedited reporting to regulatory authorities.

For the administrative interim analysis, separate personnel with no other involvement in the study will be unblinded. A detailed description of the interim analysis to be conducted will be provided in the Statistical Analysis Plan (SAP).

## 6.4 Study Intervention Compliance

AZD5718 and placebo will be provided in blisters packed in child-resistant wallets. Enough tablets will be dispensed for daily dosing at home until the participant returns for the next study visit. Dapagliflozin will be provided in 75 cc high-density polyethylene bottle.

When the participants are dosed at the study centre, they will receive the study drugs directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in

the electronic Case Report Form (eCRF). The dose of the study drugs and study participant identification will be confirmed at the time of dosing by a member of the study centre staff other than the person administering the study drug.

When the participants self-administer study drugs at home, compliance with study drugs will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets etc., during the study centre visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of AZD5718/placebo and dapagliflozin tablets dispensed to and taken by each participant must be maintained and reconciled with study drugs and compliance records. Study drugs start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

### 6.4.1 E-Diary

The participants will be requested to download an e-Diary application on their smartphone during Visit 3, in order to set up study reminders, (ie, reminder to take their medication or collect the first morning void) as well as capture drug accountability throughout the treatment period, at sites where applicable. If needed, participants will 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 this 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 study visit.

Where completion of an e-Diary is not applicable, participant will be requested to complete a paper dosing diary.

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).

## 6.5 Concomitant Therapy

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

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

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

prior therapy.

### 6.5.1 Prohibited Concomitant Medications

Use of OTC medications, herbal supplements, vitamins, etc, from Screening through to the early discontinuation visit is discouraged. Participants must be instructed not to take any medications, including OTC products, without first consulting with the Investigator. Non-study SGLT2i or GLP1-RA should not be initiated after enrolment in the study.

Participants are not permitted to receive any of the following medications during the study.

1 Systemic (oral or injectable) corticosteroids within 28 days of Screening Visit 1 until the end of the Follow-up Period.
2 Any other immunosuppressive therapy within 3 months of randomisation until the end of the Follow-up Period.
3 Any immunotherapy within 3 months of randomisation, except for stable maintenance dose allergen-specific immunotherapy started 28 days prior to Screening Visit 1 until the end of Follow-up Period.
4 Interferon gamma within 3 months of randomisation until the end of the Follow-up Period.
5 Investigational products other than AZD5718 within 4 months or 5 half-lives of randomisation until the end of the Follow-up Period.
6 Immunoglobulin or blood products within 28 days of Screening Visit 1 until the end of the Follow-up Period.
7 Ongoing use of any biologic drug or small molecule targeting the immune system (for example, tumour necrosis factor blockers, anakinra, rituximab, abatacept, azathioprine, tocilizumab, mycophenolate, corticosteroids other than topical or inhaled).
8 Any serum creatinine-altering drugs within 1 month prior to Screening Visit 1 including but not limited to amphotericin, cimetidine, clofibrate, dronedarone, ketoconazole, probenecid, ranolazine, trimethoprim, cyclophosphamide, aminoglycosides, or cephalosporins until the end of the Follow-up Period.
9 Any medication that alters leukotriene levels or actions within 4 weeks of Screening Visit 1, eg, zileuton cilastatin, and montelukast until the end of the Follow-up Period.
10 Simvastatin, lovastatin, or atorvastatin at doses > 40 mg per day within 1 month of Screening Visit 1 until the end of the Follow-up Period.

### 6.5.2 SGLT2 Inhibitors

If the participants are on SGLT2i treatment prior to enrolment into this study, they must have been on a stable dose for at least 4 weeks prior to randomisation visit. No new additional SGLT2i therapy is permitted until the 8-week extension period.

Participants receiving SGLT2i treatment prior to randomisation as standard of care will have to continue the treatment at the same dose through the study and it must not be changed unless prescribed by the Investigator.

In general, any dose changes of SGLT2i treatment should be avoided during the study unless due to medical necessity. If the participant needs to interrupt SGLT2i treatment for any reason, they should be allowed to re-start it again once the respective medical condition gets resolved.

For Treatment Period 2, any existing SGLT2i treatment, including fixed-dose combination preparations, will be discontinued and replaced by dapagliflozin 10 mg once daily until the end of the treatment period. For participants on fixed-dose combinations, the non-SGLT2i drugs should be prescribed as single agent preparations, at the discretion of the PI.

### 6.5.3 Rescue Medicine

If a participant's medical condition requires rescue therapy, the participant should be treated at the Investigator's discretion. Rescue therapy should be recorded in the eCRF. Diabetic participants may require adjustment of their other glucose-lowering treatments on commencing dapagliflozin to avoid hypoglycaemia.

## 6.6 Dose Modification

No dose modifications are permitted during the study due to its short duration. However, study drug dose(s) may be withheld if clinically necessary.

In the case of delayed or missed dose for any reason, subsequent doses should be administered according to the original schedule (ie, at the planned timepoint relative to first dose of the study drug).

## 6.7 Intervention After the End of the Study

After completing dosing with study drugs at Week 20 and the Follow-up Visit at Week 24, the participants will have completed the study. AZD5718 will not be provided for post-study use. Both the study drugs (AZD5718 and dapagliflozin) will be withdrawn after Week 20 and participants should be returned to their previously prescribed treatment regimen, at the discretion of the Investigator.

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Drugs

Participants are free to discontinue study drugs at any time, without prejudice to further treatment.

- Participants who choose to discontinue AZD5718 prior to the end of Treatment Period 1 will not proceed to Treatment Period 2 and are expected to complete the assessments per Discontinuation Visit and Follow-up Visit.
- Participants who choose to discontinue either AZD5718 or dapagliflozin prior to the end of Treatment Period 2 are expected to continue in the study on the remaining study therapy and are expected to complete the study assessments according to the schedule of study procedures for the remainder of the study.
- Participants who choose to discontinue both AZD5718 and dapagliflozin prior to the end of Treatment Period 2 are expected to complete the study assessments according to the schedule of study procedures for the remainder of the study.

See the SoA (Table 1) for data to be collected at the time of discontinuation of study drugs and follow-up and for any further evaluations that need to be completed.

The Investigator and/or Study Physician may determine that an individual participant will not receive any further study drug if any of the following occur in that participant:

- Withdrawal of consent from further treatment with study drugs.
- Lost to follow-up.
- Safety reasons as judged by the Investigator and/or Sponsor where continued treatment may put the participant at undue risk.
- Incorrectly randomised participant in whom inclusion/exclusion criteria violation would put the participant at undue risk.
- Participant noncompliance that, in the opinion of the Investigator or Sponsor, warrants treatment discontinuation for safety reasons (eg, refusal or inability to adhere to scheduled visits).
- Pregnancy.
- Any of the following liver function abnormalities:
  - ALT or AST > 8 × ULN
  - ALT or AST > 5 × ULN for more than 2 weeks
  - ALT or AST > 3 × ULN and (total bilirubin > 2 × ULN or international normalised ratio [INR] > 1.5); see Appendix E for additional details regarding reporting of participants with ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN with unknown aetiology (ie, Hy's Law [HL] cases)
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

If an unexpected, acute decline in GFR is observed (> 15% decrease in eGFR from the

Screening Visit values), the participant should be promptly evaluated. Volume depletion, hypotension, inter-current medical problems, and concomitant drugs may cause increases in blood creatinine. Urinary tract infection and urinary obstruction should be considered. Several drugs may cause a decline in GFR, especially NSAIDs and certain antibiotics such as trimethoprim. If any drug is suspected of causing or contributing to worsening kidney function, their use should be re-considered. The Investigator together with the Study Physician should consider the discontinuation of the investigational medicinal product (IMP) if eGFR decreases by more than 30% of Screening Visit values.

Consider temporary interruption of dapagliflozin if DKA is suspected. The participant should be promptly evaluated. If DKA is confirmed, dapagliflozin should be discontinued permanently.

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

Participants who are permanently discontinued from receiving the study drugs will be followed for protocol-specified assessments, including follow-up of any AEs, unless consent is withdrawn specifically from further study participation (Section 7.2), the participant is lost to follow-up (Section 7.2), or the participant is enrolled in another clinical study.

A participant who decides and/or is recommended by the treating physician or the Investigator to permanently discontinue the study drugs will always be asked about the reason(s) for discontinuation and about the presence of any AEs. All efforts must be taken to ensure that the participant will be seen and assessed by an Investigator and, as scheduled for other participants, all end of treatment visit assessments should be completed at the time of discontinuation of study drug.

### 7.1.1 Temporary Discontinuation

For participants needing treatment with prohibited concomitant medications, study drugs must be discontinued or interrupted temporarily.

For decisions around discontinuation, the Study Physician can be consulted as appropriate.

## 7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

- At the time of withdrawal from the study, if possible, an Early Study Drug Discontinuation Visit should be conducted, as shown in the SoA. See SoA (Table 1) for the data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study drugs and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what is stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

## 7.3 Lost to Follow-up

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

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

- The study centre must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Study centre personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

## 7.4 Study Termination

AstraZeneca may terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD5718. Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

# 8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be included in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Efficacy Assessments

### 8.1.1 Primary Efficacy Assessment

#### 8.1.1.1 Urinary Albumin Creatinine Ratio

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

During this clinical study, a spot urine sample is collected during the Screening Visit 1 and at the remaining timepoints, participants are required to collect first morning void urine samples on 3 consecutive days (ideally day of visit and preceding 2 days [refrigerated overnight]

which are returned on the day of visit) as described in SoA (Table 1). 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. The containers to collect the urine samples are dispensed to the participant during Screening Visit 1 and as required at other visits during the course of the study. Urine ACR will be calculated as follows.

Urine ACR (mg/g) = urine albumin (mg/dL) / urine creatinine (g/dL)

At each visit, the geometric mean of the triplicate measurements will be computed centrally and used for all analyses of urine ACR.

### 8.1.2 Secondary Efficacy Assessments

#### 8.1.2.1 Estimated Glomerular Filtration Rate

Estimated GFR is another marker that is considered as a standard for assessment of kidney function. It is calculated based on serum creatinine values using the widely validated and accepted CKD-EPI equation (Levey et al, 2009). Blood samples for estimation of serum creatinine are collected at various timepoints during the course of the study as shown in SoA (Table 1). Estimated GFR is then calculated as follows.

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

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.

Estimated GFR calculations will be performed by the central laboratory.

Alternatively, serum cystatin-C alone provides GFR estimates that are nearly as accurate as serum creatinine adjusted for age, sex and race thus providing an alternative GFR estimate that is not linked to muscle mass (Stevens et al, 2008). Blood samples will also be collected for measurement of cystatin-C at specified time points in the SoA (Table 1).

### 8.1.3 CCI

[redacted]


## 8.2 Safety Assessments

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

### 8.2.1 Physical Examinations

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

Physical examination will be performed at timepoints as specified in the SoA (Table 1).

### 8.2.2 Vital Signs

Vital signs will be performed at time points as specified in the SoA (Table 1). Vital signs will include BP, heart rate (HR), respiratory rate, body temperature, and pulse oximetry. Vital signs 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 bloods draws. Vital signs should be

collected pre-dose on the days of study drug dosing and before blood draws. Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Route of body temperature and pulse oximetry measurements will be conducted according to local procedures but should be consistent throughout the study for an individual participant.

### 8.2.3 Electrocardiograms

Triplicate 12-lead ECGs will be performed at timepoints as specified in the SoA, Table 1 using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS, QT, and QTc intervals.

The ECGs should be performed after the participant has rested for at least 10 minutes in supine position. Three individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 10 minutes.

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. Abnormal values shall not be recorded as AEs unless deemed clinically significant. The printout of the ECG is to be signed, dated and filed in participant medical record as source document.

### 8.2.4 Clinical Safety Laboratory Assessments

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Table 1). Safety sampling will be done after at least 8 hours of fasting, except for Screening Visit 1.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

The clinical chemistry, haematology, coagulation, and urinalysis will be performed at the central laboratory, except for tests completed using urine dipsticks which will be done locally (see Table 4 for details of these tests). Laboratory kits used locally will be provided by the central laboratory.

Where 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, serum potassium.

The following laboratory variables will be measured.

**Table 4 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[a,b] |
| **Coagulation** | S/P-Luteinising hormone[a,b] |
| B-International normalised ratio | S/P-Thyroid stimulating hormone (TSH) |
| B-Activated partial thromboplastin time | S/P-Free triiodothyronine (fT3) |
| B-Fibrinogen | S/P-Free thyroxine (fT4) |
| **Urinalysis[c]** | S/P-Creatinine (for eGFR quantification) |
| U-Glucose (dipstick) | S/P-Chloride |
| U-Albumin (quantification/semi-quantification) | S/P-Bicarbonate |
| U-Glucose | S/P-Magnesium |
| U-Blood (dipstick) | S/P-Human chorionic gonadotropin hormone[b] |
| U-White blood cells | S/P-Albumin |
| U-human chorionic gonadotropin hormone (dipstick)[b] | S/P-Total protein |
| **Other Clinical Safety Panels[a] (serum or plasma)** | |
| S/P-Hepatitis B surface Antigen | |
| S/P-Hepatitis C virus antibody | |

Abbreviations: B = whole blood; eGFR = estimated glomerular filtration rate; P = plasma; S = serum; U = urine

[a] Screening Visit 1 only

[b] All women

[c] If urinalysis is positive for blood or white blood cells then microscopy through central laboratory, including white blood cells, red blood cells, and casts, should be completed

**NOTE:** In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix E. Actions required in cases of increases in liver biochemistry and evaluation of HL, for further instructions.

### 8.2.5 Ambulatory Blood Pressure Monitoring

24-hour ABPM will be performed at timepoints as specified in the SoA (Table 1). Participants will be provided the ABPM cuff and instructed to use the device 24 hours prior to the next visit.

Training for Application and Wearing of ABPM Device:

Participants will be given training at their local study site about how to set up and apply the ABPM device. In brief, an appropriate size BP cuff will be selected, and the device will be fitted to the nondominant arm of the participant, with the bladder placed over the artery and an initial test reading performed. The participants will be advised that for the first reading, the device will inflate to a pressure of 180 mmHg, and thereafter the device will adapt to inflate to a pressure just above the last recorded BP. The participant will be advised to undergo normal daily activities while wearing the cuff, and he/she will be advised to avoid any strenuous form of activity, bathing or showering while wearing the cuff. The participant will be advised to remain still during a measurement with the arm relaxed at heart level. The participant will also be given advice on how to wear the device during the day and at night while sleeping, and what to expect in terms of frequency of readings during the day and overnight. During ABPM, systolic BP, diastolic BP, heart rate pressure, HR, and mean arterial pressure readings will be recorded over a period of 24 hours. The participant may also visit the site for APBM cuff placement 1 day before their next assessment visit, as scheduled in the SoA (Table 1).

The site should ensure that the following validity criterion of the ABPM session is met prior to completing any other study assessments at the visit. An ABPM session may be repeated once if the following validity criterion has not been met:

- A minimum 20 h recording with at least 70% of expected measurements being successful

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, as described in the SoA (Table 1).

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 validity criterion after the repeat session.

### 8.2.6 Glycated Haemoglobin

Blood samples for assessment of glycated haemoglobin (HbA1c) will be collected at

timepoints as specified in the SoA (Table 1).

## 8.3 Adverse Events and Serious Adverse Events

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

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

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

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

### 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

Serious AEs will be recorded from time of signature of the ICF and all AEs will be collected after the participant has received the first dose of study drug. The collection of AEs/SAEs will continue throughout the treatment period and including the Follow-up Period.

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

### 8.3.2 Follow-up of Adverse Events and Serious Adverse Events

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

**Adverse Event Variables**

The following variables will be collected for each AE:

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

- Outcome

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

### 8.3.3 Causality Collection

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

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

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

### 8.3.4 Adverse Events Based on Signs and Symptoms

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

### 8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol (CSP) mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR).

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

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

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

### 8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.7 Reporting of Serious Adverse Events

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

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

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

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

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

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

The AstraZeneca representative will advise the Investigator/study centre staff how to proceed.

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

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug AZD5718.

### 8.3.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study drugs.

#### 8.3.8.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, the study drugs should be discontinued immediately.

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.3.8) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

When the eCRF module is used include the following: The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the

outcome of the pregnancy.

#### 8.3.8.2 Paternal Exposure

As a precaution, all male participants should avoid fathering a child by either true abstinence or the use of 2 effective means of contraception (a male condom with spermicide; see Inclusion Criterion #6, Section 5.1, for regions where male condoms with spermicide are not available) with their partner from the time of study drug administration (Day 1) until 3 months after the last dose of study drugs.

Sperm donation

Male participants should not donate sperm for the duration of the study and for at least 3 months after the last day of study drugs.

### 8.3.9 Medication Error

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.7) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

## 8.4 Overdose

### 8.4.1 AZD5718

For this study, any dose of the AZD5718 greater than that specified in this CSP will be considered an overdose.

### 8.4.2 Dapagliflozin

Dapagliflozin has been well tolerated at doses up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy volunteers and patients with T2DM. Only suspected single intake of more than 500 mg dapagliflozin or repeated intake of more than 100 mg dapagliflozin should be reported on the eCRF overdose module. If an overdose is suspected, monitoring of vital functions as well as treatment should be performed as appropriate.

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within **one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.7) and within **30 days** for all other overdoses.

## 8.5 Human Biological Samples

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

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

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

### 8.5.1 Pharmacokinetics

- Venous blood samples will be collected for measurement of plasma concentrations of AZD5718 and dapagliflozin as specified in the SoA (Table 1).
- Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

- Plasma samples will be used to analyse the PK of AZD5718 and dapagliflozin. Samples collected for analyses of AZD5718 and/or dapagliflozin plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.
- 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 4 additional PK samples taken within 1-2 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 hour between 2 subsequent samples) for analysis of AZD5718. As indicated in the SoA (Table 1), 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.

#### 8.5.1.1 Determination of Drug Concentration

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.

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

### 8.5.2 Immunogenicity Assessments

Immunogenicity analysis will not be assessed in this study.

### 8.5.3 Pharmacodynamics

#### 8.5.3.1 Collection of Samples

Plasma and urine samples for measurement of CCI will be collected at specified time points in the SoA (Table 1). For urine samples, creatinine level will also be measured to allow the CCI level to be normalised.

For storage, re-use and destruction of pharmacodynamics (PD) samples see Section 8.5 and

Appendix C.

## 8.6 Human Biological Sample Biomarkers

CCI [redacted]

[redacted]

[redacted]

[redacted].

### 8.6.2 Collection of Optional Biomarker Samples for Future Use

Collection of optional samples for biomarker research is also part of this study as specified in the SoA and is subject to agreement to optional consent.

CCI [redacted]

For storage, re-use and destruction of biomarker samples see Section 8.5.

## 8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA (Table 1) and is subject to agreement in the ICF addendum.

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

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

For storage and destruction of genetic samples see Appendix D.

## 8.8 Health Economics

This section is not applicable.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 Statistical Hypotheses

The primary hypothesis for this study is that AZD5718 will reduce urine ACR compared with placebo on treatment with dapagliflozin as future standard of care. Dose response will be evaluated.

The secondary hypotheses of this study are:

- AZD5718 will reduce urine ACR compared with placebo on current standard of care.
- AZD5718 will exhibit an acceptable safety profile in participants with proteinuric CKD.
- AZD5718 will exhibit an acceptable ambulatory BP in participants with proteinuric CKD.
- AZD5718 will exhibit an acceptable PK profile in participants with proteinuric CKD.

## 9.2 Sample Size Determination

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).

## 9.3 Populations for Analyses

The following populations are defined:

**Table 5 Populations for Analysis**

| Population/Analysis set | 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.<br>The Full Analysis Population will be used for all analyses of demographic 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 |

| Population/Analysis set | Description |
|---|---|
| | 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.<br>If a participant received a different treatment dose than randomised throughout the study, they will be analysed according the treated dose, not the randomisation dose. If a participant received study drug from the wrong kit for only part of the treatment duration, they will be analysed according to their randomisation dose.<br>The Safety Analysis Population will be used for all safety analyses. |
| Ambulatory Blood Pressure Monitoring Population | All participants in the Full Analysis Population who have valid ambulatory blood pressure data for change from baseline analyses. |
| Pharmacokinetic Population | All participants in the Full Analysis Population who have at least one detectable AZD5718 plasma concentration measurement post-treatment.<br>The Pharmacokinetic Population will be used for all PK analyses. |

## 9.4 Statistical Analyses

The SAP will be finalised prior to first participant in and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the primary, secondary and safety endpoints.

### 9.4.1 General Considerations

Relevant demographic and baseline characteristics will be summarised descriptively for each study treatment group and overall.

There are 4 planned study periods:

- Screening period (4 weeks)
- Treatment Period 1 (12 weeks)
- Treatment Period 2 (8 weeks)
- Follow-up period (4 weeks)

All efficacy and safety variables will be summarised by study treatment group using descriptive statistics (n, geometric mean, SD, median, minimum and maximum for continuous data and n, frequencies and percentages for categorical data). Data will be summarised by visit as applicable. Safety outputs will also include a pooled AZD5718 group.

The statistical methods and how the variables are presented will be further detailed in the SAP.

The potential impact of missing data and methods will be described fully in the SAP.

## 9.4.2 Efficacy

### 9.4.2.1 Primary Endpoint

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

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.

### 9.4.2.2 Secondary Endpoints

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.

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 an eGFR 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 Full Analysis population will be used for this analysis and eGFR will be evaluated on the original scale.

Ambulatory BP will be analysed to determine the effect of AZD5718 on BP. This will be assessed by the change in 24-hour mean SBP at Week 12. It will be analysed using ANCOVA, adjusting for DM stratification factor, treatment group, plus baseline 24-hour mean SBP and BMI as covariates. The Full Analysis population will be used for this analysis.

The AZD5718 plasma concentrations will be summarised by descriptive statistics for each visit and each sample point for AZD5718-treated participants by dose cohort. Further details of this will be provided in the SAP. Additional PK analyses may be conducted as appropriate. If the data allow, population PK analysis will be performed, but will not be reported in the CSR.

CCI [redacted]

### 9.4.3 Safety

All safety analyses will be performed on the Safety Analysis population.

Adverse events (and also separately SAEs) will be summarised by study treatment group in incidence summaries by MedDRA System Organ Class (SOC) and Preferred Term (PT). 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.

Adverse events will be assigned to the period where they start. 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. Adverse events will be coded using the MedDRA by SOC and PT. Specific AEs will be counted once for each participant for calculating rates but will be presented in total in participant listings. In addition, if the same AE occurs multiple times within a particular participant, the highest severity and level of causality will be reported. All treatment emergent AEs will be summarised overall and by deaths and SAEs. Treatment discontinuations due to AEs will be summarised.

Clinical laboratory safety tests including serum chemistry, haematology, coagulation, and urinalysis parameters will be summarised using descriptive statistics at each time point by treatment group. Change from baseline to each post baseline time point in these data will also be summarised, where appropriate. A shift table will be provided for these clinical laboratory parameters as well, where possible.

Vital signs and clinical laboratory data and ECG will be summarised at each time point. Change from baseline to each post baseline time point will also be summarised, where appropriate.

### 9.4.4 Other Analyses

The change from baseline in urine ACR at 12 and 20 weeks will be analysed using the Multiple Comparison Procedure – Modelling approach (Pinheiro et al, 2006**).** Multiple candidate dose response models will be assessed. The best fitting model based on Akaike's Information Criteria will be used as a reference for dose selection. This will be assessed on the Full Analysis population.

CCI [redacted] will be summarised by treatment group.

CCI [redacted]

## 9.5 Interim Analyses

An interim analysis will be conducted when approximately 200 participants have completed the 20-week treatment period. 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 regardless of the interim results.

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

## 9.6 Data Monitoring Committee

Not applicable.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

# Appendix A Regulatory, Ethical, and Study Oversight Considerations

## A 1 Regulatory and Ethical Considerations

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

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilising medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will

review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

## A 2 Financial Disclosure

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

## A 3 Informed Consent Process

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

All rescreened participants are required to sign a new consent form.

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

## A 4 Data Protection

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

## A 5 Dissemination of Clinical Study Data

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

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for as outlined in Clinical Study Agreement after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## A 7 Source Documents

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

## A 8 Study and Site Start and Closure

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

The first act of recruitment is the first participant screened at any study site and will be the study start date.

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

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

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

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

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

## A 9 Publication Policy

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

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

## B 1 Definition of Adverse Events

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

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

## B 2 Definitions of Serious Adverse Event

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

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

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

**Life-threatening**

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

**Hospitalisation**

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

**Important Medical Event or Medical Treatment**

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

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

**Intensity Rating Scale:**

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

It is important to distinguish between serious and severe AEs. Severity is a measure of

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

## B 3 A Guide to Interpreting the Causality Question

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

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

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

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

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

The causality assessment is performed based on the available data including enough

information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

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

## B 4 Medication Error

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

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

Medication error includes situations where an error

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

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

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

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

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

- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

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

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

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

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

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

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

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

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

The Investigator:

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

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the

withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

## C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES**

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

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

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

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

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

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

# Appendix D Optional Genomics Initiative Sample

## D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

## D 2 Genetic Research Plan and Procedures

**Selection of Genetic Research Population**

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

**Inclusion Criteria**

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

**Exclusion Criteria**

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

**Withdrawal of Consent for Genetic Research:**

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary

withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in section 7.2 of the main CSP.

**Collection of Samples for Genetic Research**

- The blood sample for this genetic research will be obtained from the participants at Visit 3. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

**Coding and Storage of DNA Samples**

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

**Ethical and Regulatory Requirements**

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

**Informed Consent**

- The genetic component of this study is optional, and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both

the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

**Participant Data Protection**

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

**Data Management**

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

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

## E 1 Introduction

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

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

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

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

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the study drug.

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

## E 2 Definitions

**Potential Hy's Law**
Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** total bilirubin ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

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

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

## E 3 Identification of Potential Hy's Law Cases

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

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

**Central Laboratories Being Used:**

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

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

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

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

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

## E 4 Follow-up

### E 4.1 Potential Hy's Law Criteria Not Met

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

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

### E 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study medication (See Section E 4.2).
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important Medical Event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For participants who met PHL criteria prior to starting study drug, the Investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition

- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data

- Subsequent to this contact the Investigator will:

  – Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  – Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  – Complete the 3 Liver eCRF Modules as information becomes available

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

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

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study drug, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

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

If it is agreed that there is **no** explanation that would explain the ALT or AST and total bilirubin elevations other than the study drug:

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

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

- Provides any further update to the previously submitted SAE of PHL, (report term now ‘Hy’s Law case’) ensuring causality assessment is related to study drug and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## E 6 Laboratory Tests

### Hy's Law Lab Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT (Gamma-glutamyl transferase)<br>LDH (Lactate dehydrogenase)<br>Prothrombin time<br>INR (International Normalised Ratio) |
| Viral hepatitis | IgM anti-HAV (Hepatitis A Virus)<br>IgM and IgG anti-HBc<br>HBsAg (Hepatitis B Surface Antigen)<br>HBV DNA [a] (Hepatitis B Virus DNA)<br>IgG anti-HCV (Hepatitis C Virus)<br>HCV RNA [a](Hepatitis C Virus RNA)<br>IgM anti-HEV (Hepatitis E Virus)<br>HEV RNA (Hepatitis E Virus RNA) |
| Other viral infections | IgM & IgG anti-CMV (Cytomegalovirus)<br>IgM & IgG anti-HSV (Herpes Simplex Virus)<br>IgM & IgG anti-EBV (Epstein Barr Virus) |
| Alcoholic hepatitis | Carbohydrate deficient transferrin (CD-transferrin) [b] |
| Autoimmune hepatitis | Antinuclear antibody (ANA)<br>Anti-Liver/Kidney Microsomal Ab (Anti-LKM)<br>Anti-Smooth Muscle Ab (ASMA) |
| Metabolic diseases | alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin [b]<br>Transferrin saturation |

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive
[b] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

# E 7 References

**Aithal et al, 2011**

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

**FDA Guidance for Industry, July 2009**

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

# Appendix F COVID-19 Specifics

## F 1 Background to COVID-19

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

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

## F 2 Risk Assessment for COVID-19 Pandemic

There are 2 study drugs with different mechanisms of action that are unlikely to impact on the course of infection with SARS-CoV-2. AZD5718 does have an anti-inflammatory mode of action with inhibition of leukotriene production. While, this poses a theoretical risk of adversely influencing the antiviral response, this is judged to be unlikely. Dapagliflozin is an anti-glycaemic agent and is believed not to cause immune suppression. Therefore, risk of the participants exposed to SARS-CoV-2 or to suffer from COVID-19 is expected to be similar to the background population with the same co-morbidities as those in the study, in particular CKD and T2DM. The risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

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

- This study is going to start enrolling only when the Sponsor and CRO in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic imposed by the local authorities are compatible with safe conduct of the study.

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

## F 3 Restrictions Related to COVID-19

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

the Investigator and site staff and guided by local requirements.

## F 4 Data Quality Assurance Related to COVID-19

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

In addition, where possible, other measures for carrying out protocol related activities, such as but not limited to home nursing, may be employed as required.

## F 5 References

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2. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, March 2020, Updated on April 16, 2020 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

# Appendix G Abbreviations

| Abbreviation or special term | Explanation |
|---|---|
| 5-LO | 5-lipoxygenase |
| ABPM | Ambulatory Blood Pressure Monitoring |
| ACEi | Angiotensin Converting Enzyme Inhibitors |
| ACR | Albumin to Creatinine Ratio |
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| ALP | Alkaline Phosphatase |
| ANCOVA | Analysis of Covariance |
| AST | Aspartate Aminotransferase |
| ARB | Angiotensin Receptor Blocker |
| AZRand | AstraZeneca randomisation solution |
| BA | Bioavailability |
| CCI | [redacted] |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CAD | Coronary Artery Disease |
| CONSORT | Consolidated Standards of Reporting Trials |
| COVID-19 | Coronavirus Disease-2019 |
| CCI | [redacted] |
| CKD | Chronic Kidney Disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CRO | Contract Research Organisation |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| DDI | Drug-Drug interaction |
| DILI | Drug-Induced Liver Injury |
| DKA | Diabetic Ketoacidosis |
| DKD | Diabetic Kidney Disease |
| DNA | Deoxyribonucleic Acid |
| DM | Diabetes Mellitus |
| CCI | [redacted] |
| EC | Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC) |
| ECG | Electrocardiogram |

| Abbreviation or special term | Explanation |
|---|---|
| eCRF | electronic Case Report Form |
| EDC | Electronic Data Capture |
| eGFR | Estimated Glomerular Filtration Rate |
| EMA | European Medicines Agency |
| CCI | [redacted] |
| FDA | U.S. Food and Drug Administration |
| FLAP | 5-Lipoxygenase Activating Protein |
| FSH | Follicle Stimulating Hormone |
| fT3 | Free triiodothyronine |
| fT4 | Free thyroxine |
| GCP | Good Clinical Practice |
| GLP1-RA | Glucagon-like peptide-1 Receptors Agonists |
| HbA1c | Glycated Haemoglobin |
| hCG | Human Chorionic Gonadotropin |
| HIPAA | Health Insurance Portability and Accountability Act |
| HL | Hy's Law |
| HR | Heart rate |
| CCI | [redacted] |
| IATA | International Airline Transportation Association |
| IB | Investigator's Brochure |
| ICH | International Council for Harmonisation |
| ICF | Informed Consent Form |
| IgG | Immunoglobulin G |
| CCI | [redacted] |
| IMP | Investigational Medicinal Product |
| INR | International Normalised Ratio |
| IRT | Interactive Response Technology |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| LH | Luteinising Hormone |
| CCI | [redacted] |
| CCI | [redacted] |
| CCI | [redacted] |
| CCI | [redacted] |
| MedDRA | Medical Dictionary for Regulatory Activities |

| Abbreviation or special term | Explanation |
|---|---|
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| CCI | [redacted] |
| OTC | Over the Counter |
| PD | Pharmacodynamics |
| PHL | Potential Hy's Law |
| PK | Pharmacokinetic |
| CCI | [redacted] |
| PT | Preferred Term |
| QTc | Corrected QT interval |
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SBP | Systolic Blood Pressure |
| SCr | Serum Creatinine |
| SD | Standard Deviation |
| SMAD | Single-Multiple Ascending Dose |
| SoA | Schedule of Activities |
| SOC | System Organ Class |
| SGLT2i | Sodium-Glucose Cotransporter-2 inhibitor |
| SUSARs | Suspected Unexpected Serious Adverse Reactions |
| T1DM | Type 1 Diabetes Mellitus |
| T2DM | Type 2 Diabetes Mellitus |
| TSH | Thyroid stimulating hormone |
| ULN | Upper Limit of Normal |
| WHO | World Health Organisation |

# Appendix H Protocol Amendment History

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Version 2.0, Amendment 1 | 05-Aug-2020 |
| Version 1.0 | 29-May-2020 |

The Protocol Amendment Summary of Changes Table for the current amendment (Amendment 2) is located directly before the Table of Contents.

### Amendment 1 (05-August-2020)

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

### Overall Rationale for the Amendment

The original CSP, Final 1.0, dated 29 May 2020, is updated following the FDA safety review (10 Jul 2020) and updates have been made to correct errors and further clarify processes.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1, Synopsis<br>Section 3, Objectives and Endpoints | Coagulation is included to the laboratory parameters for the secondary endpoint: To evaluate the safety and tolerability of AZD5718 in participants with proteinuric CKD | Omitted in error, included for consistency |
| Section 1.1, Synopsis<br>Section 4.1, Overall design | The number of countries included in the study are updated from 10 to 12 | Additional countries will be included in the study |
| Section 1.1, Synopsis<br>Section 1.3, Table 1 Schedule of Activities<br>Section 4.1, Overall design<br>Section 8.1.1.1, Urinary Albumin Creatinine Ratio | Clarification of how the ACR result is calculated to determine exclusion of participants from Treatment Period 2 | Process clarification |
| Section 1.3, Table 1 Schedule of Activities | Abbreviated physical examinations are not completed at Visits 5 and 7 (X removed) | A full physical examination is required at these visits; both abbreviated and full were included at these visits in error |
| Section 1.3, Table 1 Schedule of Activities<br>Section 8.2.4 Clinical Safety Laboratory Assessments, Table 4 | Footnotes to clarify that serum hCG, FSH, and LH tests, and a urine pregnancy test are required for all women, not only women with intact uterus | Increasing clarity of pregnancy testing approach in response to feedback from trial sites |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.3, Table 1 Schedule of Activities | Coagulation is included in the safety laboratory assessments row | Omitted in error |
| | Deletion of duplicate row for urinalysis assessments (safety laboratory assessments) | Duplicate row included in error |
| Section 1.3, Table 1 Schedule of Activities | Sampling timepoints for plasma and urine CCI are reduced; samples will not be collected at Visits 2, 4, 6, and 10 | Changes to the plan for analysis of CCI |
| | The correct footnote is applied to the row: Reminder to collect first morning void urine samples, 3 days before visit (*Site should follow-up directly with the participant via phone to remind the participant*) | Incorrect footnote included in error |
| | The correct footnote is applied to the row: Study drug dispensation (*Study drug refers to AZD5718/placebo during Treatment Period 1 and AZD5718/placebo + dapagliflozin during Treatment Period 2*) | Incorrect footnote included in error |
| Section 1.3, Table 1 Schedule of Activities<br>Section 8.2.4, Clinical safety laboratory Assessments | Note is included to clarify the local and central laboratory assessment procedures. Section 8.2.4 is updated to clarify the use of local urine dipstick tests | Process clarification |
| Section 1.3, Table 1 Schedule of Activities<br>Section 8.2.2, Vital Signs | Pulse oximetry is included in the vital signs assessments | FDA request to monitor oxygen saturation to check for respiratory depression |
| Section 1.3, Table 1 Schedule of Activities<br>Section 8.1.3, CCI | CCI | Process clarification |
| Section 1.3, Table 1 Schedule of Activities<br>Section 6.4.1 | Text added to clarify that where completion of an e-Diary is not applicable, participant will be requested to complete a paper dosing diary<br>Details of an e-Diary satisfaction survey added | Process clarification |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 5.1, Inclusion Criterion #5 | Clarification that females must be of non-childbearing potential and that a pregnancy test is required for all female participants | Process clarification |
| Section 5.1, Inclusion Criterion #6<br>Section 8.3.8.2, Paternal Exposure | Text added to clarify the contraceptive requirements for male participants in regions where male condoms with spermicide are not available | Process clarification |
| Section 5.2, Exclusion Criterion #6 (h) | Clarification that alcohol and drug screening is completed locally using laboratory kits provided by the central laboratory, and that screening must be completed for all participants | Process clarification |
| Section 6.1.1 Investigational Products, Table 3 | Table updated stating that Dapagliflozin is taken once daily | Clarification |
| Section 6.5.2, SGLT2 Inhibitors | Clarification of SGLT2i fixed-dose combination treatments allowed during Treatment Period 2 | Clarification |
| Section 7.1, Discontinuation of Study Drugs | Greater than (>) is changed to ≥ for ALT, AST, and total bilirubin where the CSP refers to Hy's Law | Consistency with Hy's Law Appendix E |
| Section 8.2.4, Clinical Laboratory Assessments | Additional safety samples do not need to be recorded in the eCRF | Process clarification |
| Section 9.4.3, Safety (Statistical Analyses) | Coagulation and urinalysis are included in the description of the statistical analysis for laboratory safety tests | Omitted in error, included for consistency |
| Throughout | Minor editorial and document formatting revisions | Minor, therefore have not been summarised |

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# SIGNATURE PAGE

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