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

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CEA	Clinical event adjudication
CKD-EPI	Chronic kidney disease epidemiology collaboration equation
CSP	Clinical study protocol
CV	Cardiovascular
DAE	Adverse event leading to discontinuation of investigational product
DMC	Data monitoring committee
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
EQ5D-5L	EuroQol five-dimensional five-level questionnaire
FAS	Full analysis set
HbA1c	Glycosylated haemoglobin
HF	Heart failure
HR	Hazard ratio
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
KM	Kaplan-Meier
LTFU	Lost to follow-up
MA	Marked abnormality
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
PACD	Primary analyses censoring date
SAE	Serious adverse event
SED	Study end date
SCV	Study closing visit
T2D	Type 2 diabetes

Abbreviation or special term	Explanation
UACR	Urine albumin creatinine ratio
WoC	Withdrawal of consent

AMENDMENT HISTORY

SAP date	Brief description of change
1 February 2017 Version 1.0	Version 1.0 signed
15 April 2020 Version 2.0	Clarified that eGFR endpoints will be derived programmatically and will not be adjudicated, in accordance with protocol version 2.0 dated 26 September 2017. [Section 1.3, 3, 3.1, 4.1, 4.1.5, 4.2.3]
	Expanded AESI categories to include AEs leading to a risk for lower limb amputations, in accordance with protocol version 2.0 dated 26 September 2017. [Section 1.1.3, 3.3]
	Added exploratory objectives of MACE and composite endpoint of chronic dialysis/renal transplant/renal death, in accordance with protocol version 3.0 dated 22 January 2020. [Section 1.1.4, 4.2.6]
	Clarified that doubling of serum creatinine will be analysed as time to first event, in accordance with protocol version 3.0 dated 22 January 2020. [Section 1.1.4, 4.2.6]
	Removed interim analysis and updated alpha level for the final analysis, in accordance with protocol version 4.0 dated 17 March 2020. [Section 1.4, 4.1.2, 4.1.3,5]
	Clarified that eGFR will be calculated based on central laboratory serum creatinine measurement. [Section 4.1]
	Clarified the definition of T2D at baseline in accordance with protocol. [Section 4.1]
	Clarified that time to event analysis should contain 15 or more events to be produced. [Section 4.1]
	Clarified definition of baseline in relation to date of randomisation. [Section 4.1]
	Added Japan and UK in regional subgroups. [Section 4.2.3.2]
	Removed ACEI/ARB as a sub-group variable due to small sample size on patients without ACEI/ARB. [Section 4.2.3.2]
	Clarified two variables for subgroup analysis: T2D at baseline and UACR at baseline. [Section 4.2.3.2]
	Clarified that subgroup analysis will be conducted for all secondary endpoint. [Section 4.2.4]
	Clarified that the on+off treatment period will be the primary approach fro the analysis of fractures and amputations. [Section 4.2.5, 4.2.5.4]
	Added details for the analysis of eGFR slope and UACR. [Section 4.2.6]

1. STUDY DETAILS

1.1 Study objectives

1.1.1 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/1.73m2 and albuminuria (UACR ≥200 and ≤5000 mg/g).	Time to the first occurrence of any of the components of this composite: 1. ≥50% sustained decline in eGFR 2. Reaching End Stage Renal Disease (ESRD) Sustained eGFR <15 ml/min/1.73m^2 or, Chronic dialysis treatment or, Receiving a renal transplant 3. CV death 4. Renal death

1.1.2 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: 1. ≥50% sustained decline in eGFR 2. Reaching End Stage Renal Disease (ESRD) Sustained eGFR <15 ml/min/1.73m^2 or, Chronic dialysis treatment or, Receiving a renal transplant 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 hospitalization for heart failure.	Time to the first occurrence of either of the components of this composite: 1. CV death 2. Hospitalization 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

1.1.3 Safety objectives

Safety Objective:	**Outcome Measure:**
To evaluate the safety and tolerability of dapagliflozin in this patient population.	1. Serious Adverse Events (SAEs) 2. Discontinuation of IP due to Adverse Events (DAEs) 3. Changes in clinical chemistry/haematology parameters 4. Adverse events 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”])

1.1.4 Explorative 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 the chronic dialysis, renal death or receiving a renal transplant	Time to the first occurrence of any of the components of this composite: 1. Chronic dialysis 2. Receiving renal transplant 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 any of the components of this composite: 1. ≥50% sustained decline in eGFR 2. Reaching End Stage Renal Disease (ESRD) Sustained eGFR <15 ml/min/1.73m^2 or, Chronic dialysis treatment or, Receiving a renal transplant 3. Renal death OR 4. CV death
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: 1. ≥30% decline in eGFR from baseline 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: 1. From baseline to end of treatment 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 lab levels of serum potassium: • >6.0 mmol/L • >5.5 mmol/L • <3.5 mmol/L • <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 with the most recent laboratory measurement).
To determine whether dapagliflozin compared with placebo will reduce the incidence of diagnosis of T2D in patients without diabetes at baseline.	Proportion of patients without T2D 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 subgroup.	Changes in HbA1c from baseline.
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: 1. CV death 2. MI 3. Stroke
To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of heart failure hospitalization.	Time to first hospitalization 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 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.

1.2 Definitions

1.2.1 Primary analysis censoring date

The executive committee and AstraZeneca will monitor the accrual of endpoint events and when appropriate define the primary analysis censoring date (PACD) at which time at least the pre-defined target number of 681 events for the primary composite endpoint is expected to have occurred. The study sites will be instructed to plan for study closure visits to be performed after PACD.

The analyses of the endpoint events will include events with onset on or prior to PACD. Event free patients who have not been prematurely censored due to incomplete information (see Sections 3.1 and 3.2) will be censored at PACD. Endpoint events with onset after PACD will also be adjudicated and reported descriptively.

1.2.2 Withdrawal of informed consent

Withdrawal of consent (WoC) means withdrawal from study and should only occur if the patient does not agree to any kind of further assessment at all.
No data after date of WoC should be collected, with the exception of vital status (dead or alive) at the end of the study collected from public sources, which will be included in the analysis of death from any cause as a sole outcome and in patient disposition summaries. Data collected on or prior to date of WoC will be included in analyses.

1.2.3 Discontinuation from study drug

Discontinuation from study drug does not mean WoC. Optimally, patients who discontinue from study drug should continue study visits according to plan until study closure.

Alternatively, if the patient does not agree to this approach, modified follow-up should be arranged. Data from patients who did not withdraw consent will be included in the ITT

analyses irrespective of whether the event occurred before or following discontinuation of study drug.

1.2.4 Vital status

Known vital status at the end of the study will be defined when the patient is dead or has date last know alive on or after the PACD.

For patients who have withdrawn consent, the investigator will attempt to collect vital status from publicly available sources at study closure in compliance with local privacy laws/practices.

1.2.5 Lost to follow-up

The term lost to follow-up (LTFU) will be limited to patients with unknown vital status at the end of the study as defined in Section 1.2.4. Other measures will be used to describe incomplete follow-up of the primary endpoint (Section 4.1.5).

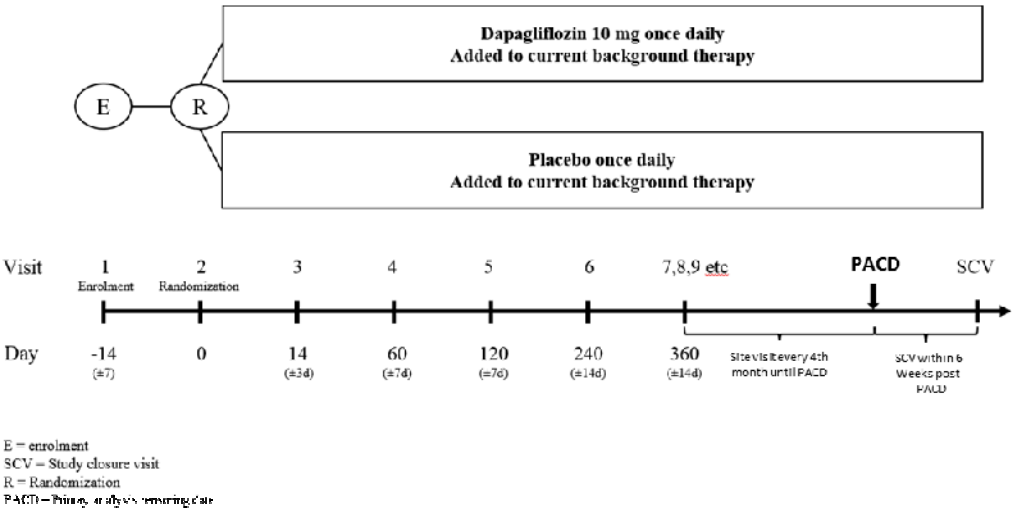
1.3 Study design

This is an international, multicentre, event-driven, randomized, 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 10000 patients at approximately 450 study sites in approximately 20 countries will be enrolled to reach the target of approximately 4000 randomized patients.

The anticipated duration of the study is approximately 45 months. The study closure procedures will be initiated when the predetermined number of confirmed primary endpoints is predicted to have occurred (n=681), ie, the study end date (SED) (see Figure 1). This date, which in the CSP is termed study end date (SED), will be the common censoring date for efficacy time-to-event analyses. Thus, it will in this SAP be termed the primary analysis censoring date (PACD).

Figure 1 Study flow chart



E = enrolment
SCV = Study closure visit
R = Randomization
PACD = Primary analysis censoring date

1.3.1 Randomization

Patients will be randomized 1:1 to either dapagliflozin 10 mg or placebo. Randomization will be stratified by:

- T2D status (with or without) at visit 1
- UACR [200,1000] or [1001,5000] mg/g at visit 1

T2D is defined as established diagnosis of T2D or HbA1c more or equal to 6.5% (48 mmol/mol) shown at central laboratory test at enrolment (visit 1).

Randomization will be performed in balanced blocks of fixed size. The randomization codes will be computer generated and loaded into the IxRS database.

Capping

Randomization 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 randomization, due to intolerance, will be monitored to ensure that the target population is reflected in regard to background therapy.

The number of randomized patients with and without T2D will be monitored in order to ensure a minimum of 30% in each sub-population. Randomization may be capped in IxRS (ie, no more patients in a specific sub-population can be randomized) 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 randomization, shown with a laboratory test at enrolment (visit 1), will be monitored and randomization in

IxRS may be capped to ensure that the number of patients in this sub-population does not exceed approximately 10%.

1.4 Number of patients

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 assumed hazard ratio of 0.78 is considered as clinically relevant and has taken into account the renal outcomes in the EMPA-REG Outcome 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. The number of patients with incomplete follow-up of endpoints is expected to be small; hence, these are not considered in the determination of the sample size.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Full analysis set

All patients who have been randomized 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 randomized 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.

2.1.2 Safety analysis set

All randomized patients who receive at least one dose of randomized treatment will be included in the safety population. Patients will be analyzed according to the treatment actually received. For any patients given incorrect treatment, ie randomized to one of the treatment groups but actually given the other treatment, the treatment group will be allocated as follows: Patients who got both incorrect and correct treatment will be analyzed according to their randomized treatment. Patients who got only the incorrect treatment will be analyzed according to that treatment.

The Safety analysis set will be considered the primary analysis set for all safety variables.

2.2 Violations and deviations

The important protocol deviations listed below will be summarised by randomized treatment group

- Patients who were randomized but did not meet inclusion and exclusion criteria
- Patients who received the wrong study treatment at any time during the study.
- Patients who received prohibited concomitant medication

As the primary analysis is intention-to-treat analysis, protocol deviation will not imply exclusion from analysis.

3. PRIMARY AND SECONDARY VARIABLES

Potential endpoint events and event dates will be adjudicated by an independent clinical event adjudication (CEA) committee. The eGFR events will not be adjudicated. The committee members will not have access to the treatment codes for any patient. The CEA procedures and event definitions will be described in the CEA charter.

The primary and secondary efficacy variables will only include confirmed or adjudicated events (referred to collectively as 'confirmed events' hereafter). Death after WoC which will be based on eCRF data.

All confirmed events from randomization until WoC or PACD will be included in the analysis of primary and secondary endpoints, except for the analysis of all-cause death as a sole outcome, which also will include deaths (not adjudicated) after WoC, but on or before PACD. For analysis of time to first event, data will be expressed as two variables:

- A binary variable indicating if the event in question occurred or the patient was censored.
- An integer variable for the number of days from randomization to the first occurrence of an event (start date of the event – randomization date + 1), or for event free patients, from randomization to censoring (censoring date – randomization date + 1).

Event free patients will be censored as described below for each respective endpoint.

3.1 Primary variable

The primary efficacy variable is time from randomization to the first occurrence of any event in the composite of ≥50% sustained decline in eGFR from baseline, reaching end stage renal disease (ESRD), renal death or an CV death.

ESRD is defined as any of the following components:

- Sustained eGFR<15mL/min/1.72m^2
- Chronic dialysis
- Receiving a renal transplant

Sustained eGFR decline of ≥50% from baseline and sustained eGFR <15 ml/min/1.73m2 will be based on two consecutive central laboratory values at least 28 days apart below the respective limit. The start date of the event is the date of the first of the two qualifying consecutive central laboratory values. Thus, the analysis will include eGFR events with onset prior to PACD that are confirmed after PACD, in addition to those eGFR events confirmed prior to PACD. These two types of eGFR events will be derived programmatically.

Chronic dialysis will be adjudicated as dialysis treatment ongoing for at least 28 days, or when the ESRD is deemed irreversible and the dialysis treatment was stopped before day 28. Similar to the eGFR events, the onset date of chronic dialysis will be the date when the qualifying dialysis treatment started.

Receiving a renal transplant and renal death will be independently adjudicated as defined in the CEA charter.

Deaths adjudicated as 'cause undetermined' with regard to CV death or non-CV death will be included in the analyses as CV deaths but will not be considered as renal deaths.

Patients who do not have an endpoint event will be censored at the earliest of date of WoC or non-CV death or non-renal death when applicable, and otherwise at the earliest of date of last clinical event assessment and PACD. Clinical event assessment will be captured by the question for potential renal events on the eCRF event assessment page. The earliest assessment date among components will be used as the censoring date. For example, for the last clinical event assessment, if the central laboratory eGFR assessment is not done in conjunction with the assessment of dialysis and renal transplant, the date of last available central laboratory eGFR measurement will be used as the censoring date.

3.2 Secondary variables

The secondary endpoints are included in a hierarchical testing sequence following the primary endpoint as ordered in Section 3.2.1–3.2.3

3.2.1 The composite of ≥50% sustained decline in eGFR, end stage renal disease and renal death

The efficacy variable is time from randomization to the first occurrence of any event in the composite of ≥50% sustained decline in eGFR, reaching end stage renal disease (ESRD) and renal death (as defined in 3.1).

All components of the composite endpoint will be defined in the same way as the primary endpoint (see Section 3.1 for more details).

Deaths adjudicated with 'undetermined' cause will not be considered as renal death.

Patients who do not have an endpoint event will be censored at the earliest of date of WoC and non-renal death when applicable, and otherwise at the earliest of date of last clinical event assessment and PACD. Clinical event assessment will be captured by the questions for potential renal events on the eCRF event assessment page. Full assessment of the composite endpoint requires a central laboratory eGFR value taken on the visit.

3.2.2 The composite of CV death and hospitalisation of heart failure

The efficacy variable is time from randomization to the first occurrence of any event in the composite of CV Death and hospitalization for HF.

Definition of CV death and hospitalisation of heart failure is described in CEA charter. Deaths adjudicated as 'cause undetermined' with regard to CV death or non-CV death will be included in the analyses as CV deaths.

Patients who do not have an endpoint event will be censored at the earliest of date of WoC and non-CV death when applicable, and otherwise at the earliest of date of last clinical event assessment and PACD.

Deaths adjudicated as 'cause undetermined' with regard to CV death or non-CV death will be included in the analyses as CV deaths. Last clinical event assessment is defined as the last date when the event assessment question for a potential heart failure event was completed on the eCRF event assessment page.

3.2.3 All cause mortaility

The efficacy variable is time to from randomization to death from any cause. All deaths on or prior to PACD, including death after WoC will be included. Patients who are alive will be censored at the earliest of date last known alive and PACD.

Deaths occurring after WoC will not be adjudicated. For such events, the date of death will be collected only in eCRF.

3.3 Safety variables

The safety and tolerability of dapagliflozin will be evaluated from serious adverse events (SAEs), adverse events leading discontinuation (DAEs) of study drug, changes in clinical/haematology parameter and adverse events (AEs) of interest (volume depletion, renal events, major hypoglycaemic events, fractures, diabetic ketoacidosis AEs leading to amputation and AEs leading for a risk for lower limb amputations ["preceding events"]).

SAEs will be collected from time of informed consent until and including the patient's last visit.

Non-serious AEs will be collected from randomization until and including the patient's last visit, only if it is a DAE, an AE of interest, an AE leading to a potential endpoint or the AE is the reason for interruption of study drug or dose reduction.

Endpoint such as deaths and HF events will not be reported to health authorities to avoid unnecessary unblinding of efficacy endpoints that are fulfilling the SAE criteria. If it is determined by the CEA committee that a potential endpoint does not meet the endpoint criteria, then the event will be recorded as an SAE and reported to AZ patient safety data entry site and, if applicable, sent to health authorities.

4. ANALYSIS METHODS

4.1 General principles

No multiplicity adjustment will be made to confidence intervals as they will be interpreted descriptively and used as a measure of precision. All p-values will be unadjusted. P-values for variables not included in the confirmatory testing sequence, or following a non-significant test in the sequence will be regarded as nominal.

The primary and secondary analyses include confirmed events occurring on or prior to PACD. Events with onset after PACD will be tabulated.

Stratification of analyses for T2D and UACR status will be performed using the stratification values as entered in IxRS to determine the randomization assignment.

T2D at baseline will be defined as established diagnosis of T2D (recorded in eCRF medical history) or central laboratory HbA1c ≥6.5% at both visit 1 (enrollment) and visit 2 (randomization).

No hazard ratio estimates with confidence interval and p-values will be given when less than 15 events in total, both treatment groups combined.

Incomplete dates
All efforts should be made to obtain complete dates of clinical assessments and events. For analyses requiring complete dates, partially missing dates will be imputed based on available corroborating information. Absent of any additional corroborating information, partially missing dates will be imputed as follows: if only the year part of a date is available (YY), then the date will be set to YY0701. If only the year and month is available (YYMM), then the date will be set to YYMM15. Additional imputation rules will be defined as appropriate to ensure that eg, dates will not be imputed as prior to randomization, after death or end date after start date.

Baseline value
Baseline value is defined as the last value on or prior to date of randomization.

eGFR and UACR
Baseline eGFR and UACR will be calculate as mean of visit 1 and visit 2, in case of re-screening and retake the mean of latest value at each of visit 1 and visit 2 on or prior to randomization will be used.

The eGFR values will be calculated using central laboratory S-Creatinine value and take precedence over central laboratory eGFR if any discrepancies.

The formula used for calculating eGFR in (in mL/min/1.73 m^2) will be the CKD-EPI equation (Levey at al 2009).

Study drug compliance
The percentage of study drug compliance for the overall treatment period will be derived for each patient based on pill counts as the number of pills taken (dispensed – returned), relative to the expected number of pills taken. The expected number of pills taken is defined as: 1*(date of last dose – data of first dose +1), excluding days of interruption.

Study drug compliance will be presented descriptively, including mean, median, quartiles and 5% and 95% percentiles.

4.1.1 Estimand for primary and secondary outcomes

The primary and secondary objectives will be evaluated under the treatment policy estimand to reflect the effect of the initially assigned randomized study drug, irrespective of adherence to randomized study treatment. Specifically, the analysis will be performed for the full analysis set including all events that occurred on or prior to PACD, including events following premature discontinuation of study drug.

4.1.2 Hypotheses

To control the overall type I error rate at 2.5% one-sided. For the primary endpoint the following null hypothesis will be tested at the 2.5% one-sided significance level

H0: HR [dapagliflozin:placebo] ≥1

versus the alternative hypothesis

H1: HR [dapagliflozin:placebo] <1

The secondary endpoints included in confirmatory statistical testing using a closed testing procedure (Section 4.1.3) will be based one similar one-sided alternative hypothesis for the respective treatment difference.

4.1.3 Confirmatory testing procedure

A closed testing procedure including a pre-specified hierarchical order 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 1.1.1 and 1.1.2. 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 null hypothesis for the preceding endpoint is not rejected at a one-sided 0.025 level.

4.1.4 Presentation of time-to-event analyses

In general, summary tables of time-to-event analyses will include the number and percent of patients with event per treatment group, event rate, hazard ratio with 95% confidence interval and p-value. The event rate will be derived as the number of patients with event divided by the total duration of follow-up across all patients in a given group.

Kaplan-Meier (KM) estimates of the cumulative proportion of patients with events will be calculated and plotted per treatment group, with the number of patients at risk indicated below the plot at specific time points. The KM plots will be presented for all time to event analyses, including the individual components of the composite endpoints.

4.1.5 Vital status and follow-up of endpoints

Potential endpoints will be collected and confirmed from randomization throughout the study until and including the patient's last visit. The investigator will attempt to collect vital status (dead or alive) at the end of the study for all patients, including vital status from publicly available sources for patients who have withdrawn consent, in compliance with local privacy laws/practices.

Known vital status at the end of the study will be defined when the patient is dead or has date last know alive (entered on the eCRF final status form) on or after the PACD. In patient disposition the number of patients who are dead, alive or with unknown vital status will be reported separately for patients who did/did not withdraw consent. The term lost to follow-up (LTFU) will be limited to only patients with unknown vital status.

Follow-up of the primary endpoint will be defined in terms of assessment as described for censoring in Section 3.1. Thus, a patient that is not LTFU, i.e. with known vital status, may have incomplete follow-up of endpoints.

Complete follow up of the primary endpoint will be defined as the patient had a primary endpoint event, died from non-CV death or non-renal death or had complete event assessment on or after the PACD.

In addition to the number and percent of patients with complete follow-up, the proportion of total patient time with complete follow-up will be reported per treatment group.

Patient time with complete follow-up will be defined as time from randomization until the earliest of first primary endpoint event, death, WoC, censoring due to incomplete event assessment or PACD. The denominator, representing maximum complete follow-up, will be the time to first primary endpoint event, death or PACD.

4.2 Analysis methods

4.2.1 Demographics and baseline characteristics

Demographic and baseline characteristics will be summarized, using frequency distributions and summary statistics based on the FAS data set, for each treatment group as well as for all patients combined. No statistical test will be performed for comparison of any baseline measurement among treatment groups.

4.2.2 Concomitant and baseline medication

Baseline medication is defined as medication with at least one dose taken before date of randomization and with no stop date before date of randomization.

Concomitant medication is defined as medications taken post randomization, irrespective of study drug.

The frequency of baseline and concomitant medication will be presented for the FAS per ATC class and treatment group.

Summaries of prohibited medication (as defined in CSP Section 7.7.2) will be presented.

4.2.3 Analysis of the primary efficacy variable

The primary variable is the time to first event included in the primary composite endpoint. The primary analysis will be based on the ITT principle using the FAS, including confirmed events with onset on or prior to PACD.

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 randomization stratification factors (T2D, UACR), and adjusting for baseline eGFR. The analysis will use censoring of patients without any primary event as described in Section 3.1 . The Efron method for ties and p-value based on the score statistic will be used. The event rates, p-value, 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. In the analysis of the components, all first event of the given type will be included irrespective of any preceding non-fatal composite event of a different type. Methods similar to those described for the primary analysis will be used to separately analyze the time from randomization to the first occurrence of each component in the composite endpoint.

Kaplan-Meier estimates of the cumulative proportion of patients with event will be calculated and plotted, for the composite endpoint and for the individual components.

4.2.3.1 Sensitivity analyses of the primary endpoint

Chronic dialysis
A sensitivity analysis of the primary endpoint excluding chronic dialysis events ongoing less than 90 days will be performed.

Undetermined cause of death
A sensitivity analysis of the primary endpoint where deaths adjudicated as 'undetermined' cause are not included as CV deaths, but treated as censoring events, will be performed.

Missing data and informative censoring
The time-to-event analysis using the Cox regression depends on the assumption of non-informative or ignorable censoring, corresponding to the missing-at –random assumption. The missing data in this context are patients who are prematurely censored due to WoC, LTFU or otherwise incomplete follow-up of endpoints. The amount of missing data will be described e.g., in terms of the number of patients and patient time with incomplete follow-up as described in Section 4.1.5.

Patient retention and follow-up are at the forefront of study planning and conduct, and the amount of incomplete follow-up is expected to be small. To assess the impact of missing data and the robustness of the results with regard to the assumption of non-informative censoring, sensitivity analysis will be planned based on the evaluation of the missing follow-up and discussed in relation to the observed efficacy signal. This may include analysis where scenarios in terms of increased risk in censored patients are explored to identify a 'tipping point' where statistical significance would be lost.

4.2.3.2 Subgroup analysis of the primary endpoint

Exploratory subgroup analyses of the primary composite endpoint will be performed for the characteristics listed in Table 1. The Cox proportional hazards models for subgroup analyses will include a factor for treatment group, stratified by randomization stratification factors (T2D, UACR), adjusting for baseline eGFR, and include the relevant subgroup variable and the interaction between treatment and the subgroup variable. In the subgroup analysis by T2D status (or UACR status), the variable for the specific randomization stratification factor will be replaced by a variable based on CRF information.
In addition to the number and percent of patients with event, event rate estimate, HR with 95% confidence interval and p-value for each subgroup, the interaction p-value will be presented. HRs with confidence interval will be presented in a forest plot, also including the event rate and interaction p-value. The p-values for the subgroup analyses and interaction will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively.

Table 1 Characteristics and categories for sub group analysis of the primary endpoint

Characteristic	Categories
Age (years)	≤65, >65
Sex	Male, female
Race	White, Black or African, Asian, Other
Geographic region	**Asia** (China, India, Japan, Philippines, South Korea, Vietnam) **Europe** (Denmark, Germany, Hungary, Poland, Russia, Spain, Sweden, Ukraine, UK) **North America** (Canada, US) **Latin/South America** (Argentina, Brazil, Mexico, Peru)
Type 2 diabetes at baseline	Yes, No
UACR at baseline	=<1000, >1000
eGFR (ml/min/1.73m^2) at baseline*	<45, ≥45
Systolic blood pressure (mmHg) at baseline	>130, ≤130

*The subgroup of eGFR will not include eGFR as covariate in the model.

4.2.4 Analysis of the secondary efficacy variables

The time-to-event secondary variables will be analysed in the similar manner as the primary variable. That is, using a Cox proportional hazards model with a factor for treatment group, stratified by randomization stratification factors (T2D, UACR), and adjusting for baseline eGFR. Censoring is described in Section 3.2 for each endpoint.

Subgroup analysis for the secondary endpoints will be conducted in the same way as the subgroup analysis for the primary endpoint (Section 4.2.3.2).

4.2.5 Analysis of safety variables

For safety analyses, all summaries will be based on the safety analysis set (see Section 2.1.2).

The total exposure to study drug will be defined as the length of period on study drug, calculated for each patient as date of last dose – data of first dose +1.

An alternative measure where days of interruption are removed will be calculated and termed actual exposure.

Total and actual exposure will be presented descriptively.

The on-treatment period will include events with an onset date on or after first dose of randomized study drug and on or before 30 days after last dose of study drug.

Additional presentations will include all events with onset on or after first dose of study drug regardless of whether patients are on or off study treatment at the time of the event (the 'on +off ' treatment period.). For fractures and amputations on+off treatment periods will be considered the primary approach, while the on-treatment period will be used as primary approach for other AEs of interest.

4.2.5.1 Adverse events

Summaries of AEs will primarily be based on the on-treatment period.

In addition to SAEs, the collection of AEs that are not serious is limited to DAEs, AEs leading to interruption of IP or dose reduction and AEs of interest (see CSP 6.3.2). Thus, summaries of AEs will be limited to these categories and general summaries of all AEs are not planned.

AEs will be classified according to MedDRA by the medical coding team at AstraZeneca data management centre, using the most current version of MedDRA possible.

Summary table of the total number and percent and patients in AE categories per treatment group will be provided as well as summaries by SOC and PT levels on relevant AE category.

No statistical tests to compare crude AE frequencies between treatment groups will be performed.

4.2.5.2 Serious adverse events

SAEs will be presented as described below both on treatment and on+off treatment.

The number and percent of patients with SAEs will be presented by SOC, PT and treatment group. The most common SAEs will also be presented by PT only.

AEs with outcome death will be presented separately by SOC and PT.

4.2.5.3 Adverse events leading to discontinuation, interruption or dose reduction

The number and percent of patients will be presented by SOC and PT for AEs leading discontinuation, AEs leading to temporary interruption and dose reduction (separately for each of the three categories based action taken "Drug Permanently Discontinued", "Drug Interrupted" and "Drug Reduced" respectively).

4.2.5.4 Adverse events of interest

Each category of AEs of interest will be presented separately. AEs of interest fall in the categories volume depletion, renal events, major hypoglycaemic events, fractures, diabetic ketoacidosis and AEs leading to amputation.

For each AE of interest a summary table including the number of percent of patients with any event in the AE category, SAE, DAE, AE leading to interruption and dose reduction. Each AE of interest category will also be tabulated with frequency by SOC and PT.

In addition to presentations of the number of patients with event, the total number of events counting multiple events per patient will be presented for AE of special interest, where relevant eg for major hypoglycaemic events.

4.2.5.5 Laboratory Evaluation

All summaries of clinical chemistry/haematology parameters will be based on samples analyzed at the central laboratory, and presented in SI units.

The result and the change from baseline of each clinical chemistry/haematology tests, including eGFR and creatinine clearance, will be summarized by treatment group at each scheduled visit using descriptive statistics, including n, mean, SD, median and quartiles.

Doubling of serum creatinine
Serum creatinine will be collected and change from last value will be calculated from lab and adjudicated when potential doubling. Doubling of serum creatinine will be summarized by treatment group.

4.2.5.6 Marked laboratory abnormalities

The number and percent of patients with a marked abnormality in clinical laboratory tests will be summarized over time by treatment group.

Laboratory abnormalities will be evaluated based on marked abnormality (MA) criteria. The list of MAs is provided in Appendix A.

An on-treatment value will be considered an MA if either

- the on-treatment value is beyond an MA limit AND the baseline value is not beyond the same limit,
  OR
- both the baseline and on-treatment value are beyond the same MA limit AND the on-treatment values is more extreme (farther from the limit) than was the baseline

Laboratory MAs occurring during the on-treatment period will be summarized by treatment group. The directions of changes (high or low) in MAs will be indicated in the tables. Additionally, for each patient with a MA for a parameter, all the patient's values of that parameter over the treatment period will be listed.

4.2.5.7 Vital signs

Vital signs will be presented descriptively by treatment group.

4.2.6 Analysis of exploratory objectives

The analysis of the exploratory variables will in the same fashion as the primary and secondary efficacy variables be based on the ITT principle, including data irrespective of whether the patient has discontinued study drug.

The following time to event endpoints will be analysed with the same methods as the primary endpoint:

- Sustained eGFR decline from baseline (≥30% and ≥40%), as described in Section 3.1
- Composite of chronic dialysis, renal transplant and renal death MI
- Stroke
- First occurrences of serum potassium falling above/below defined thresholds
- Doubling of S-Creatinine

Change in eGFR over time

Change in eGFR from baseline to end of treatment will be analyzed as eGFR total slope while change in eGFR from day 14, i.e., the first on treatment measurement, to end of treatment will be analyzed as eGFR chronic slope.

The changes in eGFR will be analyzed using a two-slope mixed effects linear spline model based on restricted maximum likelihood (REML) estimation, with day 14 visit defined as the 'knot' in the model. The model will include fixed, categorical effects of treatment and stratification factors and fixed continuous covariates of baseline eGFR, time, and treatment-by-time interaction. The intercept, acute slope (baseline to day 14 visit), and chronic slope (day 14 visit to end of treatment) will be included as random effects to account for variation in progression rates over time. An unstructured covariance will be used to model the within-patient errors. The time variable represents the duration from baseline to each eGFR assessment during acute and chronic phases. This model will include all observed on-treatment eGFR measurements (Vonesh et al 2019).

Linear contrasts will be constructed to estimate the acute, chronic and total slope in eGFR. LS means of the treatment different with 95% confidence interval and corresponding two-sided p-value will be presented. The total slope will be estimated at 30 months after baseline, in consideration of the anticipated data availability and duration of treatment.

The adjusted LS mean of eGFR change from baseline at each visit, based on a repeated measures model, will be plotted over time by treatment group to depict the pattern of eGFR over time.

Analysis of repeated measures

Changes from baseline over time for eGFR, UACR, HbA1c, body weight, systolic BP, KDQOL-36 and EQ-5D-5L will be analysed with a repeated measures method. The model will include terms for treatment group, visit, visit*treatment group and baseline measurement as a covariate. All non-missing visit data will be used, including measurements after discontinuation of study drug. The analysis of HbA1c will be limited to patients with T2D at baseline. The analysis of UACR will use log transformed values. The model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided p-value. Missing data will not be imputed.

Analysis of proportions

The proportion of patients with new T2D diagnosis during study will be analyzed by a logistic regression with treatment group and baseline HbA1c. The proportion of patients entering CKD4 during study will be analyzed by a logistic regression with treatment group and baseline eGFR. The odds ratio between treatment groups and its 95% confidence interval and corresponding two-sided p-value will be presented.

5. INTERIM ANALYSES

N/A

6. CHANGES OF ANALYSIS FROM PROTOCOL

N/A

7. REFERENCES

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Vonesh E, Tighiouart H, Ying J, Heerspink HL, Lewis J, Staplin N, Inker L, Greene T; Mixed-effects models for slope-based endpoints in clinical trials of chronic kidney disease. Statistics in Medicine. 2019; 38:4218-4239

8. APPENDIX

Appendix A Laboratory Abnormality Criteria

Table 2 provides the criteria for assessing marked abnormalities in safety laboratory parameters. When there is more than one limit for a variable in Table 2, summaries will be provided for each limit.

If both the baseline and on-treatment values of a parameter are beyond the same MA limit for that parameter, then the on-treatment value will be considered a MA only if it is more extreme (farther from the limit) than was the baseline value.

The following three criteria will also be summarized by treatment group in examination of the elevated AT (ALT and/or AST) and total bilirubin:

- (AST or ALT > 3XULN) and (Total Bilirubin > 1.5XULN within 14 days on or after AT elevation)
- (AST or ALT > 3XULN) and (Total Bilirubin > 2XULN within 14 days on or after AT elevation)
- (AST or ALT > 3XULN) and {(Total Bilirubin > 2XULN and no ALP ≥ 2XULN) within 14 days on or after AT elevation}

Table 2 Marked abnormality criteria for safety laboratory variables and elevated AT (ALT and/or AST) and total bilirubin

		Marked Abnormality Criteria	
Clinical laboratory variables	**Units**	**Low**	**High**
Hematology			
HCT females	vol	< 0.20	> 0.55
HCT males	vol		> 0.60
Hemoglobin females	g/L	< 60 g/L	> 180 g/L
Hemoglobin males	g/L		> 200 g/L

		Marked Abnormality Criteria	
Clinical laboratory variables	**Units**	**Low**	**High**
Blood Chemistry			
ALP	U/L		> 1.5X ULN
ALP	U/L		> 3X ULN
ALT	U/L		> 3X ULN
AST	U/L		> 3X ULN
AST or ALT	U/L		> 3X ULN
ALT	U/L		> 5X ULN
AST	U/L		> 5X ULN
AST or ALT	U/L		> 5X ULN
ALT	U/L		> 10X ULN
AST	U/L		> 10X ULN
AST or ALT	U/L		> 10X ULN
ALT	U/L		> 20X ULN
AST	U/L		> 20X ULN
AST or ALT	U/L		> 20X ULN
Total Bilirubin	µmol/L		> 1.5X ULN > 2X ULN
Na (Sodium)	mmol/L	< 130 mmol/L	> 150 mmol/L
Na (Sodium)	mmol/L	< 120 mmol/L	
K (Potassium)	mmol/L	≤ 2.5 mmol/L	≥ 6.0 mmol/L
Creatinine	µmol/L		≥1.5X BL CREAT

BL is the baseline measurement

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