AstraZeneca

| **Clinical Study Protocol** | |
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| Drug Substance | Dapagliflozin |
| Study Code | D169AC00001 |
| Version | 4.0 |
| Date | 17 March 2020 |

# A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease

**Sponsor: AZ AB, 151 85 Södertälje, Sweden**



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

# VERSION HISTORY

| **Version 1.0, 26 October 2016** | |
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| Initial creation | |
| **Version 2.0, 26 September 2017** | |
| **Section** | **Summary of change** |
| Multiple | Correcting typos, cross-references and AstraZeneca (AZ) House style. |
| 2.3 Safety objectives<br><br>6.3.1 Time period for collection of adverse events<br><br>6.3.2.6 Adverse events (AEs) leading to amputation AEs leading to a risk for lower limb amputations ("preceding events") | Expanding the adverse event of interest category of amputations to also include: AEs leading to a risk for lower limb amputations ("preceding events"). This AE of interest was added based on discussion with regulatory authorities. |
| 3.2 Inclusion/Exclusion criteria | Clarifying inclusion criteria number 4 and exclusion criteria number 11. Extending requirement for contraceptives (exclusion criteria 13), based on feedback from some regulatory authorities and to harmonise with informed consent form (ICF). |
| 3.4 Procedures for handling incorrectly randomised patients | Clarifying text regarding how to handle incorrectly randomised patients. |
| 3.9.1 Evaluation of volume status and investigational product (IP) dose reduction/interruption | Clarification added to provide additional guidelines regarding essential treatment in the setting of acute worsening of heart failure or other acute situations. |
| 4 Study plan and timing of procedures<br><br>5.2.1 Laboratory assessments | Removal of parathyroid hormone (PTH) central laboratory assessment since the analysis of PTH can be done, if applicable, using biomarker samples and no separate sampling is needed.<br><br>Change in table 1, footnote a) and clarifying removal of 21 days window for optional lab assessment. |
| 4.2.8 Study closure visit (SCV) | Clarification regarding the investigator responsibility in terms of standard of care treatment after the patient stops IP. |

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| 5.1.1 Endpoint reporting overview<br><br>5.1.3 Potential renal endpoints | Removing the requirement of adjudicating potential endpoints related to estimated glomerular filtration rate (eGFR) decline. The rational for this change is that the endpoint criteria are not justifying adjudication of these events. |
| 6.3 Recording of adverse events<br><br>6.3.2.2 Renal events | Clarification added based on feedback that the criteria was too vague, regarding what is considered an adverse event (AE) of interest in terms renal events. |
| 6.3 Recording of adverse events<br><br>6.3.7 Adverse events based on examination and tests | Limiting the recording of AEs to not include potential renal endpoints that are based on examination and tests, i.e., laboratory results only, unless fulfilling the serious adverse event (SAE) criteria or Discontinuation of investigational product due to adverse event (DAE) criteria. The reason not to record these endpoints related to laboratory findings is that protocol mandated laboratory values will be systematically analysed. |
| 6.4.1 Reporting of SAEs considered to be potential endpoints | Limiting the event types that are being withheld from reporting to health authorities to include only heart failure endpoints and fatal AE. i.e., AEs related to renal endpoints will not be withheld. The rationale for this limitation is to simplify the SAE reporting and to minimise the risk for withholding renal AEs of interest, which should be reported, and which could be confused for being a primary or secondary renal endpoint. |
| 6.9 Medication Error | Adding information about Medication Error definition and reporting. |
| 7.7.2 Prohibited medication | Clarifying that open label treatment with Sodium glucose co-transporter 2 (SGLT2) in combination with IP is not allowed and that open label treatment with SGLT2 inhibitors should be avoided during the course of the study, i.e., clarifying that usage of open label treatment with SGLT2 inhibitors are not prohibited if the patient is not taking study medication but should be avoided. The rational for this update is to clarify that it is administration of an open label SGLT2 inhibition in combination with IP that is a protocol deviation and not if the patient is off IP. |
| 7.7.3 Recording of concomitant medication | Including cardiovascular (CV) medications to be recorded in detail in the electronic case report form (eCRF) during the course of the study. |

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| 8.5.6 Interim analysis | Clarifying that the Data Monitoring Committee (DMC) have the possibility to do more than one interim analysis of efficacy if they deem necessary. |
| Appendix D and E | Appendices (D and E) have in the previous version been separated from the main clinical study protocol (CSP) but are now incorporated for practical reasons. No changes made to the content. |
| **Version 3.0, 22 January 2020** | |
| **Section** | **Summary of change** |
| 2.4 Exploratory objectives | New Exploratory Objective added:<br><br>*To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of the composite endpoint of chronic dialysis, renal death or receiving a renal transplant.*<br><br>The rational for this update is to prespecify a renal composite objective that only include hard renal and no surrogate (eGFR) endpoint. |
| 2.4 Exploratory objectives | New Exploratory Objective added:<br><br>*To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of the composite endpoint of CV death, MI or stroke.*<br><br>The rational for this update is to prespecify a CV composite objective to better evaluate the overall CV efficacy. |
| 2.4 Exploratory objectives | Typo error corrected in the second paragraph (numbering removed before "or") |
| 2.4 Exploratory objectives | Update and change the outcome measure of the exploratory objective determining whether dapagliflozin compared with placebo will result in a reduction of the incidence of events of doubling of serum creatinine. Measured by the time of first occurrence of an event instead of number of events.<br><br>The rational for this update is to correct the text so the objective reflects the statistical analysis that will be used. |
| 5.2.1. Table 2 Laboratory variables | Administration updates in the table: |

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| | U-albumin and U-creatinine added to the Spot urinalysis to clarify the laboratory analyses performed to calculate UACR. |
| 9.4 Data management by AstraZeneca (AZ) | Cognizant replaced with IQVIA Ltd due to Data Management vendor change. |
| Appendix D Patient Reported Outcome (PRO) questionnaires<br><br>Appendix E Genetic Research | The document headers were added, because they were missing in the V2.0 of CSP. |
| **Version 4.0, 17 March 2020** | |
| Protocol Synopsis | Removal of the interim analysis paragraph.<br><br>The planned interim analysis has been removed as it is foreseen that the outcome of this analysis will be close to the planned study end date. |
| 3.11 Discontinuation of the study<br><br>8.2 Sample size estimate<br><br>8.5.1 Hypotheses<br><br>8.5.2 Closed testing procedure<br><br>8.5.6 Interim analysis | Removal of all text around the interim analysis. Accordingly, the statistical testing level for endpoints have been corrected, now 2.5% instead of 2.496%. |

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# PROTOCOL SYNOPSIS

## A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease


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### Study site(s) and number of patients planned

| Study period | | Phase of development |
|---|---|---|
| Estimated date of first patient enrolled | Q1 2017 | Phase III |
| Estimated date of last patient completed | Q4 2020 | |

### Study design

This is an international, multicentre, event-driven, randomised, double-blind, parallel group, placebo-controlled study, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to standard of care, to prevent the progression of chronic kidney disease (CKD) or cardiovascular (CV)/renal death.

## Objectives

| **Primary Objective:** | **Outcome Measure:** |
|---|---|
| To determine if dapagliflozin is superior to placebo in reducing the incidence of the primary composite endpoint of ≥50% sustained decline in estimated glomerular filtration rate (eGFR), reaching end stage renal disease (ESRD), CV or renal death when added to current background therapy in patients with eGFR ≥25 and ≤75 mL/min/1.73m$^2$ and albuminuria (urine albumin creatinine ratio [UACR] ≥200 and ≤5000 mg/g). | Time to the first occurrence of any of the components of this composite:<br>1. ≥50% sustained* decline in eGFR<br>2. Reaching ESRD<br>– Sustained* eGFR <15 mL/min/1.73m$^2$ or,<br>– Chronic* dialysis treatment or,<br>– Receiving a renal transplant<br>3. CV death<br>4. Renal death<br>**As defined in the Clinical Event Adjudication (CEA) charter* |

| **Secondary Objective:** | **Outcome Measure:** |
|---|---|
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of the composite endpoints of worsening of renal function. | Time to the first occurrence of any of the components of this composite:<br>1. ≥50% sustained decline in eGFR<br>2. Reaching ESRD<br>3. Renal death |
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of the composite endpoint of CV death or hospitalisation for heart failure. | Time to the first occurrence of either of the components of this composite:<br>1. CV death<br>2. Hospitalisation for heart failure |
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of all-cause mortality. | Time to death from any cause |

| **Safety Objective:** | **Outcome Measure:** |
|---|---|
| To evaluate the safety and tolerability of dapagliflozin in this patient population. | 1. Serious adverse event (SAE)<br>2. Discontinuation of investigational product (IP) due to adverse event (DAE)s<br>3. Changes in clinical chemistry/haematology parameters<br>4. Adverse events (AEs) of interest (volume depletion, renal events, major hypoglycaemic events, fractures, diabetic ketoacidosis (DKA), Adverse events (AEs) leading to amputation and AEs leading to a risk for lower limb amputations ["preceding events"]) |

**Target patient population**

The target population will have CKD (eGFR ≥25 and ≤75 mL/min/1.73m$^2$) with albuminuria (urine albumin creatinine ratio [UACR] ≥200 and ≤5000 mg/g) with or without type 2 diabetes (T2D). However, patients with known polycystic kidney disease, glomerulonephritis with flares (lupus or anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis) or ongoing active renal inflammation will be excluded.

**Duration of treatment**

This study is event-driven. The anticipated duration of the study is approximately 45 months with an estimated mean treatment period for a patient of 33 months. The study closure procedures will be initiated when the predetermined number of primary endpoints are predicted to have occurred (n=681), i.e., the study end date (SED). The study duration may be changed if the event rate or randomisation rate is different than anticipated. The study may be terminated early if either a clear beneficial or harmful effect of the study treatment is detected during the Data Monitoring Committee (DMC) review.

**Investigational product (IP), dosage and mode of administration**

Patients will be randomised 1:1 to either dapagliflozin 10 mg or placebo. Every attempt should be made to maintain patients on dapagliflozin 10 mg or matching placebo during the course of the study. In addition to the preferred 10 mg dose, the 5 mg dose of dapagliflozin

can be used in the study when clinically indicated. If the dose has been decreased to 5 mg, the dose should be increased back to dapagliflozin 10 mg or matching placebo as soon as, in the opinion of the investigator, the patient's condition is stable.

**Statistical methods**

The primary objective of the study is to determine the superiority of dapagliflozin versus placebo in reducing the incidence of the primary composite endpoint. Assuming a true hazard ratio of 0.78 between dapagliflozin and placebo, using a one-sided alpha of 2.5%, 681 primary endpoint events will provide a statistical power of 90% for the test of the primary composite endpoint. This is based on an overall 1:1 allocation between dapagliflozin and placebo. The study is event-driven.

With an annual event rate of 7.5% in the placebo treatment group, 4000 patients are estimated to provide the required number of primary events, based on an anticipated recruitment period of 24 months and an average follow-up period of approximately 33 months.

All patients who have been randomised to study treatment will be included in the full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. The primary variable is the time to first event included in the primary composite endpoint. The primary analysis will be based on the intention to treat (ITT) principle using the FAS. In the analysis of the primary composite endpoint, dapagliflozin versus placebo will be compared using a Cox proportional hazards model with a factor for treatment group, stratified by randomisation stratification factors (T2D, UACR), and adjusting for eGFR.

A closed testing procedure including a pre-specified hierarchical ordering of the primary and secondary endpoints will be utilized. No multiplicity control is placed on the exploratory endpoints.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

| Abbreviation or special term | Explanation |
|---|---|
| ACE-I | Angiotensin converting enzyme inhibitor |
| ALP | Alkaline phosphatase |
| ALT | Alanine transaminase |
| ANCA | Anti-neutrophil cytoplasmic antibody |
| ARB | Angiotensin receptor blockers |
| AST | Aspartate transaminase |
| AZ | AstraZeneca, sponsor |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CABG | Coronary artery bypass grafting |
| CEA | Clinical Event Adjudication |
| CKD | Chronic kidney disease |
| CRO | Clinical research organization |
| CSA | Clinical study agreement |
| CSR | Clinical study report |
| CV | Cardiovascular |
| DAE | Discontinuation of investigational product due to adverse event |
| DGR | Dangerous Goods Regulations |
| DKA | Diabetic ketoacidosis |
| DMC | Data Monitoring Committee |
| DMP | Data management plan |
| E-code | Enrolment number |
| EASD | European Association of the Study of Diabetes |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| eGFR | Estimated glomerular filtration rate |
| EMA | European Medicines Agency |

| Abbreviation or special term | Explanation |
|---|---|
| EQ-5D-5L | EuroQol five-dimensional five-level questionnaire |
| ESRD | End stage renal disease |
| FAS | Full analysis set |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| Hb | Haemoglobin |
| HbA1c | Glycated haemoglobin |
| hCG | Human chorionic gonadotropin |
| HR | Hazard ratio |
| IATA | International Airline Transportation Association |
| IB | Investigator's brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| IRB/IEC | Institutional review board/independent ethics committee |
| International Ccoordinating investigator | If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the investigators and/or activities internationally. |
| IP | Investigational Product (dapagliflozin or matching placebo) |
| ITT | Intention to treat |
| IxRS | Interactive Voice/Web Response System |
| KDQOL™-36 | Kidney Disease Quality of Life-36 |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial infarction |
| NYHA | New York Heart Association |
| PCI | Percutaneous coronary intervention |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| PRO | Patient reported outcomes |
| PTH | Parathyroid hormone |
| PTDV | Premature treatment discontinuation visit |
| RAAS | Renin-angiotensin-aldosterone system |
| SAE | Serious adverse event |

| Abbreviation or special term | Explanation |
|---|---|
| SAP | Statistical analysis plan |
| SCV | Study closure visit |
| SED | Study end date |
| SGLT2 | Sodium glucose co-transporter 2 |
| SU | Sulfonylurea |
| T1D | Type 1 diabetes |
| T2D | Type 2 diabetes |
| TIA | Transient ischemic attack |
| UACR | Urine albumin creatinine ratio |
| ULN | Upper limit of normal |
| WBDC | Web based data capture |

# 1. INTRODUCTION

## 1.1 Background and rationale for conducting this study

Chronic kidney disease (CKD) affects approximately 10% of the adult population worldwide (Eckart et al 2013). The most common causes of CKD are diabetes, hypertension and chronic glomerulonephritis. Treatment for CKD encompasses angiotensin converting enzyme inhibitor (ACE-I) and angiotensin II receptor blockers (ARBs), lipid and blood pressure (BP) control as well as a tight glucose control in diabetic patients.

Dapagliflozin (Forxiga™/Farxiga™) is a highly selective and reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2), the major transporter responsible for glucose reabsorption in the kidney. Dapagliflozin's mechanism of action results in a direct and insulin independent elimination of glucose by the kidneys, which results in reduced blood glucose levels in type 2 diabetes (T2D) patients. In addition, dapagliflozin has a mild diuretic and natriuretic effect. The persistent loss of glucose with associated calories in the urine, results in a consistent and maintained reduction of the total body weight, predominantly a result of a reduction in fat mass including both visceral and subcutaneous adipose tissue. Moreover, dapagliflozin has also been shown to reduce BP and albuminuria, two essential prognostic risk factors for progression of CKD.

There is a growing body of evidence indicating that SGLT2 inhibition is nephroprotective. This effect is thought to be achieved partly by mechanisms independent of blood glucose reductions (Rajasekeran et al 2016, Heerspink at al 2016b), such as reduced intra-glomerular pressure through an enhanced tubuloglomerular feedback mechanism (De Nicola et al 2014, Thomas 2014), reduced glucose and sodium transport over the proximal tubule cells (Komala et al 2013, Pollock et al 1991), increased natriuresis (Heerspink et al 2013) and reduced systemic BP (Baker et al 2015, Sjöström et al 2015a). Interestingly, there is a theoretical rationale for an improved oxygen availability in the impaired kidney during dapagliflozin treatment. This could potentially be achieved via two mechanisms. Firstly, an improved oxygen delivery due to a small but consistently observed haemo-concentration and secondly through a reduced renal oxygen consumption due to a reduced energy requirement from the potassium sodium pump situated on the basal-lateral membrane striving to retain the sodium gradient over the tubular cells (Gilbert RE 2016, Korner et al 1994). Finally, there are emerging theories around metabolic benefits connected to a mild ketosis induced by SGLT2 inhibition (Mudaliar et al 2016).

Notably, the total amount of glucose excreted in the urine following dapagliflozin administration, declines with decreasing kidney function and clinically important reduction in glycated haemoglobin (HbA1c) has not been demonstrated in T2D patients with estimated glomerular filtration rate (eGFR) <45 ml/min (Kohan et al 2014). However, similar reductions of non-glycaemic variables such as BP, body weight and albuminuria have been observed with

dapagliflozin (Kohan et al 2014) and other SGLT2 inhibitors (Barnett et al 2014, Yale et al 2013) in patients with impaired renal function as in patients with normal renal function.

Furthermore, post-hoc analyses of data from the dapagliflozin phase II and phase III programme have shown in T2D patients with moderate renal impairment on renin-angiotensin-aldosterone system (RAAS) blockade a reduction of around 40% in albuminuria and stabilization of eGFR decline for up to one year (Sjöström et al 2015b) and two years (Fioretto et al 2016). The EMPA-REG outcome trial, examining the cardiovascular (CV) effect of empagliflozin in T2D patients has further indicated beneficial renal effects of SGLT2 inhibition. After an initial drop in eGFR, kidney function was stable over time while a progressive decrease in eGFR was seen in the placebo group. The trial also suggested substantial risk reductions for new onset of macroalbuminuria, doubling of serum creatinine and initiation of dialysis treatment (Wanner et al 2016).

**Nephroprotective effects not related to glucose excretion, rationale for use in non-T2D**

As indicated above many of the effects from SGLT2 inhibition thought to contribute to a nephroprotective effect seem to be largely unrelated to glucose control per se. Accordingly, regression analyses on data from the dapagliflozin phase III program indicate that the albuminuria lowering effect is not dependent on the glucose lowering actions seen during SGLT2 inhibition (Heerspink et al 2016, Fioretto et al 2016). Furthermore, pooled data from the phase III program does not indicate a reduced effect on volume constriction (as measured by changes in haematocrit), systolic BP, pulse pressure, albuminuria and body weight in subjects with low glucose excretion due to renal impairment as compared with subjects excreting larger amounts of glucose in the urine (Sjöström et al 2016, EASD 2016).

Data on the effect of SGLT2 inhibition in patients without diabetes is limited. However, dapagliflozin has safely been administered in healthy volunteers over a broad dose range (up to 500 mg given as single dose) (Kasichayanula et al 2014). Dapagliflozin effectively inhibited SGLT2 also in healthy volunteers without any observed events of hypoglycaemia. Furthermore, a clinical trial with canagliflozin, showed clinically relevant BP and weight reductions in obese non-diabetic patients without an increased incidence of hypoglycaemia (Bays et al 2013).

Overall, the available data strongly indicate that non-diabetic CKD patients would also benefit from SGLT2 inhibition induced changes in variables important for nephroprotection. As a consequence, this study will include CKD patients with and without T2D.

## 1.2 Rationale for study design, doses and control groups

### 1.2.1 Rationale for study design and study population

This is a randomised, double-blind, parallel-group study. Randomisation and double blinding will minimize potential bias. Parallel group design was chosen because a crossover study cannot assess major renal outcome events. The study will be multicentre in numerous geographic regions to provide a wide applicability of results.

The study population chosen for this study is a broad population of patients with impaired kidney function. Patients with CKD are at high risk of CV events, terminal renal failure and death (Go et al 2004). Albuminuria adds to this risk, hence, the target population will have CKD (eGFR ≥25 and ≤75 mL/min/1.73m$^2$) with albuminuria (urine albumin creatinine ratio [UACR] ≥200 and ≤5000 mg/g). However, patients with known polycystic kidney disease, glomerulonephritis with flares (lupus or anti-neutrophil cytoplasmic antibodies [ANCA] associated vasculitis) or ongoing active renal inflammation will be excluded.

There is scientific rationale for beneficial effects of SGLT2 inhibition also in patients with CKD but without diabetes. Patients with CKD have similar clinical picture with increased intra-glomerular pressure, hypertension, proteinuria and fluid/sodium overload regardless of underlying disease. SGLT2 inhibition can improve on all these abnormalities through metabolic-independent mechanisms. Moreover, the reduction on CV and renal events with empagliflozin cannot be explained by the glucose lowering effect alone (Rajasekeran et al 2016, Mudaliar et al 2016, Gilbert RE 2016).

### 1.2.2 Rationale for primary outcome measure

The primary outcome measure is based on the requirements as outlined in the European Medicines Agency (EMA)'s draft guideline, which states that a composite endpoint of ≥50% sustained decline in eGFR, end stage renal disease (ESRD) and renal death (death due to ESRD when dialysis is not given) are acceptable outcome measures (EMA 2016). This endpoint has also been used in a number of previous outcome studies.

CV mortality is added as a component of the composite endpoint since CV mortality in the population being studied is high and the risk for CV death correlates with the risk of developing ESRD. Thus, CV mortality is a competitive risk component and dapagliflozin is expected to have a beneficial effect on both CV death and renal outcome (Wanner et al 2016).

### 1.2.3 Rationale for secondary outcome measure

It is of importance to separately look at the effect on composite renal endpoints and the composite heart failure endpoints (hospitalisation for heart failure and CV death). Heart failure is particularly common in patients with CKD. SGLT2 inhibition has previously shown to have beneficial effects on heart failure outcomes in patients with T2D and established CV disease (Zinman et al 2015). All-cause mortality will be assessed as a secondary endpoint because it is important to evaluate the effect of dapagliflozin on non-CV, as well as CV, mortality and hence overall mortality.

### 1.2.4 Rationale for dose selection

The marketed dose, 10 mg, of dapagliflozin has been demonstrated to be well tolerated and effective for the treatment of T2D and post hoc analyses in patients with CKD and albuminuria have shown that this dose effectively reduces renal surrogate markers, i.e., BP and albuminuria, independent of the glucose lowering effect. In a dedicated CKD 3 study (eGFR 30 to 60 mL/min/1.73m$^2$) this dose was found to be well tolerated (Kohan et al 2014). From a pharmacokinetics (PK) and pharmacodynamics perspective, dapagliflozin 10 mg is appropriate

for use in patients with renal impairment. The marketed 5 mg dose of dapagliflozin may be used in the study, but it is expected to provide less inhibition of SGLT2 and thus exert less pharmacodynamics effects (for details on when 5 mg or matching placebo can be used, see Section 3.9.1).

## 1.3 Benefit/risk and ethical assessment

Dapagliflozin has global market approval and based on global cumulative sale figures up to March 2016 it is estimated that dapagliflozin has been administered for >1 000 000 patient years.

### 1.3.1 Potential risks

The potential risks of treatment with dapagliflozin are described in the Investigator's Brochure (IB). Additional considerations relevant for the target population are described below.

Dapagliflozin has not been shown to induce hypoglycaemia in non-diabetes patients. In clinical pharmacology studies, healthy subjects have been treated with single oral doses up to 500 mg and multiple oral doses of 100 mg up to 14 days without any hypoglycaemic event.

Events related to volume depletion (including reports of dehydration, hypovolemia, or hypotension) and events related to changes in renal function have been thoroughly evaluated in the dapagliflozin phase III program. In a large pool consisting of 21 active- and placebo-controlled studies, serious adverse events (SAEs) of volume depletion were infrequently reported and the proportion was even lower for subjects treated with dapagliflozin than control (0.1% versus 0.2%). SAEs of renal impairment/failure were also rarely reported and balanced between treatment groups in the clinical trial program. In total, 9 (0.2%) SAEs were reported in the dapagliflozin group and 5 (0.1%) SAEs in the control group.

Although the phase III data in patients with CKD 3 show an increased frequency of overall renal events in patients treated with dapagliflozin as compared with placebo, most of these events have been related to laboratory detected transient increases in creatinine.

In an analysis using pooled data on a subset of patients with CKD 3, micro or macro albuminuria and treatment with ACE-I or ARB there was no meaningful difference between dapagliflozin and placebo in terms of SAEs of renal impairment/failure or SAEs of volume depletion (Sjöström et al 2015b).

Similarly, in a recent analysis of patients with pre-existing heart failure (HF) using pooled data from previous dapagliflozin studies (Kosiborod et al 2016), the rate of hypovolemic events was similar between patients treated with dapagliflozin and patients treated with placebo.

Loop-diuretics are widely used in the target patient population and are also allowed in this study. In the dapagliflozin phase III program, patients using loop diuretics were more likely to have an event related to volume depletion regardless of whether they were treated with dapagliflozin or placebo. A pooled analysis of the short-term treatment periods showed 6 (2.5%) subjects with events in patients on dapagliflozin 10 mg and 4 (1.5%) in patients on

placebo. When including the long-term extension periods of the phase III trials in the analysis, the corresponding values were 7 (3.0%) versus 7 (2.7%) for dapagliflozin and placebo, respectively.

Furthermore, other post hoc safety analyses of importance to the current target population have not identified any indication of an increased risk of marked abnormalities in potassium levels (≥6 mmol/L) in either patients with CKD 3 and ACE-I/ARB treatment (Sjöström et al 2015b) or in patients on concomitant treatment with potassium sparing agents (Kosiborod et al 2016).

#### 1.3.1.1 Protection against risks

This study has been designed with appropriate measures in place to monitor and minimize any potential health risks to participating patients. In order to ensure the safety of all patients participating in AstraZeneca (AZ) sponsored studies, reviews of all safety information from all ongoing clinical dapagliflozin studies are conducted as they become available. In addition, an independent Data Monitoring Committee (DMC) will be responsible for safeguarding the interests of the patients by reviewing safety data throughout the study.

### 1.3.2 Potential benefits to patients

In this study, the dose of dapagliflozin 10 mg was chosen based on previous clinical experience. Dapagliflozin is believed to be nephroprotective through non-glycaemic mechanisms and the hypothesis is that patients treated with dapagliflozin will have delayed progression of CKD and reduction in CV mortality. Dapagliflozin has been shown to reduce UACR, HbA1c, BP and body weight in patients with T2D.

Patients, irrespective of treatment, in clinical studies may receive greater medical care/attention than in ordinary clinical practice.

### 1.3.3 Conclusion

At the time of writing this clinical study protocol, no available SGLT2 inhibitors are indicated for treatment of CKD in patients with and without T2D. Considering the non-clinical and clinical experience with dapagliflozin and the precautions included in the study protocol, participation in this study should present a minimal and thus acceptable risk to patients who meet the inclusion/exclusion criteria and consent to take part in the study.

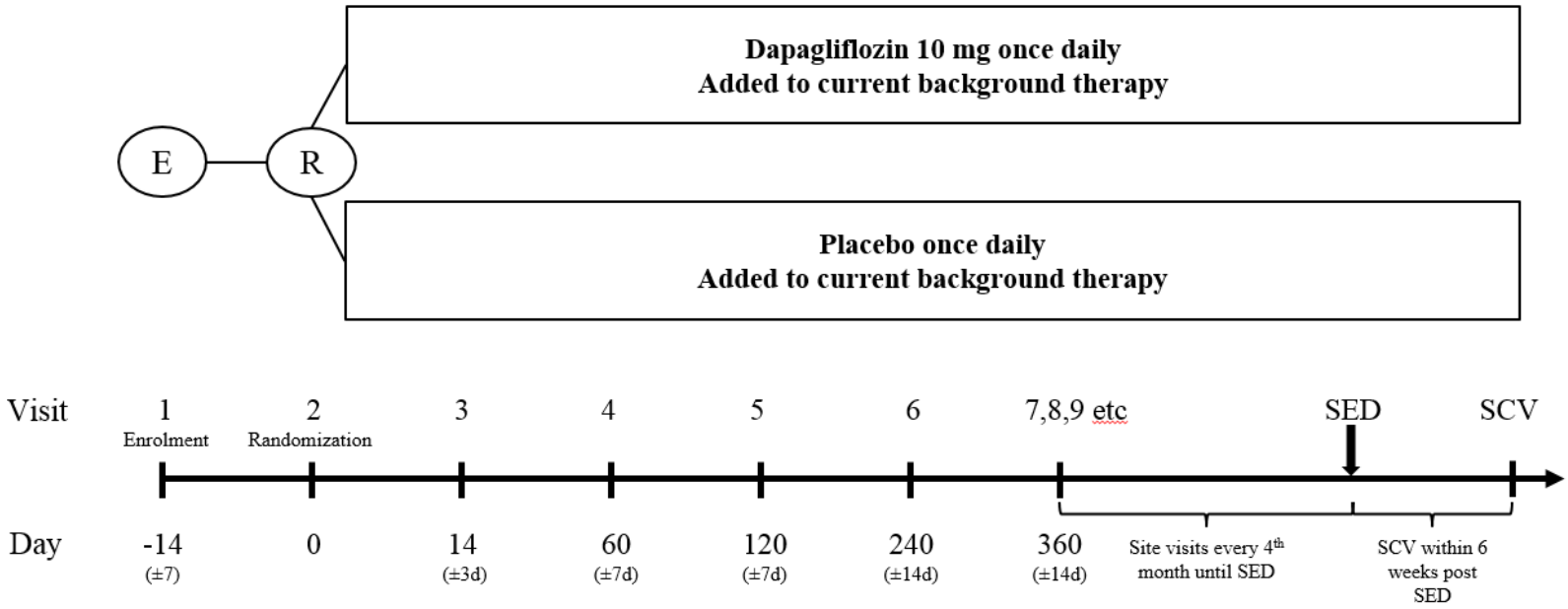
## 1.4 Study design

This is an international, multicentre, event-driven, randomised, double-blind, parallel-group, placebo-controlled study, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to standard of care, to prevent the progression of CKD or CV/renal death.

It is estimated that approximately 10 000 patients at approximately 450 study sites in approximately 20 countries will be enrolled to reach the target of approximately 4000 randomised patients.

The anticipated duration of the study is approximately 45 months. The study closure procedures will be initiated when the predetermined number of primary endpoints is predicted to have occurred (n=681), i.e., the study end date (SED) (see Figure 1). The study duration may be changed if the event rate or randomisation rate is different than anticipated. The study may be terminated early if either a clear beneficial or harmful effect of the study treatment is detected during the DMC review.

**Figure 1 Study design**




SED = Study end date (ie, date when the predetermined number of adjudicated primary events is predicted to have occurred)
E = enrolment
SCV = Study closure visit
R = Randomization

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

| **Primary Objective:** | **Outcome Measure:** |
|---|---|
| To determine if dapagliflozin is superior to placebo in reducing the incidence of the primary composite endpoint of ≥50% sustained decline in eGFR, reaching ESRD, CV or renal death when added to current background therapy in patients with eGFR ≥25 and ≤75 mL/min/1.73m$^2$ and albuminuria (UACR ≥200 and ≤5000 mg/g). | Time to the first occurrence of any of the components of this composite:<br>1. ≥50% sustained* decline in eGFR<br>2. Reaching ESRD<br>– Sustained* eGFR <15 mL/min/1.73m$^2$ or,<br>– Chronic* dialysis treatment or,<br>– Receiving a renal transplant<br>3. CV death<br>4. Renal death<br>**As defined in the Clinical Event Adjudication (CEA) charter* |

## 2.2 Secondary objectives

| **Secondary Objective:** | **Outcome Measure:** |
|---|---|
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of the composite endpoints of worsening of renal function. | Time to the first occurrence of any of the components of this composite:<br>1. ≥50% sustained decline in eGFR<br>2. Reaching ESRD<br>3. Renal death |
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of the composite endpoint of CV death or hospitalisation for heart failure. | Time to the first occurrence of either of the components of this composite:<br>1. CV death<br>2. Hospitalisation for heart failure |
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of all-cause mortality. | Time to death from any cause |

## 2.3 Safety objectives

| Safety Objective: | Outcome Measure: |
|---|---|
| To evaluate the safety and tolerability of dapagliflozin in this patient population. | 1. Serious adverse event (SAE)<br>2. Discontinuation of investigational product (IP) due to adverse event (DAE)s<br>3. Changes in clinical chemistry/haematology parameters<br>4. AEs of interest (volume depletion, renal events, major hypoglycaemic events, fractures, diabetic ketoacidosis (DKA), AEs leading to amputation and AEs leading to a risk for lower limb amputations [“preceding events”]) |

## 2.4 Exploratory objectives

| Exploratory Objective: | Outcome Measure: |
|---|---|
| To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of the composite endpoint of chronic dialysis, renal death or receiving a renal transplant. | Time to the first occurrence of any of the components of this composite:<br>1. Chronic dialysis<br>2. Receiving renal transplant<br>3. Renal death |
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of the individual components of the primary endpoint. | Time to the first occurrence of each of the individual components:<br>1. ≥50% sustained decline in eGFR<br>2. Reaching ESRD<br>3. CV death<br>or<br>4. Renal death |

| **Exploratory Objective:** | **Outcome Measure:** |
|---|---|
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of sustained reduction in kidney function. | Time to the first occurrence of two consecutives central laboratory values showing either of the following:<br>1. ≥30% decline in eGFR from baseline<br>2. ≥40% decline in eGFR from baseline |
| To determine whether dapagliflozin compared with placebo will have an effect on eGFR over time. | The effect on eGFR over time will be measured:<br>1. From baseline to end of treatment<br>2. From first on treatment measurement to end of treatment |
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of patients reaching CKD 4 (eGFR <30 mL/min/1.73m$^2$). | Proportion of patients with eGFR >40 mL/min/1.73m$^2$ at baseline that enter CKD 4 during the study. |
| To determine whether dapagliflozin compared with placebo will have effect on UACR. | Changes in UACR from baseline. |
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of hyper- and hypokalaemia. | Time to the first occurrence of each of any of the following central laboratory levels of serum potassium:<br>• >6.0 mmol/L<br>• >5.5 mmol/L<br>• <3.5 mmol/L<br>• <3.0 mmol/L |
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of events of doubling of serum creatinine. | Time to the first occurrence of an event of doubling of serum creatinine (compared to the most recent central laboratory measurement) |
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of new diagnosis of T2D in patients without diabetes at baseline. | Proportion of patients without diabetes at baseline with a new diagnosis of T2D during the study |
| To determine whether dapagliflozin compared with placebo will have effect on HbA1c in T2D patient subgroup. | Changes in HbA1c from baseline |

| **Exploratory Objective:** | **Outcome Measure:** |
|---|---|
| To determine whether dapagliflozin compared with placebo will have an effect on systolic BP. | Change in systolic BP from baseline |
| To determine whether dapagliflozin compared with placebo will have an effect on body weight. | Change in body weight from baseline |
| To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of the composite endpoint of CV death, MI or stroke. | Time to the first occurrence of any of the components of this composite:<br>1. CV death<br>2. MI<br>3. Stroke |
| To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of heart failure hospitalisation. | Time to first hospitalisation for heart failure |
| To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of myocardial infarction (MI). | Time to first fatal or non-fatal MI |
| To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of any stroke (ischemic, haemorrhagic, or undetermined). | Time to first fatal or non-fatal stroke of any cause |
| To compare the effect of dapagliflozin versus placebo on the Kidney Disease Quality of Life-36 (KDQOL™-36) questionnaire. | Change from baseline in the overall summary score of the KDQOL™-36 |
| To compare the effect of dapagliflozin versus placebo on health status assessed by EuroQol five-dimensional five-level questionnaire (EQ-5D-5L) to support health economic analysis and health technology assessment. | Changes in health status measured by the EQ-5D-5L |
| To collect and analyse PK samples for dapagliflozin concentration. | Not applicable. Results will be reported separately. |
| To collect and store blood/urine samples for future exploratory biomarker and genetic research. | Not applicable. Results will be reported separately. |

# 3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

## 3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of signed informed consent prior to any study specific procedures
2. Female or male aged ≥18 years at the time of consent
3. eGFR ≥25 and ≤75 mL/min/1.73m$^2$ (CKD-EPI Formula) at visit 1
4. Evidence of increased albuminuria 3 months or more before visit 1 and UACR ≥200 and ≤5000 mg/g at visit 1
5. Stable, and for the patient maximum tolerated labelled daily dose, treatment with ACE-I or ARB for at least 4 weeks before visit 1, if not medically contraindicated

## 3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis
2. Receiving cytotoxic therapy, immunosuppressive therapy or other immunotherapy for primary or secondary renal disease within 6 months prior to enrolment
3. History of organ transplantation
4. Receiving therapy with an SGLT2 inhibitor within 8 weeks prior to enrolment or previous intolerance of an SGLT2 inhibitor
5. Type 1 diabetes mellitus (T1D)
6. New York Heart Association (NYHA) class IV Congestive Heart Failure at the time of enrolment (see Appendix C)
7. MI, unstable angina, stroke or transient ischemic attack (TIA) within 12 weeks prior to enrolment
8. Coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or valvular repair/replacement within 12 weeks prior to enrolment or is planned to undergo any of these procedures after randomisation
9. Any condition outside the renal and CV disease area, such as but not limited to malignancy, with a life expectancy of less than 2 years based on investigator´s clinical judgement

10. Active malignancy requiring treatment at the time of visit 1 (with the exception of successfully treated basal cell or treated squamous cell carcinoma).

11. Hepatic impairment (aspartate transaminase [AST] or alanine transaminase [ALT] >3x the upper limit of normal [ULN]; or total bilirubin >2x ULN at time of enrolment). An isolated increase in bilirubin in patients with known Gilbert's syndrome is not a reason for exclusion.

12. Known blood-borne diseases such as specified in Appendix B (category A and B).

13. Women of child-bearing potential (i.e., those who are not chemically or surgically sterilised or who are not post-menopausal) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator, from the time of signing the informed consent throughout the study and 4 weeks thereafter, OR women who have a positive pregnancy test at enrolment or randomisation OR women who are breast-feeding.

14. Involvement in the planning and/or conduct of the study (applies to both AZ personnel and/or site personnel).

15. Previous randomisation in the present study.

16. Participation in another clinical study with an IP during the last month prior to enrolment.

17. Inability of the patient, in the opinion of the investigator, to understand and/or comply with IP, procedures and/or follow-up OR any conditions that, in the opinion of the investigator, may render the patient unable to complete the study.

    - Patients who cannot complete the patient reported outcome (PRO) assessments can still participate in the study (see Section 5.1.8.3 for details regarding the patient exclusion from the PRO assessments during certain circumstances).

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

## 3.3 Patient enrolment and randomisation

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the patient or their guardian/legal representative before any study specific procedures are performed.

2. Assign the patient a unique enrolment number (E-code), beginning with 'E#', which will be used to identify the patient throughout the study. The E-code to be assigned in the Interactive Voice/Web Response System (IxRS).

3. Determine patient eligibility. See Section 3.

4. At visit 2, perform the randomisation transaction in the IxRS.

Re-enrolment is allowed one single time considering that the patient was not randomised. The same E-code that the patient received at the first enrolment will be used. All enrolment assessments and procedures (see Section 4.1.1), including re-signing the informed consent form (ICF), should be performed again.

## 3.4 Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive IP. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AZ study physician immediately, and a discussion should occur between the AZ study physician and the investigator regarding whether to continue or discontinue the patient from treatment. Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. In those cases where continuation of study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. Regardless of what is decided about IP all randomised patients should remain in the study and the patients should continue to be followed up in accordance with defined study procedures.

## 3.5 Methods for assigning treatment groups

Randomisation to IP will be performed via IxRS at visit 2 in balanced blocks to ensure approximate balance between the treatment groups (1:1).

The IxRS will allocate the IP through a randomisation scheme and provide the randomisation number and the appropriate Kit IDs from IP available at the study site. The randomisation codes will be computer generated and loaded into the IxRS database.

At all visits where IP is dispensed, site personnel will do a kit verification in IxRS before providing the IP bottle to the patient.

Detailed instruction on use of the IxRS system will be provided to study sites.

### 3.5.1 Stratification and capping

The recruitment will be continuously monitored in order to achieve adequate proportions of patient sub-populations.

Randomisation of patients based on geographic region will be monitored to ensure a global representation. Also, the proportion of patients not on ACE-I or ARB at randomisation, due to intolerance, will be monitored to ensure that the target population is reflected in regards to background therapy.

#### 3.5.1.1 Stratification

Randomisation will be stratified in IxRS based on patients with and without T2D at the time of randomisation in order to ensure approximate balance between treatment groups within each sub-population. T2D at the time of randomisation is based on:

- Established diagnosis of T2D

  OR

- HbA1c more or equal to 6.5% (48 mmol/mol) shown at central laboratory test at enrolment (visit 1)

Randomisation will also be stratified in IxRS for patients with UACR >1000 mg/g to ensure an equal proportion of patients in each treatment group.

#### 3.5.1.2 Capping

The number of randomised patients with and without T2D will be monitored in order to ensure a minimum of 30% in each sub-population. Randomisation may be capped in IxRS (i.e., no more patients in a specific sub-population can be randomised) if the pre-determined limit is reached.

The number of patients with eGFR 60 to 75 mL/min/1.73m$^2$ at the time of randomisation, shown with a laboratory test at enrolment (visit 1), will be monitored and randomisation in IxRS may be capped to ensure that the number of patients in this sub-population does not exceed approximately 10%.

## 3.6 Methods for ensuring blinding

The blinding of treatment is ensured by using a double-blind technique. The dapagliflozin tablets and the respective placebo tablets will be identical in size, colour, smell, and taste. The bottles with IP will be labelled with unique identification numbers.

No member of the extended AZ study team, site personnel, or any clinical research organization (CRO) handling study data will have access to the randomisation scheme during the study. The AZ personnel or delegate generating the randomisation scheme and the Supply Chain Study Management may be able to access the randomisation scheme as appropriate.

## 3.7 Methods for unblinding

Individual treatment codes, indicating the randomised treatment for each patient, will be available to the Investigator(s) or pharmacists from the IxRS. Instructions for code breaking/ unblinding will be described in the IxRS user manual that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AZ, without revealing the treatment given to patient to the AZ personnel. It is always the investigator who decides when to unblind but it is recommended that the investigator first contacts the AZ study physician for consultation regarding the need for unblinding. If unblinding is deemed necessary, the investigator will perform the unblinding in IxRS and must document all actions taken. The number of individuals at the study site who become aware of treatment status should be kept to the absolute minimum (including keeping the patient blinded if possible). Treatment with study medication should be continued if possible.

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

### 3.7.1 Unblinding for bioanalytical laboratory personnel

PK samples will be analysed at the bioanalytical laboratory only for patients on active IP. The bioanalytical laboratory will therefore have access to the treatment codes but will not share the codes with the sponsor or others involved in the study until the blinding is broken for the study after closure.

## 3.8 Restrictions

There are no specific dietary or activity restrictions. For restricted concomitant medications see Section 7.7.

## 3.9 Discontinuation of investigational product

If the patient temporarily or permanently discontinues from IP, it is important that the scheduled study visits, data collection and procedures continue according to the study protocol until study closure (see Section 3.9.3).

Patients may be discontinued from IP in the following situations:

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.

2. AE or other safety reasons that, in the opinion of the investigator contraindicates further dosing with IP.

3. Severe non-compliance with the study protocol.

4. DKA, consider to temporary interrupt IP if DKA is suspected. If DKA is confirmed, IP should be discontinued permanently.

5. Positive pregnancy test (discontinue IP and notify AZ representative).

### 3.9.1 Evaluation of volume status and investigational product (IP) dose reduction/interruption

Dapagliflozin is a SGLT2 inhibitor which by its mechanism of action reduces the reabsorption of glucose and sodium in the proximal tubules in the kidney. SGLT2 inhibition has a mild diuretic effect and an initial haemodynamic change with an initial increase in creatinine may occur.

**Unexpected acute declines in eGFR**

If an unexpected, acute decline in kidney function is observed, the patient should be 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 (the latter especially in men). Several drugs may cause a decline in kidney function, especially non-steroidal anti-inflammatory drugs (NSAID) 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.

**Volume depletion/hypotension**

Patients with clinically relevant symptoms/signs of suspected volume depletion and/or hypotension, should have their regular medication reviewed, and consideration given to reducing the dose of, or stopping concomitant non-essential medications, as assessed on an individual basis, including diuretics and drugs that lower BP (except essential treatments – see below). The need for conventional diuretics (or the dose of diuretic used) should be re-evaluated in light of the patient's symptoms and signs. In patients with heart failure, discontinuation of diuretic should only be undertaken cautiously. Hypotension may also occur with other BP lowering drugs and once again the need for (and dose of) non-essential agents of this type (e.g., calcium channel blockers, alpha adrenoceptor antagonists and nitrates) should also be re-considered.

**Essential treatments**

Essential disease modifying/evidence based treatments such as ACE-I/ARBs, for patients with proteinuric CKD and ACE-I/ARBs, sacubitril/valsartan, mineralocorticoid receptor antagonists and beta-blockers for patients with heart failure, should NOT be reduced in dose or discontinued unless all other measures fail to improve the patient's situation. In the setting of acute worsening of HF or other acute situations it may be acceptable to interrupt treatment

on a temporary basis in certain circumstances (e.g., an ACE-I/ARB if the patient has experienced a significant deterioration in renal function, a beta-blocker if the patient is unduly bradycardic or hypotensive, a mineralocorticoid receptor antagonist (MRA) if the patient has hyperkalaemia).

**IP dose reduction**

If the above mentioned measures do not lead to a resolution of clinically relevant volume depletion, hypotension and/or unexpected worsening of kidney function, a dose reduction of IP to dapagliflozin 5 mg or matching placebo may be considered and the patient's condition re-evaluated.

**Patients at risk of volume depletion**

Temporary interruption of IP may be considered in patients thought to be at risk of volume depletion/hypotension, such as patients with an acute medical illness potentially causing volume depletion because of inadequate fluid intake or fluid/blood loss (e.g., gastroenteritis, gastrointestinal haemorrhage), or those undergoing major surgery.

### 3.9.2 Investigational product (IP) restart or dose increase from dapagliflozin 5 mg to 10 mg or matching placebo

Restart of randomised IP is always encouraged. Even if a premature treatment discontinuation visit (PTDV) was completed due to the discontinuation of IP, this should not prevent the patient to return to randomised treatment if deemed appropriate.

Every attempt should be made to maintain patients on dapagliflozin 10 mg or matching placebo during the course of the study. If the dose has been decreased to 5 mg or interrupted, the dose should be increased back to dapagliflozin 10 mg or matching placebo or re-introduced as soon as, in the opinion of the investigator, the patient's condition is stable.

### 3.9.3 Procedures for discontinuation of a patient from investigational product (IP)

At any time, patients are free to discontinue IP. A patient that decides to discontinue will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an investigator. Adverse events will be followed up, see Section 6, and all IP should be returned by the patient.

Generally, AEs, SAEs and potential endpoint events should not lead to IP discontinuation, unless there is a clear clinical rationale to do so.

Discontinuation from IP is not the same as complete withdrawal from the study. If a patient is completely withdrawn from study, see Section 3.10.2.

It is essential to collect data for all patients throughout the study. Optimally, a patient who discontinue from IP should for that reason attend all study visits according to plan until study closure. Alternatively, if the patient does not agree to this approach, modified follow-up should be arranged. Patients who agree to some kind of modified follow up are still

participating in the study. The modified visits and procedures that are done will be recorded in the electronic Case Report Form (eCRF).

If a patient for some reason cannot be reached during the study, every attempt should be made to retrieve as much information regarding this patient as possible. The site should continuously try to reach the patient, the patient's family or pre-identified appropriate contact person(s) and, search for information regarding the patient's status in applicable sources to protect the validity of data. The attempts should be registered in the medical records.

#### 3.9.3.1 Patient undergoes the premature treatment discontinuation visit (PTDV) and continues according to plan

The preferred follow-up approach for all patients who prematurely and permanently discontinue IP is that the patient undergoes the PTDV and then continues study visits according to plan (Table 1). The PTDV should be done as soon as possible after last IP dose.

#### 3.9.3.2 Patient agrees to undergo modified follow-up

If the patient does not agree to continue study visits according to plan, but agrees to undergo modified follow up, a PTDV should be done (Table 1). The subsequent visits until the study closure will be done as modified follow-up (e.g., less frequent visits, regular telephone contacts, a contact at study closure, or other means) in order to ascertain whether any endpoints or safety events have occurred.

## 3.10 Criteria for withdrawal

### 3.10.1 Screen failures

Screen failures are enrolled patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Screen failure' (i.e., patient does not meet the required inclusion/exclusion criteria) in the eCRF. This reason for study withdrawal is only valid for screen failures (not randomised patients).

### 3.10.2 Withdrawal of informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment. Withdrawal of consent should only occur if the patient does not agree to any kind of further assessments or contact whatsoever. If agreed by the patient, a PTDV should be performed. Discontinuation of IP in itself is not considered withdrawal of consent.

Withdrawal of consent must be ascertained and documented in writing by the investigator who must inform the AZ representative and document the withdrawal of consent in the eCRF and medical records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The investigator will follow up AEs reported outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrolment and randomisation codes cannot be reused. Withdrawn patients will not be replaced. Data generated to the time of complete withdrawal from the study will not be destroyed.

To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially vital status (dead or alive) at study closure (also for patients who have withdrawn their informed consent). The investigator will therefore attempt to collect information on all patients' vital status from publicly available sources at study closure, even if informed consent has been withdrawn completely, in compliance with local privacy laws/practices.

## 3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AZ, patients are placed at undue risk because of clinically relevant findings. The judgment may be based on recommendations from the DMC, see DMC Charter for details.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

# 4. STUDY PLAN AND TIMING OF PROCEDURES

The schedule of study visits and assessments is shown in Table 1 and explained further in Sections 4.1 and 4.2.

**Table 1 Study plan**

| Activity | Enrolment | Randomi-sation | Site visits | | | | | Premature treatment discontinua-tion visit | Study closure visit | Reference in CSP |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit number** | **1** | **2** | **3** | **4** | **5** | **6** | **7, 8, 9 etc.** | **PTDV** | **SCV** | |
| **Day** | **-14** (±7) | **0** | **14** (±3) | **60** (±7) | **120** (±7) | **240** (±14) | **360** (±14 and every 4th month) | | ≤6 weeks from SED | |
| Sign Informed Consent Form (ICF) | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | 3.1/3.2 |
| Enrolment in IxRS | X | | | | | | | | | 3.3 |
| Randomisation in IxRS | | X | | | | | | | | 3.3 |
| Demography | X | | | | | | | | | |
| Medical/surgical history | X | | | | | | | | | |

## Table 1 Study plan

| Activity | Enrolment | Randomi-sation | Site visits | | | | | Premature treatment discontinua-tion visit | Study closure visit | Reference in CSP |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit number** | **1** | **2** | **3** | **4** | **5** | **6** | **7, 8, 9 etc.** | **PTDV** | **SCV** | |
| **Day** | **-14** (±7) | **0** | **14** (±3) | **60** (±7) | **120** (±7) | **240** (±14) | **360** (±14 and every 4th month) | | ≤6 weeks from SED | |
| Vital signs *(BP, pulse and body weight)* | X | X | X | X | X | X | X | X | X | 5.2.4 |
| Height | X | | | | | | | | | 5.2.4 |
| Local laboratory assessment [a] | X [a] | | | | | | | | | 5.2.1 |
| Central laboratory assessment [b] | X | X | X | X | X | X | X | X | X | 5.2.1 |
| Spot UACR, central laboratory sampling | X | X | X | X | X | X | X | X | X | 5.2.1 |
| Pregnancy testing | X | X | | | | | | | | 5.2.1 |
| Sample for biomarker research, if applicable [c] | | X | | | | | X [c] | | | 5.7 |
| Sample for genetic research, if applicable [c] | | X | | | | | | | | Appendix E |

## Table 1 Study plan

| Activity | Enrolment | Randomi-sation | Site visits | | | | | Premature treatment discontinua-tion visit | Study closure visit | Reference in CSP |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit number** | **1** | **2** | **3** | **4** | **5** | **6** | **7, 8, 9 etc.** | **PTDV** | **SCV** | |
| **Day** | **-14** (±7) | **0** | **14** (±3) | **60** (±7) | **120** (±7) | **240** (±14) | **360** (±14 and every 4th month) | | ≤6 weeks from SED | |
| PK sampling (pre-dose) | | | | | | | X [d] | | | 5.4 |
| Potential endpoints, SAEs DAEs etc, AEs of interest [e] | X [e] | X | X | X | X | X | X | X | X | 6 |
| KDQOL™-36 questionnaire | | X | | | | | X [f] | X | X | 5.1.8.1 |
| EQ-5D-5L questionnaire | | X | | | X | X | X [f] | X | X | 5.1.8.2 |
| General physical examination | | X | | | | | | X | X | 5.2.2 |
| Targeted physical examination | | | X | X | X | X | X | | | 5.2.2 |
| Electrocardiogram (ECG) | | X | | | | | | | | 5.2.3 |
| Concomitant medication | | X | X | X | X | X | X | X | X | 7.7 |

## Table 1 Study plan

| Activity | Enrolment | Randomi-sation | Site visits | | | | | Premature treatment discontinua-tion visit | Study closure visit | Reference in CSP |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit number** | **1** | **2** | **3** | **4** | **5** | **6** | **7, 8, 9 etc.** | **PTDV** | **SCV** | |
| **Day** | **-14** (±7) | **0** | **14** (±3) | **60** (±7) | **120** (±7) | **240** (±14) | **360** (±14 and every 4th month) | | ≤6 weeks from SED | |
| Dispense (including kit verification in IxRS)/Collect IP | | X | | | X | X | X | X | X | 3.5 |
| IP compliance reminder | | X | X | X | X | X | X | | | |

[a] Local laboratory assessment is optional and may be used to assess eligibility (according to local routine) of eGFR and/or albuminuria. If used, the ICF needs to be signed before the optional assessment starts.

[b] Central laboratory assessments include alkaline phosphatase (ALP), ALT, AST, bilirubin, blood urea nitrogen (BUN), creatinine (including eGFR assessment), haematocrit, haemoglobin (Hb), HbA1c, phosphate, potassium, and sodium will be analysed as specified in Table 2.

[c] Blood and urine samples for future biomarker and/or genetic research is optional. The biomarker and/or genetic sampling is subject to separate consent by the patient. Biomarker samples will be collected at visit 2 and 7, and genetic samples will be collected at visit 2.

[d] PK samples will be collected at visit 7.

[e] SAEs will be collected from the time of informed consent throughout the study until and including the patient's last visit. Potential endpoints, DAEs, AEs leading to dose reduction and temporary interruptions and AEs of interest will be collected from randomisation throughout the study until and including the patient's last visit.

[f] The PRO questionnaires will be completed as specified until visit 7 and thereafter every 12 months, and at PTDV and study closure visit (SCV).

## 4.1 Enrolment period

### 4.1.1 Visit 1, enrolment (day -14 ±7)

During enrolment period the following assessments and procedures will be completed:

- Patient signs the **ICF** before any study procedures.
  - Patients who agree to the optional sampling of blood and urine for potential future biomarker and/or genetic research will provide their consent.
- Patient will be **enrolled** and assigned an **E-code in IxRS**.
- **Optional local laboratory assessment**

  Failure to meet the criteria for eGFR and/or albuminuria is expected to be the main reason for screen failure in this study. Therefore, sites will be allowed to perform an optional assessment, which will include local laboratory assessments of eGFR and/or albuminuria. Investigators will only assess patients who are potentially eligible for the study based on their medical conditions and existing therapies, and only those who are expected to meet all other entry criteria.

  Local laboratory assessments of eGFR and/or albuminuria will be done according to local routine.

  When the local results of eGFR are available and indicate that the patient may be eligible based on the clinical judgement of the investigator, the patient may proceed to further enrolment procedures.

- The investigator reviews the **inclusion and exclusion criteria**. Patients who do not meet these criteria must not be randomised in the study.
- **Demography** (date of birth, sex, race, ethnic group) and **relevant medical and surgical history,** including **smoking history**, will be recorded.
- **Vital signs** (BP, pulse and body weight) and **height** will be assessed and recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.

- Due to high day to day variability of creatinine (eGFR) and UACR, one central laboratory retest is allowed, if in the opinion of the investigator values are close to the inclusion criteria.

- **Pregnancy test** for women of child-bearing potential will be done locally with a dipstick provided by central laboratory.

## 4.2 Treatment period

### 4.2.1 Visit 2, randomisation (day 0)

Prior to visit 2, the investigator assesses eligibility based on the laboratory results received from central laboratory from visit 1. Patients not eligible will be considered screen failures and should not continue to visit 2.

At randomisation, the following assessments and procedures will be done:

- **KDQOL™-36** and **EQ-5D-5L** will be completed by the patient prior to any other site activities and before the patient meets the investigator.

- The investigator will re-assess the **inclusion** and **exclusion criteria**.

- The investigator will perform a **general physical examination.**

- **Vital signs** will be assessed and recorded.

- Electrocardiogram (**ECG**) will be done.

- **Randomisation** to IP will be done in IxRS.

  - For stratification/capping purposes (see Section 3.5.1), information about eGFR and UACR (based on results received from central laboratory), and whether patient has T2D or not will be recorded in IxRS.

- **Concomitant medication** will be recorded.

- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.

  - Patients who have consented to sampling for potential future **biomarker analysis and/or genetic research**, will provide blood and urine samples.

- **Pregnancy test** for women of child-bearing potential will be done locally with a dipstick provided by central laboratory.

- If the patient has experienced any **SAEs** since last visit, this will be recorded in the eCRF.
- The IP will be dispensed via IxRS to the patient. The patient will be instructed to take the IP in accordance with protocol without interruptions.

### 4.2.2 Visit 3 (day 14 ±3)

At visit 3, the following assessments and procedure will be done:

- The investigator will perform a **targeted physical examination.**
- **Vital signs** will be assessed and recorded.
- Any relevant changes in **concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs, and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- The patient will be reminded to take the IP in accordance with the protocol and without interruptions.

### 4.2.3 Visit 4 (day 60 ±7)

At visit 4, the following assessments and procedure will be done:

- The investigator will perform a **targeted physical examination.**
- **Vital signs** will be assessed and recorded.
- Any relevant changes in **concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs, and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- The patient will be reminded to take the IP in accordance with the protocol and without interruptions.

### 4.2.4 Visit 5 (day 120 ±7)

At visit 5, the following assessments and procedures will be done:

- **EQ-5D-5L** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
- The investigator will perform a **targeted physical examination.**
- **Vital signs** will be assessed and recorded.
- Any relevant changes in **concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs, and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- IP will be dispensed via IxRS to the patient and drug accountability of the returned medication will be checked. The patient will be instructed to take the IP in accordance with the protocol and without interruptions.

### 4.2.5 Visit 6, (day 240 ±14)

At visit 6, the following assessments and procedures will be done:

- **EQ-5D-5L** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
- The investigator will perform a **targeted physical examination.**
- **Vital signs** will be assessed and recorded.
- Any relevant changes in **concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs, and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- IP will be dispensed via IxRS to the patient and drug accountability of the returned medication will be checked. The patient will be instructed to take the IP in accordance with the protocol and without interruptions.

- At visit 6, patient will be reminded to not take IP until after the visit at visit 7 to enable pre-dose PK sampling.

### 4.2.6 Visit 7, 8, 9 etc., on-site visits; (day 360 ±14 and; every 4th month)

At visit 7 and all subsequent visits until SCV, the following assessments and procedures will be done:

- **KDQOL™-36** and **EQ-5D-5L** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
  - The PRO questionnaires will be done at visit 7 and thereafter every 12 months.
- The investigator will perform a **targeted physical examination.**
- **Vital signs** will be assessed and recorded.
- Any relevant changes in **concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
  - At visit 7, pre-dose, a **PK sample** will be collected. The patient should not take IP before the visit this day. The date and time of last dose before sampling will be recorded in eCRF.
  - At visit 7, patients who have consented to sampling for potential future **biomarker analysis**, will provide blood and urine samples.
- If the patient has experienced any **potential endpoints, SAEs, DAEs, and/or AEs of interest** since the last visit, this will be recorded in eCRF.
- IP will be dispensed via IxRS to the patient and drug accountability of the returned medication will be checked. The patient will be instructed to take the IP in accordance with protocol without interruptions.

### 4.2.7 Premature treatment discontinuation visit (PTDV)

Patients who prematurely and permanently discontinue treatment with IP should return for a PTDV, which will be done as soon as possible after last IP dose.

- **KDQOL™-36** and **EQ-5D-5L** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
- The investigator will perform a **general physical examination.**

- **Vital signs** will be assessed and recorded.
- Any relevant changes in **concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs, and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- **Drug accountability** of the returned medication will be checked.

Patients who discontinue treatment prematurely should attend all following study visits according to plan, including the SCV.

For further details regarding discontinuations from IP, refer to Section 3.9.

### 4.2.8 Study closure visit (SCV)

All patients will be asked to return for an SCV visit when the predetermined number of primary endpoints is predicted to have occurred, i.e., the SED. All randomised patients (including any patients who have discontinued treatment with IP) should return for their SCV visit as soon as possible but no later than 6 weeks after the SED.

- **KDQOL™-36** and **EQ-5D-5L** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
- The investigator will perform a **general physical examination.**
- **Vital signs** will be assessed and recorded
- Any relevant changes in **concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs, and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- The patient will return remaining IP and **drug accountability** will be checked.

After stopping IP the investigator should ensure that the patient is treated according to standard clinical practice and ascertain there is a proper medical follow-up plan in place.

### 4.2.9 Unscheduled visits

An unscheduled visit may occur in-between scheduled visits e.g., to follow up on potential endpoints such as re-sampling for eGFR (see Section 5.1.3.1).

## 4.3 Follow-up period (Not applicable)

# 5. STUDY ASSESSMENTS

The Rave web based data capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs in Rave as specified in the study protocol and in accordance with the eCRF instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the clinical study agreement (CSA).

The investigator will sign the completed eCRFs. A copy of the completed eCRF will be archived at the study site.

## 5.1 Efficacy assessments

### 5.1.1 Endpoint reporting overview

Potential endpoints will be identified through laboratory data (refer to Table 2 for laboratory assessments and timings); when questioning the patient about his/her overall health; or through information received through standard medical practice. Investigators will be encouraged to have a low threshold to submit any potential/possible event that might represent an endpoint.

The following potential endpoints will be recorded in the eCRF and submitted for central adjudication:

- All deaths
- Renal endpoints:
  - Dialysis
  - Kidney transplantations
  - Doubling of serum creatinine (compared to the most recent central laboratory measurement)
- Hospitalisation for heart failure
- Cardiac ischaemic events (MI and unstable angina)
- Cerebrovascular events (stroke and TIA)

- DKA (not considered an efficacy variable but will be adjudicated as a safety variable)

In addition, eGFR declines ≥50% from baseline, eGFR values <15 mL/min/1.73m$^2$ and new diagnosis of T2D will be recorded in the eCRF but will not be adjudicated.

For each potential endpoint, the investigator or delegate will record the endpoint specific information the eCRF. If the event is subject to adjudication, relevant source documents will be assembled. The source documents and relevant eCRF data will be sent for central adjudication.

Detailed instructions regarding endpoint reporting will be provided to the study sites.

Additional details about the evaluations of potential endpoints will be described in the Clinical Event Adjudication (CEA) charter.

### 5.1.2 Classification of death

The CEA committee members will adjudicate and classify all deaths based on definitions described in the CEA charter. For the purpose of the efficacy analysis, deaths will be sub-classified into CV and non- CV as well as renal primary cause (death due to ESRD when dialysis is not given). The investigator will record the classification of death as CV or non-CV death in the eCRF.

### 5.1.3 Potential renal endpoints

#### 5.1.3.1 Endpoints related to eGFR decline

**eGFR baseline** is defined as the mean **central laboratory value** from visit 1 and visit 2.

Laboratory values related to eGFR decline will trigger an action by site in the following situations:

- **Local laboratory** values indicate that eGFR value has declined ≥50% compared with baseline, or is below 15 mL/min/1.73m$^2$.

  – As soon as possible, patient should come to the study site for confirmation by a central laboratory testing.

  OR

- **Central laboratory** values, collected during a study visit, indicating that eGFR value has declined ≥50% compared with baseline, or is below 15 mL/min/1.73m$^2$.

The central laboratory will notify site if eGFR is <15 mL/min/1.73m$^2$ or if there is ≥50% decline in eGFR compared to baseline. A re-sampling should be done at an unscheduled visit after at least 4 weeks, and preferably no later than 6 weeks after the first sampling. When a

central laboratory value is <15 mL/min/1.73m$^2$ or if there is ≥50% decline in eGFR compared to baseline it should be recorded as a potential endpoint in the eCRF.

The central laboratory will calculate eGFR using CKD-EPI equation (Levey at al 2009).

#### 5.1.3.2 Dialysis and renal transplantation

If a patient starts dialysis and or go through a renal transplantation this will be recorded in the eCRF and submitted for adjudication.

#### 5.1.3.3 Doubling of serum creatinine

Doubling of serum creatinine (compared to the most recent central laboratory measurement) will be recorded in the eCRF and submitted for adjudication.

Recording of doubling of serum creatinine compared to the most recent central laboratory result can be triggered by a local laboratory result OR a central laboratory result.

### 5.1.4 Hospitalisation for heart failure

All potential hospitalizations for heart failure should be recorded in the eCRF and submitted to adjudication. The CEA committee members will adjudicate the events as specified in the CEA Charter.

### 5.1.5 New diagnosis of type 2 diabetes (T2D)

New onset of T2D, post randomisation, is defined according to the following criteria:

- Reporting of new onset of T2D necessitating initiation of anti-diabetic medication

  OR

- HbA1c ≥6.5% (48 mmol/mol) measured by central lab at two consecutive study visits

New onset of T2D will be recorded as an AE and on a separate eCRF page.

### 5.1.6 Cardiac ischaemic events

Sites should record potential acute coronary syndromes such as MIs and unstable angina in the eCRF and submit for adjudication. The CEA committee members will adjudicate all potential cardiac ischaemic events to decide if they qualify as MIs according to the criteria defined in the CEA charter.

### 5.1.7 Cerebrovascular events

Sites should record potential strokes and TIAs in the eCRF and submit for adjudication. The CEA committee members will adjudicate all potential cerebrovascular events to decide if they qualify as stroke according to the criteria defined in the CEA charter.

### 5.1.8 Patient reported outcomes (PROs)

PROs is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become important endpoints for regulatory and reimbursement authorities when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered in the study: KDQOL™-36 and EQ-5D-5L (see Appendix D). Patients will be asked to complete the EQ-5D-5L and the KDQOL™-36 at the visits as specified in Table 1.

#### 5.1.8.1 The Kidney Disease Quality of Life-36 (KDQOL™-36)

The KDQOL™-36 is an abbreviated form of the KDQOL, which is a self-reported questionnaire that combines generic and disease-specific components for assessing the health-related quality of life of patients with CKD, see Appendix D.

#### 5.1.8.2 EuroQol five-dimensional five-level questionnaire (EQ-5D-5L)

The EQ-5D-5L is a self-reported questionnaire that is used to derive a standardized measure of health status, also referred to as a utility score, see Appendix D. EQ-5D-5L utility scores are widely accepted by reimbursement authorities and will be used to support health economic evaluations.

#### 5.1.8.3 Administration of patient reported outcomes (PROs)

All PROs will be administered electronically. Randomised patients will complete the PRO assessments at site using the same handheld electronic device (ePRO). Each site must allocate the responsibility for the administration of the ePROs to a specific individual and, if possible, assign a backup person to cover if that individual is absent.

All assessments should be completed as follows:

- Patient must not receive help from relatives, friends, or site personnel to answer or clarify the PRO questionnaires, in order to avoid bias. If a patient uses visual aids (e.g., spectacles or contact lenses) for reading and does not have them at hand, the patient will be exempted from completing the PROs questionnaires on that visit.
- Before any other study procedures are conducted at a given visit.
- Before being seen by the investigator.
- PRO questionnaires must be completed by the patient in private.
- The appointed site personnel should explain to patient the value and relevance of ePRO assessments and inform that these questions are being asked to find out, directly from patients, how he/she feels. The appointed site personnel should also stress that the information is confidential.

- The appointed site personnel must show patients how to use the ePRO device, in accordance with the instructions provided.
- The appointed site personnel should remind patients that there are no right or wrong answers, and the patient should be given sufficient time to complete the PRO questionnaires.
- If the patient is unable to read the questionnaire (e.g., is blind or illiterate), the patient will be exempted from completing the PRO questionnaires and may still participate in the study.

## 5.2 Safety assessments

### 5.2.1 Laboratory assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in Table 1. The date of central laboratory sample collection will be recorded in the eCRF, excluding local laboratory samples if taken at enrolment. All laboratory samples will be analysed at the central laboratory, with the exception of urine human chorionic gonadotropin (hCG) (pregnancy test, using a dipstick provided by the central laboratory), and laboratory samples taken at enrolment, which will be analysed locally.

All samples should be taken by adequately trained site personnel and handled in accordance with instructions in the Laboratory Manual. Up to date reference ranges will be provided during the study and laboratory results will be compared with the laboratory standard normal ranges and reported back to site.

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

The following laboratory variables will be measured:

**Table 2 Laboratory variables**

| **Haematology** | **Clinical chemistry** |
|---|---|
| Haemoglobin (Hb) [b] | Alanine transaminase (ALT) [b] |
| Haematocrit [a] | Alkaline phosphatase (ALP) [b] |
| | Aspartate transaminase (AST) [b] |
| **Urinalysis (dipstick)** | Bilirubin [b] |
| hCG (pregnancy test) | Blood urea nitrogen (BUN) [a] |
| | Creatinine (including eGFR assessment) [a] |
| **Spot urinalysis** | HbA1c [a] |
| U-Albumin (including UACR assessment) [a] | Phosphate [c] |
| U-Creatinine[a] | Potassium [a] |
| | Sodium [a] |

[a] Central laboratory analysis at all visits
[b] Central laboratory analysis at visit 1, PTDV and SCV
[c] Central laboratory analysis at visit 2, 5, PTDV and SCV

The Investigator should make an assessment of the laboratory results with regards to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the study site as source data for laboratory variables.

#### 5.2.1.1 Unscheduled laboratory assessments

Unscheduled laboratory samples will be requested by the central laboratory for follow-up on e.g., eGFR values. Follow-up samples related to eGFR should be collected during an unscheduled visit and sent to central laboratory for analysis.

### 5.2.2 Physical examination

A general physical examination, including volume status, will be performed at the time of randomisation and when the patient stops IP.

A targeted physical examination with focus on volume status will be performed as specified in the study plan (see Table 1).

The assessment dates will be recorded in the eCRF.

### 5.2.3 Electrocardiogram (ECG)

A 12-lead ECG (standard ECG with a paper speed of 25 to 50 mm/second covering at least 6 sequential beats) will be recorded at randomisation (visit 2) after the patient has been lying down to rest for at least 5 minutes. The baseline ECG should be made available for CEA upon

request, to facilitate adjudication of potential cardiac ischaemic events. The ECG date will be recorded in the eCRF.

### 5.2.4 Vital signs

Vital signs will be assessed according to the study plan, Table 1.

#### 5.2.4.1 Pulse and blood pressure (BP)

Pulse and BP will be measured three times at all visits, and all measurements will be recorded in the eCRF. The measurements should be done before any blood sampling using a standardized cuff adapted to the size of the patient's arm after the patient has been sitting and resting for least 5 minutes. Preferably, the same arm should be used at all visits.

#### 5.2.4.2 Body weight and height

The patient's body weight will be measured with light clothing and no shoes at all visits. If the patient has a prosthetic limb, this should be consistently worn or not worn during all weight measurements. The patient's height will be measured at visit 1, with no shoes. The weight and height will be recorded in the eCRF.

## 5.3 Other assessments (not applicable)

## 5.4 Pharmacokinetics (PK)

### 5.4.1 Collection of samples

One pre-dose blood sample for determination of the dapagliflozin concentration in plasma will be taken at visit 7. Information about last intake of IP and sampling ID, date and time will be recorded in the eCRF.

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

### 5.4.2 Determination of drug concentration

Samples for determination of dapagliflozin concentration in plasma will be analysed by the bioanalytical laboratory on behalf of AZ, using an appropriate validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

### 5.4.3 Storage and destruction of pharmacokinetics (PK) samples

PK samples will be analysed during the course of the study and disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier). The results of the PK analyses will be kept at the laboratory until the end of the study to prevent unblinding.

PK samples may be disposed of or destroyed and 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 clinical study report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

## 5.5 Pharmacodynamics (not applicable)

## 5.6 Genetics

Refer to Appendix E for details regarding optional genetic sampling.

For withdrawal of consent to the optional genetic sampling, refer to Section 5.7.4.

## 5.7 Biomarker analysis

Serum and plasma as well as urine will be collected and stored for potential future analysis for exploratory biomarkers to assess correlations with disease activity, effects of dapagliflozin, clinical outcomes and toxicity. Biomarker samples will be collected, handled and shipped as detailed in the laboratory manual.

It is mandatory to obtain the patient's consent to the donation and use of biological samples. The consent date will be recorded in the eCRF. Patient not consenting to donate biological samples for future biomarker analysis are still able to participate in the study, but without providing samples for biomarker analysis.

The biomarkers to be studied will be selected on possible relevance on pathophysiology of the studied diseases.

### 5.7.1 Storage, re-use and destruction of biological samples

Samples will be stored in AZ biobank for a maximum of 15 years from the date of the last patient's last visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with dapagliflozin to generate hypotheses to be tested in future research.

### 5.7.2 Labelling and shipment of biological samples

The Principal Investigator (PI) ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AZ and appropriate labelling, shipment and containment provisions are approved. Samples can be shipped to specialist labs around the world and analysed by academic collaborators or commercial partners.

### 5.7.3 Chain of custody of biological samples

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

The PI at each site keeps full traceability of collected biological samples from the patients while in storage at the study site until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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 documentation of receipt of arrival.

AZ keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AZ biobank during the entire life cycle.

### 5.7.4 Withdrawal of informed consent for donated biological samples

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

As collection of donated biological samples is an optional part of the study, the patient may continue in the study.

The PI:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified as soon as possible to AZ.
- Ensures that biological samples from that patient, if stored at the study site, are identified as soon as possible, disposed of /destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent as soon as possible and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the patient and AZ are informed about the sample disposal.

AZ ensures the laboratory(ies) or biobank holding the samples is/are informed about the withdrawn consent as soon as possible and that samples are disposed of/destroyed and the action documented and returned to the study site.

# 6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

## 6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs. The term AE in this document refers only to the categories of events described in Section 6.3.

## 6.2 Definitions of serious adverse event (SAE)

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol.

## 6.3 Recording of adverse events

### 6.3.1 Time period for collection of adverse events

AEs will be collected from randomisation (visit 2) throughout the treatment period until and including the patient's last study visit.

SAEs will be recorded from the time of informed consent throughout the treatment period until and including the patient's last visit.

AEs should be recorded in the eCRF only if:

- It qualifies as an **SAE** (as defined in Section 6.2)
- The AE is the reason for permanent discontinuation from IP (**DAE**)
- The AE is the reason for **IP interruption or dose reduction**
- It qualifies as an **AE of interest**
  - Volume depletion
  - Renal events
  - Major hypoglycaemic events
  - Fractures
  - Potential DKAs
  - AEs leading to amputation and AEs leading to a risk for lower limb amputations ("preceding events")
- A potential endpoint (see Section 5.1) fulfils the AE criteria. NB: not all potential endpoints are per definition an AE e.g., a potential endpoint solely related to laboratory findings (see Section 6.3.7) should not be recorded unless any of the above mentioned criteria is met.

An AE/SAE could be associated with more than one potential endpoint. In such scenario, only one AE/SAE should be recorded but all potential endpoints should be recorded individually.

### 6.3.2 Adverse events of interest

#### 6.3.2.1 Volume depletion

Events of volume depletion (e.g., dehydration, hypovolemia, or hypotension) will be recorded in the eCRF as AEs.

#### 6.3.2.2 Renal events

Renal events, such as an acute clinically relevant decline in kidney function as judged by the investigator, will be recorded in the eCRF as AEs. If the event also qualifies as a potential endpoint as defined in Section 5.1.3.2, a separate eCRF will be completed.

#### 6.3.2.3 Major hypoglycaemic events

A major hypoglycaemic event is defined as an event that requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions.

Plasma glucose concentrations may not be available during an event, but neurological recovery following the corrective actions is considered sufficient evidence that the event was induced by a low plasma glucose concentration. Major hypoglycaemic episodes will be recorded in the eCRF as an AE and on an additional eCRF page.

#### 6.3.2.4 Fractures

All fractures will be recorded in the eCRF as AEs.

#### 6.3.2.5 Diabetic ketoacidosis (DKA)

All potential events of DKA will be recorded in the eCRF and submitted to an independent DKA Adjudication Committee (see Section 6.8.5).

#### 6.3.2.6 Adverse events (AEs) leading to amputation and AEs leading to a risk for lower limb amputations ("preceding events")

To ensure that data on amputations is systematically collected, amputations and underlying conditions relevant to amputation will be recorded on a specific eCRF page. The adverse event leading to amputation should be recorded in the eCRF as AE/SAE.

In addition, non-serious and serious events potentially placing the patient at risk for a lower limb amputation ("preceding events") should also be recorded in the eCRF as AE/SAE, whether or not an amputation has taken place. The lower limb "preceding events" of interest include diabetic foot related conditions, vascular, wounds/injury/trauma, infection and neuropathy. If any of these or other potentially relevant event have occurred, relevant information must be provided (this will be collected on a dedicated eCRF page - for details see eCRF instruction).

### 6.3.3 Follow-up of unresolved adverse events

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

### 6.3.4 Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date when the AE started and stopped

- Maximum intensity (mild/moderate/severe)
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Outcome

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

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- 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) and/or other medication
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria described in Section 6.2. 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 Section 6.2. 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 Section 6.2.

### 6.3.5 Causality collection

The investigator will assess causal relationship between IP 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 IP?’

For SAEs causal relationship will 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 A.

### 6.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient, or reported in response to the open question from the site personnel: *'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 (if fulfilling the criteria for recording as specified in Section 6.3.1). 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.

### 6.3.7 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared with baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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 (e.g., anaemia versus low Hb value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

## 6.4 Reporting of serious adverse events (SAEs)

All SAEs have to be reported, whether or not considered causally related to the IP, 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 AZ representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AZ representative works with the investigator to ensure that all the necessary information is provided to the AZ Patient Safety data entry site **within 1 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 is undertaken immediately. Investigators or other site personnel inform AZ

representatives of any follow-up information on a previously reported SAE within one calendar day i.e., 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 WBDC system, an automated email alert is sent to the designated AZ representative.

If the WBDC system is not available, then the investigator or other site personnel reports a SAE to the appropriate AZ representative by telephone in accordance with SAE reporting timelines.

The AZ representative will advise the investigator/site personnel how to proceed.

### 6.4.1 Reporting of serious adverse events (SAEs) considered to be potential endpoints

In order to avoid unnecessary unblinding of efficacy endpoint events, certain SAEs which are also potential endpoints (i.e., fatal events and heart failure events) will not be reported to health authorities. Clinical data for the above mentioned events will be recorded as AEs/SAEs as well as on separate event forms in the eCRF. Recording of a suspected endpoint should be done within the same timeframes as defined for SAEs (see Section 6.4).

In addition, fatal AEs and potential heart failure endpoints will be centrally adjudicated by an independent CEA committee (see Section 5.1.1 and 6.8.4). If adjudication confirms the endpoint, the SAE will not be reported to health authorities. However, if it is determined by the CEA committee that a potential endpoint in the above mentioned categories does not meet the endpoint criteria, the event will be reported (according to the timelines specified in Section 6.3.1) to AZ patient safety data entry site and if applicable to the health authorities (note that the clock starts when the adjudication results are available).

## 6.5 Overdose

Dapagliflozin has been well tolerated at doses of 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 T2D. Suspected single intake of more than 50 tablets of 10 mg dapagliflozin tablets or repeated intake of more than 10 tablets of 10 mg dapagliflozin tablets should be recorded in the eCRF. If an overdose is suspected, monitoring of vital functions as well as treatment should be performed as appropriate.

For further information regarding overdose, refer to the IB.

- 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 recorded in the Overdose eCRF module.

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

The designated AZ representative works with the investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply (see Section 6.4). For other overdoses, reporting must occur within 30 days.

## 6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AZ.

### 6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study IP should be discontinued immediately.

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

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

The designated AZ representative works with the investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

## 6.7 Management of IP related toxicities (not applicable)

## 6.8 Study governance and oversight

### 6.8.1 Executive Committee

Together with AZ the Executive Committee will be responsible for the final overall study design, including the development of the study protocol and eCRF, and any protocol

amendments, supervision of the study conduct and progress, development of any protocol amendments needed during the study, liaison with the CEA Committee and DMC, as needed, development of the statistical analysis plan (SAP), interpretation of the final data and reporting (presentations at international congresses and publications in peer reviewed journals) of the study.

The Executive Committee will make recommendations to AZ with regard to early stopping or modifications of the study based on the information received from the DMC. The Executive Committee will be comprised of designated international academic leaders and non-voting members of the Sponsor, and will operate under an Executive Committee charter.

### 6.8.2 National Lead Investigator (NLI) Committee

The National Lead Investigator (NLI) Committee will be comprised of NLIs from each country where the study is conducted and supervised by the Executive Committee. Members of the committee will be responsible for providing clinical guidance on study implementation, recruitment and study conduct in their respective country.

### 6.8.3 Data Monitoring Committee (DMC)

An independent DMC will be appointed and will report to the Executive Committee. The DMC will be responsible for safeguarding the interests of the patients in the study by assessing the safety of the IP during the study, and for reviewing the overall conduct of the study. The DMC will have access to the individual treatment codes and be able to merge these with the collected study data while the study is ongoing. A DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the Executive Committee.

### 6.8.4 Clinical Event Adjudication (CEA) Committee

The role of the CEA committee is to independently review, interpret and adjudicate potential endpoints that are experienced by the patients. Endpoints will be identified preliminary by the Investigators, and also by AZ personnel or in the CEA process as specified in the CEA charter.

The CEA committee members will not have access to individual treatment codes for any patient or clinical efficacy endpoint and safety event. The precise responsibilities and procedures applicable for CEA will be detailed in the CEA charter.

### 6.8.5 Diabetic Ketoacidosis Adjudication Committee T2D

All potential events of DKA will be submitted to an independent DKA Adjudication Committee. The committee will be kept blinded to the treatment codes. A separate DKA Adjudication Manual will define and describe the procedures for the collection of DKA information, handling, adjudication criteria and reporting of these events.

## 6.9 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 subject or has the potential to cause harm to the subject.

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 subject.

Medication error includes situations where an error

- occurred
- was identified and intercepted before the subject received the drug
- did not occur, but circumstances were recognized that could have led to an error

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

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

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject 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 AZ product

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

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., 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 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

# 7. INVESTIGATIONAL PRODUCT (IP) AND OTHER TREATMENTS

## 7.1 Identity of investigational product (IP)

| Investigational product (IP) | Dosage form and strength | Manufacturer |
|---|---|---|
| Dapagliflozin 10 mg | Green, plain, diamond shaped, film coated tablets 10 mg | AZ |
| Matching placebo for Dapagliflozin 10 mg | Green, plain, diamond shaped, film coated tablets placebo | AZ |
| Dapagliflozin 5 mg | Green, plain, diamond shaped, film coated tablets 5 mg | AZ |
| Matching placebo for Dapagliflozin 5 mg | Green, plain, diamond shaped, film coated tablets placebo | AZ |

Dapagliflozin and its matching placebo tablets will be packed in bottles. The tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals.

## 7.2 Dose and treatment regimens

At randomisation, visit 2 (day 0), eligible patients will be randomly assigned to 1 of 2 treatments:

- Dapagliflozin 10 mg, given once daily per oral use
- Placebo – one placebo tablet to match dapagliflozin 10 mg, given once daily per oral use

Randomisation and treatment pack assignment will be managed via an IxRS at visit 2. The IP should be taken per oral once daily in the morning and at approximately the same time every day, during the study period. If the patient, for any reason prefers not to administer the IP in the morning, any other time point during the day may be applied, provided the patient routinely administer the IP in approximate 24 hours intervals. The IP should not be altered (e.g., crushed, put in another vehicle) and should not be given by nasogastric tube or other routes.

If the dose is adjusted (i.e., lowered to 5 mg or increased back to 10 mg) during the study (see Section 3.9.1 and 3.9.2), this will be handled in IxRS and the dose change will be recorded in the eCRF.

Missed doses of dapagliflozin or placebo blinded study medication should not be compensated for (i.e., if a dose is missed, the next regularly scheduled dose should be taken and should not be doubled).

## 7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

## 7.4 Storage

All IPs should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage.

## 7.5 Compliance

The administration of all IPs should be recorded in the appropriate sections of the eCRF.

## 7.6 Accountability

The study drug provided for this study will be used only as directed.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Patients will be asked to bring all unused IP and empty packages to the study site at all visits. The investigator or delegate will record the amount of returned tablets in the eCRF. Any patient found to be noncompliant would be counselled on the importance of taking their IP as prescribed.

Any IP deliberately or accidentally destroyed must be recorded. Any discrepancy between dispensed and returned IP should be explained.

The investigator will retain the returned medication until the AZ representative or delegate collects it, along with any medication not dispensed. The AZ representative or delegate is responsible for confirming that the investigator or delegate has recorded the quantities of returned and unused tablets at a patient level before medication is destroyed. The AZ representative or delegate will advise on the appropriate method for destruction of unused IP.

## 7.7 Concomitant and other treatments

All patients should be treated according to regional standards of care for CV risk factors (e.g., BP, lipids, and antithrombotic treatment), diabetes and CKD complications (e.g., hyperphosphatemia, hyperparathyroidism, hyperkalaemia, acidosis and renal anaemia).

Background medication will not be provided by the Sponsor.

### 7.7.1 Restricted medication

Treatment with non-steroidal anti-inflammatory drugs (NSAID) should, if possible, be avoided during the study.

### 7.7.2 Prohibited medication

Concomitant treatment (i.e., treatment in combination with IP) with open label SGLT2 inhibitors e.g., dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, tofogliflozin and luseogliflozin and fix dose combinations containing these drugs is prohibited. Also in situations when the patient is not on IP, treatment with open label SGLT2 inhibitors during the study, could interfere with the interpretation of study results and should therefore not be given unless all other possibilities to treat the patient properly has been considered.

### 7.7.3 Recording of concomitant treatment

Detailed recording of medications related to CKD (see Section 7.7.4), diabetes (see Section 7.7.5) as well as other relevant cardiovascular medications (e.g., statins, antihypertensive and antithrombotic agents) will be made throughout the study. In addition, concomitant medications will be recorded at the time of any SAEs, potential endpoints and AEs of interest (as defined in Section 6.3). Recording of other concomitant medications will be made at randomisation (visit 2) and at SCV.

### 7.7.4 Chronic kidney disease (CKD) medications

To be eligible, the patient needs to be on stable and for the patient maximum tolerated labelled daily dose of ACE-I or ARB for at least 4 weeks before visit 1, if not medically contraindicated. If the patient is not on an ACE-I or ARB at the time of enrolment the reason will be recorded in the eCRF.

Details regarding the following CKD related treatments will be recorded in the eCRF throughout the study:

- RAAS inhibition: ACE-I/ARBs, renin inhibitors, mineralocorticoid antagonists
- Diuretics: Loop diuretics, thiazide diuretics and other diuretics
- Treatment of underlying kidney disease: cytotoxic agents, immunosuppressive agents, other immunotherapy
- Phosphate binders
- Potassium binders

### 7.7.5 Anti-diabetes treatment of patients with established diagnosis of type 2 diabetes (T2D)

Patients with T2D at randomisation in this study will continue their T2D treatment. Treatment should be based on established guidelines and according to local laboratory values. Patients are eligible for adjustments in their anti-diabetes treatment at the discretion of their diabetes health care provider. Diabetes medications at baseline and any changes throughout the study, will be recorded in the eCRF.

#### 7.7.5.1 Use of medications known to cause hypoglycaemia in type 2 diabetes (T2D) patients

Insulin and insulin secretagogues are known to cause hypoglycaemia. Therefore, patients treated with insulin or sulfonylurea (SU) have a higher risk of experiencing hypoglycaemic events compared with those treated with other antidiabetic agents. Therefore a lower dose of insulin or insulin secretagogues may be required to minimize the risk of hypoglycaemia when used in combination with study medication.

Reduction of insulin by 10 to 20% (total daily dose) and SU by 25 to 50% and increased frequency of blood glucose monitoring may be considered in patients receiving insulin and/or SU and with baseline HbA1c ≤7% at randomisation.

### 7.7.6 Other concomitant treatment

Medications other than described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF, as applicable.

## 7.8 Post Study Access to Study Treatment

Post-study treatment will not be provided by the Sponsor.

# 8. STATISTICAL ANALYSES BY ASTRAZENECA (AZ)

## 8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violations have been identified and documented.

A comprehensive SAP will be developed prior to first randomised patient and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

The results of the key study outcome will be independently validated by an external statistical team.

## 8.2 Sample size estimate

The primary objective of the study is to determine the superiority of dapagliflozin versus placebo in reducing the incidence of the primary composite endpoint. Assuming a true hazard ratio of 0.78 between dapagliflozin and placebo, using a one-sided alpha of 2.5%, 681 primary endpoints will provide a statistical power of 90% for the test of the primary composite endpoint. This is based on an overall 1:1 allocation between dapagliflozin and placebo. The study is event-driven. The assumed hazard ratio of 0.78 is considered as clinically relevant and has taken into account the renal outcomes in the EMPA-REG trial.

With an annual event rate of 7.5% in the placebo treatment group, 4000 patients are estimated to provide the required number of primary events, based on an anticipated recruitment period of 24 months and an average follow-up period of approximately 33 months. The assumed placebo event rate of 7.5% is based on a review of published data in the CKD population. In addition, the expected number of patients who will be lost to follow-up is expected to be small; hence, they are not considered in the determination of the sample size.

## 8.3 Definitions of analysis sets

### 8.3.1 Full analysis set (FAS)

All patients who have been randomised to study treatment will be included in the full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised IP assignment, irrespective of the treatment actually received. The FAS will be considered the primary analysis set for the primary and secondary variables and for the exploratory efficacy variables.

### 8.3.2 Safety analysis set

All patients who receive at least one dose of randomised treatment will be included in the safety population. Patients will be analysed according to the treatment actually received. The Safety analysis set will be considered the primary analysis set for all safety variables.

## 8.4 Outcome measures for analyses

### 8.4.1 Primary outcome measure

The primary outcome measures are detailed in Section 2.1.

### 8.4.2 Secondary outcome measure

The secondary outcome measures are detailed in Section 2.2.

### 8.4.3 Safety outcome measure

The safety outcome measures are detailed in Section 2.3.

### 8.4.4 Exploratory outcome measure

The exploratory outcome measures are detailed in Section 2.4.

## 8.5 Methods for statistical analyses

### 8.5.1 Hypotheses

For the primary endpoint the following hypothesis will be tested at the 2.5% 1-sided level:

H0: HR [dapagliflozin:placebo] ≥1

Versus

H1: HR [dapagliflozin:placebo] <1

### 8.5.2 Closed testing procedure

A closed testing procedure including a pre-specified hierarchical ordering of the primary and secondary endpoints will be utilized. The Type I error will be controlled at a one-sided 0.025 level for multiplicity across primary and secondary endpoints. Statistical significance will be assessed in the pre-specified order of the endpoints as specified in Section 2.1 and 2.2. The testing procedure will continue down the hierarchy if the preceding endpoint is rejected at a one-sided 0.025 level and will stop if the preceding endpoint is not rejected at a one-sided 0.025 level. Exploratory endpoints will be tested at a one-sided 0.025 level without adjustment for multiplicity.

### 8.5.3 Analysis of the primary variable (s)

The primary variable is the time to first event included in the primary composite endpoint. The primary analysis will be based on the intention to treat (ITT) principle using the FAS.

In the analysis of the primary composite endpoint, treatments (dapagliflozin versus placebo) will be compared using a Cox proportional hazards model with a factor for treatment group, stratified by randomisation stratification factors (T2D, UACR), and adjusting for eGFR. In general, the analysis will use each patient's last contact as the censoring date for patients without any primary events. The p-value, hazard ratio (HR) and 95% confidence interval will be reported.

The contribution of each component of the primary composite endpoint to the overall treatment effect will be examined. Methods similar to those described for the primary analysis will be used to separately analyse the time from randomisation to the first occurrence of each component of the primary composite endpoint. Last contact will be treated as the censoring date for patients without the endpoint of interest. Hazard ratios (HR) and 95% confidence intervals will be reported.

Kaplan-Meier estimates of the cumulative incidence to the first occurrence of any event in the primary endpoint will be calculated and plotted, for overall analysis and for the individual components.

### 8.5.4 Analysis of the secondary variables

The secondary variables will be analysed in the similar manner as the primary variable.

### 8.5.5 Subgroup analysis

Subgroup variables for the primary efficacy endpoint and secondary efficacy endpoints include demography, baseline disease characteristics, baseline concomitant medications and others. Cox proportional hazards models will be performed to examine treatment effects within relevant subgroups separately. The p-values for the subgroup analyses will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively. Event rates by treatment and HRs with 95% confidence intervals will be reported for each subgroup. HRs and CIs for overall analysis and subgroups will be presented with forest plots. Further details of the subgroup analysis, including the list of subgroup variables, will be provided in the SAP.

### 8.5.6 Interim analysis

Not applicable.

### 8.5.7 Sensitivity analysis

Details of the sensitivity analysis will be provided in the SAP.

### 8.5.8 Analysis of safety variables

The number and percent of patients with SAEs, DAEs, AEs leading to dose reductions and temporary interruptions, AEs of interest, will be summarized by treatment group. Changes in clinical chemistry/haematology parameters will be summarized over time by treatment group. In addition, the number and percent of patients with a marked abnormality in clinical laboratory tests will be summarized over time by treatment group. For safety analyses, summaries will be provided using both on treatment observations and using all observations regardless of whether patients are on or off study treatment.

### 8.5.9 Exploratory analysis

The exploratory variables (excluding PK and biomarkers for future exploratory research) will be analysed as specified in the SAP.

# 9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA (AZ)

## 9.1 Training of study site personnel

Before the first patient is entered into the study, an AZ representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the site personnel and also train them in any study specific procedures and the WBDC, ePROs system and other relevant systems utilised.

The PI will ensure that appropriate training relevant to the study is given to all site personnel, and that any new information relevant to the performance of this study is forwarded to the personnel involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other personnel).

## 9.2 Monitoring of the study

During the study, an AZ representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s) and site personnel.
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol; that data are being accurately and timely recorded in the eCRFs; that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., medical records).
- Perform source data review, i.e., review of source documentation to check quality of source, review protocol compliance, ensure critical processes and source documentation are adequate.
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AZ representative will be available between visits if the investigator(s) or other personnel at the study site needs information and advice about the study conduct.

### 9.2.1 Risk based quality management

Quality by design will be implemented, including a focus on identifying key risks to patient safety, data quality, and Good Clinical Practice (GCP)/regulatory compliance, to build quality into the design, conduct, analysis and reporting of the study.

A risk based monitoring approach will be applied for this study. This includes a mix of monitoring strategies: on-site monitoring, remote monitoring (site level monitoring activities

performed at a location other than the study site) and centralized monitoring. Monitoring strategies will be tailored to consider risks, permit timely oversight (through central/remote monitoring and use of technology), and will be focused on critical processes and critical data.

Central monitoring will be used to check that data is consistent and complete, identify unusual distribution of data, identify higher risk sites to target additional monitoring, and to ensure routine review of data is completed in real time.

### 9.2.2 Source data

Refer to the CSA for location of source data. The investigator must provide direct access to source data/documents for monitoring, audits, (institutional review board/independent ethics committee) IRB/IEC review, and regulatory inspections.

### 9.2.3 Study agreements

The PI at each/the study site should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AZ and the PI should be in place before any study related procedures can take place, or patients are enrolled.

### 9.2.4 Archiving of study documents

The investigator follows the principles outlined in the CSA.

## 9.3 Study timetable and end of study

The end of the study is defined as ‘the last visit of the last patient undergoing the study’.

The study is expected to start in Q1 2017 and to end by Q4 2020.

The study may be terminated at individual study sites if the study procedures are not being performed according to GCP, or if recruitment is slow. AZ may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with dapagliflozin.

## 9.4 Data management by AstraZeneca (AZ)

Data management will be performed by IQVIA Ltd, according to the Data Management Plan (DMP).

Data entered into the eCRF will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be reviewed, queried and updated as needed.

AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the IQVIA Ltd.

The data will be validated as defined in the DMP. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The DMP will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

**Serious adverse event (SAE) Reconciliation**

SAE reconciliation will be done between the study database and safety database.

# 10. ETHICAL AND REGULATORY REQUIREMENTS

## 10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AZ policy on Bioethics and Human Biological Samples.

## 10.2 Subject data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

## 10.3 Ethics and regulatory review

An IRB/IEC should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the site personnel.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to AZ before enrolment of any patient into the study.

The IRB/IEC should approve all advertising used to recruit patients for the study.

AZ should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AZ will handle the distribution of any of these documents to the national regulatory authorities.

AZ will provide Regulatory Authorities, IRB/IECs and PIs with safety updates/reports according to local requirements.

## 10.4 Informed consent

The PI at each site will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed ICF is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC.

## 10.5 Changes to the protocol and informed consent form (ICF)

Study procedures will not be changed without the mutual agreement of the International Coordinating Investigator and AZ.

If there are any substantial changes to the study protocol, then these changes will be implemented in a new version of the protocol.

The new version of the study protocol is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for new version protocols.

AZ will distribute any subsequent new versions of the protocol to each PI. For distribution to IRB/IEC see Section 10.3.

If a new version of the protocol requires a change of a study sites' ICF, AZ and the study site's IRB/IEC are to approve the revised ICF before the revised form is used.

## 10.6 Audits and inspections

Authorised representatives of AZ, a regulatory authority, or an IRB/IEC may perform audits or inspections at the study site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AZ immediately if contacted by a regulatory agency about an inspection at the study site.

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# Appendix A Additional Safety Information

## Further Guidance on the Definition of a Serious Adverse Event (SAE)

### Life threatening

'Life-threatening' means that the patient 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 subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

### Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., 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 patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

### Important medical event or medical intervention

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 jeopardize the patient or may require medical intervention 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 (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

## 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 patient 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? AZ 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 recognized feature of overdose of the drug?

- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that 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.

# Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

**Labelling and shipment of biohazard samples**

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

**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 e.g., Ebola, Lassa fever virus:

- Are to be packed and shipped in accordance with IATA Instruction 602

**Category B Infectious Substances** are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650

**Exempt** - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

# Appendix C New York Heart Association (NYHA) Functional Classification

## NYHA Functional Classification

| Class | Patient symptoms |
|---|---|
| I | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath). |
| II | Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath). |
| III | Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea. |
| IV | Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases. |

# Appendix D Patient Reported Outcome (PRO) questionnaires

## D1 Kidney Disease Quality of Life-36 (KDQOL™-36)

| Study Number: | | Site Number: |
|---|---|---|
| Subject Number: E_ _ _ _ _ _ _ | Visit Number: | Assessment Date: |

# Your Health
## – *and* –
# Well-Being

**Kidney Disease and Quality of Life (KDQOL™-36)**

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

***Thank you for completing these questions!***

| Study Number: | | Site Number: |
|---|---|---|
| Subject Number: E_ _ _ _ _ _ _ | Visit Number: | Assessment Date: |

# Your Health

**This survey includes a wide variety of questions about your health and your life. We are interested in how you feel about each of these issues.**

**1. In general, would you say your health is: [Mark an ☒ in the one box that best describes your answer.]**

| Excellent | Very good | Good | Fair | Poor |
|---|---|---|---|---|
| ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

**The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? [Mark an ☒ in a box on each line.]**

| | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| **2.** Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf ..... | ☐1 | ☐2 | ☐3 |
| **3.** Climbing several flights of stairs ..... | ☐1 | ☐2 | ☐3 |

| Study Number: | | Site Number: |
|---|---|---|
| Subject Number: E_ _ _ _ _ _ _ | Visit Number: | Assessment Date: |

**During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health?</u>**

| | Yes | No |
|---|---|---|
| **4.** <u>Accomplished less</u> than you would like ..... | ☐ 1 | ☐ 2 |
| **5.** Were limited in the <u>kind</u> of work or other activities ..... | ☐ 1 | ☐ 2 |

**During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

| | Yes | No |
|---|---|---|
| **6.** <u>Accomplished less</u> than you would like ..... | ☐ 1 | ☐ 2 |
| **7.** Didn't do work or other activities as <u>carefully</u> as usual ..... | ☐ 1 | ☐ 2 |

**8. During the <u>past 4 weeks,</u> how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

| Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

| Study Number: | | Site Number: |
|---|---|---|
| Subject Number: E_ _ _ _ _ _ _ | Visit Number: | Assessment Date: |

**These questions are about how you feel and how things have been with you <u>during the past 4 weeks.</u> For each question, please give the one answer that comes closest to the way you have been feeling.**

**How much of the time during the <u>past 4 weeks…</u>**

| | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| **9.** Have you felt calm and peaceful? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **10.** Did you have a lot of energy? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **11.** Have you felt downhearted and blue? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |

**12. During the <u>past 4 weeks,</u> how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?**

| All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|
| ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

| Study Number: | | Site Number: |
|---|---|---|
| Subject Number: E_ _ _ _ _ _ _ | Visit Number: | Assessment Date: |

# Your Kidney Disease

**How true or false is each of the following statements for you?**

| | Definitely true ▼ | Mostly true ▼ | Don't know ▼ | Mostly false ▼ | Definitely false ▼ |
|---|---|---|---|---|---|
| **13.** My kidney disease interferes too much with my life ..... | ☐ 1 ..... | ☐ 2..... | ☐ 3 ..... | ☐ 4..... | ☐ 5 |
| **14.** Too much of my time is spent dealing with my kidney disease ..... | ☐ 1 ..... | ☐ 2..... | ☐ 3 ..... | ☐ 4..... | ☐ 5 |
| **15.** I feel frustrated dealing with my kidney disease ..... | ☐ 1 ..... | ☐ 2..... | ☐ 3 ..... | ☐ 4..... | ☐ 5 |
| **16.** I feel like a burden on my family ..... | ☐ 1 ..... | ☐ 2..... | ☐ 3 ..... | ☐ 4..... | ☐ 5 |

| Study Number: | | Site Number: |
|---|---|---|
| Subject Number: E_ _ _ _ _ _ _ | Visit Number: | Assessment Date: |

**During the past 4 weeks, to what extent were you bothered by each of the following?**

| | Not bothered | Somewhat bothered | Moderately bothered | Very much bothered | Extremely bothered |
|---|---|---|---|---|---|
| **17.** Soreness in your muscles? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **18.** Chest pain? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **19.** Cramps? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **20.** Itchy skin? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **21.** Dry skin? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **22.** Shortness of breath? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **23.** Faintness or dizziness? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **24.** Lack of appetite? ... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **25.** Washed out or drained? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **26.** Numbness in hands or feet? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **27.** Nausea or upset stomach? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **28[a].** (Hemodialysis patient only) Problems with your access site? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **28[b].** (Peritoneal dialysis patient only) Problems with your catheter site? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

| Study Number: | | Site Number: |
|---|---|---|
| Subject Number: E_ _ _ _ _ _ _ | Visit Number: | Assessment Date: |

# Effects of Kidney Disease on Your Daily Life

**Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease <u>bother</u> you in each of the following areas?**

| | Not at all bothered | Somewhat bothered | Moderately bothered | Very much bothered | Extremely bothered |
|---|---|---|---|---|---|
| | ▼ | ▼ | ▼ | ▼ | ▼ |
| **29.** Fluid restriction? ... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **30.** Dietary restriction? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **31.** Your ability to work around the house? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **32.** Your ability to travel? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **33.** Being dependent on doctors and other medical staff | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **34.** Stress or worries caused by kidney disease? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **35.** Your sex life? ..... | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| **36.** Your personal appearance? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

***Thank you for completing these questions!***

## D2 EuroQol five-dimensional five-level questionnaire (EQ-5D-5L


# Health Questionnaire

# English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

**MOBILITY**

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

**SELF-CARE**

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

**PAIN / DISCOMFORT**

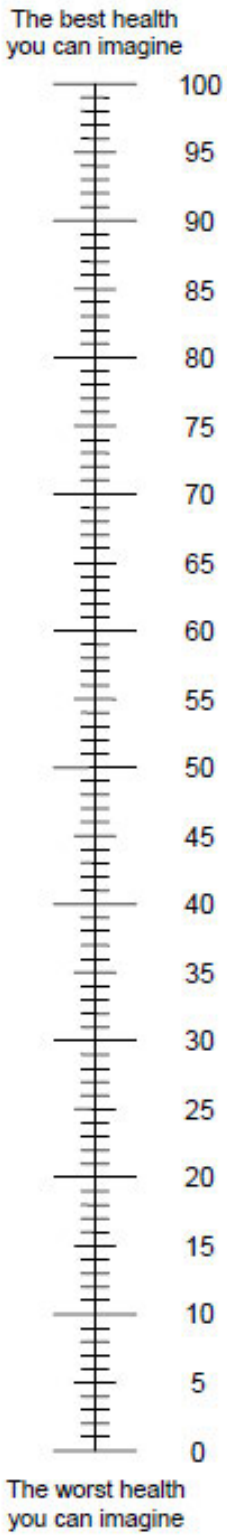
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

**ANXIETY / DEPRESSION**

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



# Appendix E Genetic Research

## Rationale and Objectives

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. 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.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

## Genetic Research Plan and Procedures

### Selection of genetic research population

### Study selection record

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

### Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in section 3.1 of the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

### Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in section 3.2 of the Clinical Study Protocol or any of the following:

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

### Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 5.6 of the main Clinical Study Protocol.

**Collection of samples for genetic research**

The blood sample for genetic research will be obtained from the subjects at Visit 2 at randomisation. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

**Coding and storage of DNA samples**

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject 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 blood sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the subject enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. 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 to trace 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 Section 10 of the main Clinical Study Protocol.

**Informed consent**

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

**Subject data protection**

AstraZeneca will not provide individual genotype results to subjects, 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 subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

**Data management**

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

The results from this genetic research may be reported in a separate report from the CSR or published in scientific journals.

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 Organization 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 subject 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.

**Statistical Methods and Determination of Sample Size**

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan will be prepared where appropriate.

# SIGNATURE PAGE

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