DAPASALT: An Open Label, Phase IV, Mechanistic, Three-Arm Study to Evaluate the Natriuretic Effect of 2-Week Dapagliflozin treatment in Type 2 Diabetes Mellitus Patients with Either Preserved or Impaired Renal Function and Non-Diabetics with Impaired Renal Function

ClinicalTrials.gov Identifier: NCT03152084

Date of Statistical Analysis Plan: 25 October 2019

STATISTICAL ANALYSIS PLAN

D1690C00049

DAPASALT: An Open Label, Phase IV, Mechanistic, Three-Arm Study to Evaluate the Natriuretic Effect of 2-Week Dapagliflozin Treatment in Type 2 Diabetes Mellitus Patients with Either Preserved or Impaired Renal Function and Non-Diabetics with Impaired Renal Function

Version: Final 3.0

Date: 25 Oct 2019

REVISION HISTORY

Version	Version Date	Author	Summary of Changes Made
Final 1.0	28Jun2017	PPD	NA
Final 2.0	06 Nov2018	PPD	NA
Final 3.0	25 Oct 2019	PPD	Updated according to Dry Run comments

SIGNATURE PAGE - ASTRAZENECA

Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

PPD

11-NOV-2019

Date (DD Mmm YY)

Principal Statistician

SIGNATURE PAGE - PAREXEL

Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

PPD

12 Nov 19

Date (DD Mmm YY)

Senior Biostatistician

TABLE OF CONTENTS

ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
CCI	
AST	aspartate aminotransferase
BIS	bioimpedance spectroscopy
BLQ	below the limit of quantification
CCI	
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cm	centimetre
CSP	clinical study protocol
CSR	clinical study report
CV	coefficient of variation
DRM	data review meeting
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ET	end of treatment
FU	follow up
HbA1c	glycosylated haemoglobin
ICG	indocyanine green
IMP	Investigational Medicinal Product
kg	kilogram(s)
L	litre(s)
LLOQ	lower limit of quantification
LSMEANS	least-squares means
m	metre

Abbreviation / Acronym	Definition / Expansion
MA	marked abnormality
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalent
min	minute
mL	millilitre
mmHg	millimetres of mercury
n	number of patients
NA	not applicable
ND	not determined
NQ	not quantifiable
CCI	[redacted]
PK	pharmacokinetic(s)
PT	preferred term
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
ST	Start of treatment
T2DM	type 2 diabetes mellitus
TLFs	tables, listings and figures
UACR	urine albumin to creatinine ratio
CCI	[redacted]
WHO-DD	World Health Organisation - Drug Dictionary

STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analysing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and analysis sets, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on the CSP Version 5.0, dated 23 April 2018. The SAP will be finalised prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made in an updated SAP. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in a SAP Addendum and discussed in the Clinical Study Report (CSR).

The SAP describes Group 1 as it was originally planned in the latest version of the CSP. it was decided that no Group 1 subjects will be enrolled onto this study (please see reference in Action log on the 22nd of March 2019), so no statistical outputs will contain Group 1 information.

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective is to investigate the change in 24-hour sodium excretion during dapagliflozin treatment between Baseline (average of Days −3 to −1) and average of Days 2 to 4 within each study group.

- Patients with type 2 diabetes mellitus (T2DM) with impaired renal function;
- Patients with T2DM with preserved renal function;
- Non-diabetic patients with impaired renal function.

1.2 Secondary Objectives

The secondary objectives of the study, to be assessed for each of the groups, are to:

- Evaluate the change in 24-hour sodium excretion from Baseline to end of treatment, and during follow-up;
- Evaluate the change in 24-hour glucose excretion;
- Evaluate the change in mean 24-hour systolic blood pressure;
- Evaluate the change in plasma volume;
- Evaluate the change in extracellular volume;
- Evaluate the pharmacokinetics of dapagliflozin;
- Evaluate the change in 24-hr urine albumin to creatinine ratio (UACR).

CCI

1.4 Safety Objectives

The safety objectives are to evaluate the safety and tolerability of dapagliflozin in each of the target patient populations.

2. STUDY DESIGN

DAPASALT is an open label, mechanistic, three-arm study to evaluate the natriuretic effect of two-week dapagliflozin treatment in T2DM patients with either preserved or impaired renal function and in non-diabetics with impaired renal function.

The study population will comprise three groups of patients:

- Group 1: T2DM patients with impaired renal function, defined as having an estimated glomerular filtration rate (eGFR), defined by Chronic Kidney Disease (CKD) Epidemiology Collaboration (CKD-EPI), of ≥ 25 and ≤ 50 millilitres/minute/1.73 metres squared (mL/min/1.73m^2);
- Group 2: T2DM patients with preserved renal function, defined as having an eGFR, defined by CKD-EPI, of > 90 and ≤ 130 mL/min/1.73 m^2 for patients aged 59 years

or younger, between >85 and ≤130 mL/min/1.73 m^2 for patients aged 60 to 69 years, and between >75 and ≤130 mL/min/1.73 $m^2$for patients aged 70 years or older;

- Group 3: Non-diabetic patients with impaired renal function, defined as eGFR range for Group 1.

A total of 51 patients are planned to be enrolled in the study, with 17 patients in each group.

The study periods and schedule of visits are presented in Section 7.1 (Tables 5 and 6) of CSP. Briefly, the efficacy measurements will, with some exceptions, be collected four times during the course of the study: Visit 4 (day 1 relative to start of treatment), Visit 5 (day 4), Visit 8 (typically, day 14) and Visit 9 (typically, day 18), with the final time point being post-treatment. A notable exception is the 24-hour urine, which will be collected on three, or four, consecutive days during four time periods, with the last day in these periods being day -1, day 4, day 14 and day 17, and 24-hr blood pressure, which will be collected at Visit 7 (typically, day 13) rather than day 14. Blood samples to evaluate pharmacokinetic (PK) properties of dapagliflozin in this population will be taken twice during the study, once during Visit 5 (pre-dose) and four times during Visit 8 (pre-dose and 1, 2, 4 h post-dose). Additional bioimpedence spectroscopy measurements will be performed at the same time as PK sampling during Visit 8.

Adverse events (AE), including serious adverse events (SAE) are collected throughout the study, with SAE collection starting at the screening visit and AE collection at dosing, both ending at the last visit (Visit 10, typically day 19). Laboratory safety assessments will generally be done at Screening (Visit 1), Visit 4 and Visit 8 (See Section 5.1.3.2), with some exceptions.

As many of the efficacy measurements will be taken at four distinctive time periods during the course of the study, namely baseline, soon after treatment start, at the end of treatment and at the end of follow up, when reporting the efficacy results of the study each measurement will be assigned to an analysis window:

- **Baseline** is the measurement obtained before initiation of treatment, typically during Visit 4. For 24-hr blood pressure, the baseline measurement is the measurement obtained the day before Visit 4.
- **Start of Treatment (ST**) is the measurement obtained after the patient has been in the study for a short time, typically on Visit 5.
- **End of treatment (ET)** is the measurement obtained on the visit corresponding to the last day of the treatment period, namely Visit 8, unless the patient attended an early termination visit. For 24-hr blood pressure, as well as CCI measurements in the 24-hr urine, the end of treatment measurement is the measurement obtained the day before Visit 8.

- **Follow-up (FU)** is the measurement obtained after the end of the treatment period, namely Visit 9. CCI [redacted]

The exception from the rules outlined above is the 24-hr urine, the collection of which will take place on consecutive days, rather than on one single day. In this case, Baseline, ST, ET and FU used in the analyses will be the averages of these consecutive samples. Explicitly, Baseline is the average of measurements obtained on day -3 to day -1, ST the average of measurements obtained on day 2 to day 4, ET the average of measurements obtained on day 12 to day 14 and FU the average of measurements obtained on day 15 to day 17.

3. STATISTICAL BASIS FOR SAMPLE SIZE

With a sample size of 15 patients per group and assuming a standard deviation (SD) of 25 milliequivalent (mEq)/24 hours in change from average Baseline in 24-hour sodium excretion, the study will have 80% power to detect an increase of at least 20 mEq/24 hours in average change from average Baseline 24-hour sodium excretion with dapagliflozin within each group at a two-sided alpha level of 0.05.

Under these same conventions for the number of patients, the SD and the alpha level, and assuming 50% power, the minimum detectable difference in change from average Baseline in 24-hour sodium excretion is approximately 13.6 mEq/24 hours.

Similarly, under the same conventions for the number of patients and the alpha level, 50% power and fixing the change from average Baseline in 24-hour sodium excretion to 20 mEq/24 hours, the maximum SD at which statistical significance can be demonstrated is approximately 37 mEq/24 hours.

It is assumed that approximately 10% of the enrolled patients will not provide evaluable data with regards to the primary endpoint, leading to 17 patients to be enrolled in each of the groups. If the non-evaluable rate is higher than expected, additional patients might be enrolled in order to ensure 15 evaluable patients.

4. RANDOMISATION

Randomisation will not be applied in this study. Patients will be enrolled to specific groups based on their diagnosis. When 17 patients have been enrolled to each specific patient group enrolment into that group will stop, and the evaluability of the data evaluated. If less than 15 evaluable patients in a particular group are found, the recruitment into that group might resume. All patients will receive dapagliflozin 10 mg tablets once daily for 14 days.

5. STATISTICAL ANALYSIS CONVENTIONS

5.1 Analysis variables

5.1.1 Demographic and baseline variables

During the screening visit, baseline patient characteristics (e.g. age, gender and race) will be collected. Relevant medical and surgical history will be recorded, as well as details of T2DM (for T2DM patients) and renal impairment (for patients with impaired renal function). Vital signs, such as pulse and blood pressure, will also be registered. For a detailed list of baseline assessments, please see Appendix A.

5.1.2 Prior and concomitant medication

Any medications administered other than dapagliflozin or indocyanine green (ICG) will be classified as prior or concomitant. The following definitions of prior and concomitant medications will be used:

- **Prior medication**: medications that have been taken prior to first dapagliflozin dose and which have a stop date which indicates that the medication has been stopped before first dapagliflozin are considered prior medication.
- **Concomitant medication**: medications with a start date on or after first dapagliflozin dose are considered concomitant medications. In addition, medications with a start date of administration prior to the date of first dapagliflozin administration, but which have an end date (or are ongoing) on or after first dapagliflozin administration will be considered as both concomitant and prior medication.

5.1.3 Safety variables

5.1.3.1 Adverse events

AEs and Serious AEs (SAEs), are defined in Section 6.2.1 of the CSP. SAEs will be collected from the time of informed consent until the end of the Follow-up period. All other AEs will be recorded from first dose until the end of the Follow-up period.

5.1.3.2 Clinical laboratory tests

Clinical laboratory tests for safety and eligibility evaluation will be performed pre-dose and during the study (refer to Table 5 and Table 6 study plan for schedule of assessments on the Clinical Study Protocol).

The following variables will be measured:

Lab	Screening	Baseline	ST	ET	FU
Clinical chemistry					
Creatinine	x	x	x	x	x
Glucose	x	x	x	x	x
Total bilirubin	x			x	
AST	x			x	
ALT	x			x	
ALP	x			x	
Haematology (a)					
Haemoglobin	x	x		x	
Haematocrit	x	x	x	x	x
HbA1C (b)	x				
Urinalysis					
UACR (b)	x				
Dipstick (c)	x			x	
Other					
Pregnancy test	x			x	

(a) Note that haematocrit, glucose and creatinine will also be analysed as efficacy endpoints. If the urine pregnancy test is positive, then a serum pregnancy test will also be performed

(b) For evaluation of the inclusion / exclusion criteria

(c) Tests performed are U-albumin, U-glucose and U-blood

5.1.3.3 Vital signs

The following measurements will be performed at each time-point:

- Blood pressure (systolic and diastolic, measured in millimetres of mercury [mmHg])
- Pulse rate (measured in beats per minute)
- Weight (kg)

5.1.3.4 12-lead safety electrocardiogram

A 12-lead electrocardiogram (ECG) will be obtained at Screening.

The Investigator will provide an overall interpretation of the ECG as normal, abnormal or borderline and the result will be recorded in the eCRF. If abnormal, the clinical significance

(clinically significant or not clinically significant), and the details of the abnormality, will also be recorded in the eCRF.

5.1.3.5 Physical examination

Documentation (yes/no) that the examination was performed will be entered in the eCRF. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

5.1.4 Pharmacokinetic variables

There will be no pharmacokinetic parameters derived. A population pharmacokinetic analysis of data may be performed as outlined in a separate population pharmacokinetic analysis plan and the results of this will be reported outside of the CSR and will not be further discussed in this SAP.

5.1.5 Efficacy variables

The full list of measurements performed during the study that are used to evaluate efficacy can be found in Appendix B .

5.1.5.1 Primary Efficacy Endpoint

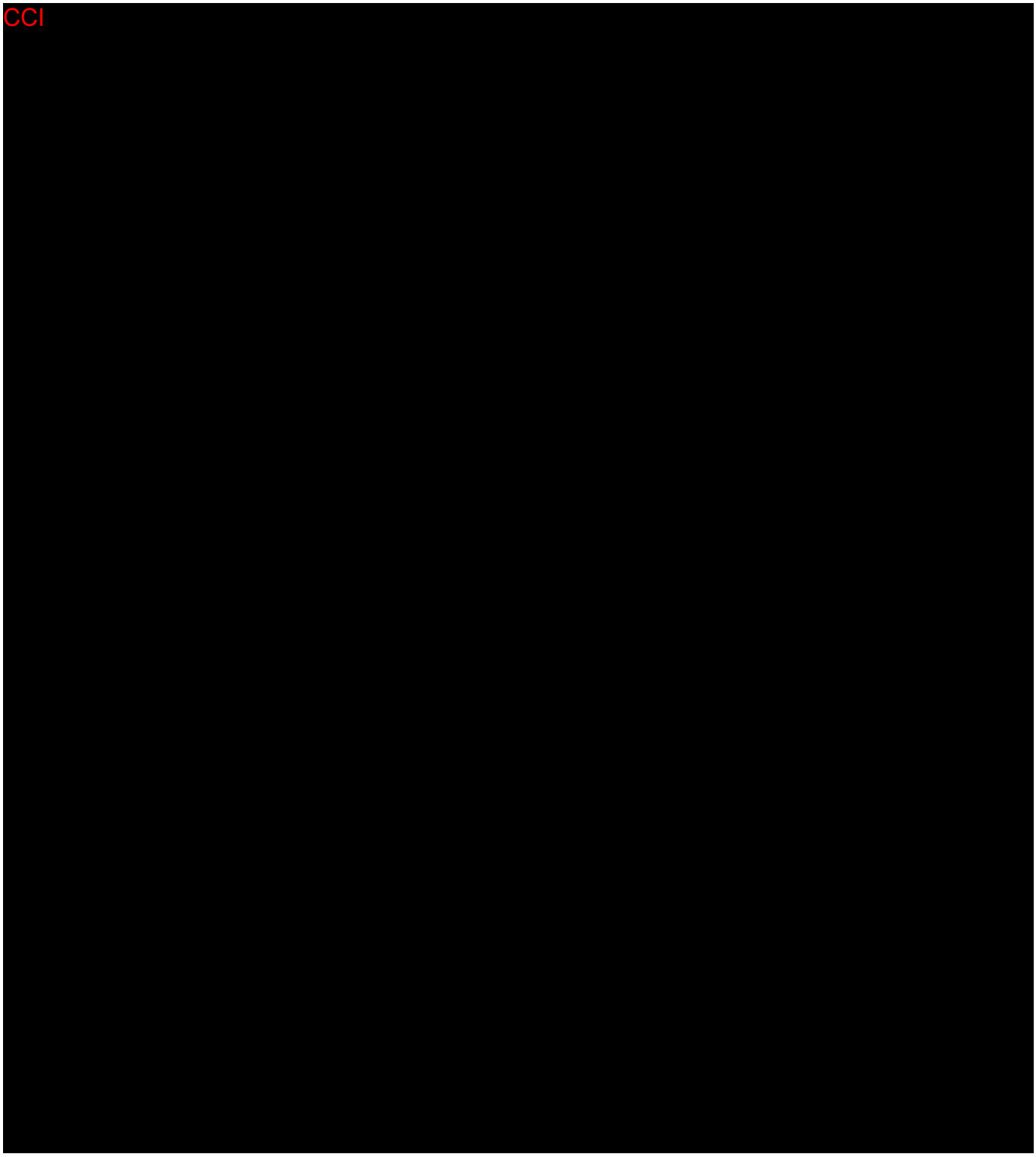
Average change in 24-hr sodium excretion from average Baseline to average values at Day 2 to 4 within each study group.

5.1.5.2 Secondary Efficacy Endpoints

The secondary endpoints to be evaluated during or following dapagliflozin treatment within each study group are:

- Average change in 24-hr sodium excretion from average Baseline values to average end of treatment values (Day 12 to 14); and from average end of treatment values (Day 12 to 14) to average values during Follow-up (Day 15 to 17).
- Average change in 24-hr glucose excretion from average Baseline values to average values at Day 2 to 4; from average Baseline values to average end of treatment values (Day 12 to 14); and from average end of treatment values (Day 12 to 14) to average values during Follow-up (Day 15 to 17).
- Change in mean 24-hr systolic blood pressure from Baseline to Day 4; from Baseline to end of treatment (Day 13); and from end of treatment (Day 13) to end of Follow-up (Day 18).
- Change in plasma volume from Baseline to Day 4; from Baseline to end of treatment (Day 14); and from end of treatment (Day 14) to end of Follow-up (Day 18).

- Change in extracellular volume from Baseline to Day 4; from Baseline to end of treatment (Day 14); and from end of treatment (Day 14) to end of Follow-up (Day 18).
- Dapagliflozin pharmacokinetics on Days 4 and 14.
- Average change in mean 24-hr UACR from average Baseline to Day 4; and from average Baseline values to average end of treatment values (Day 12 to 14).


CCI

5.2 Analysis sets

5.2.1 Enrolled Set

All patients who provided informed consent will be included in the Enrolled Set.

5.2.2 Run-in Set

All patients who received standard food boxes will be included in the Run-in Set.

5.2.3 Medication Dispensed Set

All patients who were dispensed at least one dose of study drug will be included in the Medication Dispensed Set.

5.2.4 Evaluable Subjects Data Set

This will be a subset of the Medication Dispensed Set. It will exclude primary efficacy variable data which may have been affected by protocol deviations as determined by the medical monitor or agreed by the study team. All decisions to exclude data from the Evaluable Subjects Data Set will be made prior to the database lock of the study during the Data Review Meeting (DRM).

5.2.5 Pharmacokinetic analysis set

The Pharmacokinetic (PK) analysis set will consist of all subjects in the medication dispensed set for whom at least one of the plasma concentration samples are available and who have no important protocol deviations judged to impact the analysis of the PK data.

5.2.6 Safety Set

All patients who took at least one dose of study drug and who have data from at least one post-dose safety assessment available will be included in the Safety Set.

5.3 Statistical analysis methods, general principles

Statistical evaluation will be performed by PAREXEL. Analysis Data will adhere to CDISC (Clinical Data Interchange Standards Consortium) guidance documents for Analysis Data Model (ADaM) and follow their AZ interpretation.

The term “by group” will refer to the grouping of summary data based on the groups as defined in Section 2 in all cases, unless otherwise specified:

- Group 1: T2DM patients with impaired renal function;
- Group 2: T2DM patients with preserved renal function;
- Group 3: Non-diabetic patients with impaired renal function.

In case of a pre-mature termination of the study, or a request of a report of the current results while the study is on-going, all the analyses will be performed on the data available. If there are no patients in one of the groups above, the group will be omitted from all the presentations.

5.3.1 Listings and descriptive statistics

Data will be summarised using descriptive statistics.

For each qualitative variable, frequency counts (number of patients [n] and percentages) will be made. The percentages will be calculated with respect to number of patients in each group. For continuous variables, descriptive statistics will include n, arithmetic mean, standard deviation (SD), median, minimum and maximum, and might include the first and the third quartile. Geometric coefficient of variation (geometric CV%), geometric mean and geometric SD will also be presented in the descriptive statistics for the PK concentration data.

General rounding rules will be followed with regard to the number of decimal places and presentation of data in the tables and listings unless it is deemed scientifically appropriate to display the data in a different format (see Appendix C).

5.3.2 Handling of repeat and unscheduled measurements

All repeated and unscheduled measurements will be presented in the listings. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated measurements obtained prior to the first dose of dapagliflozin the latest value (which may be scheduled or unscheduled) will be used in the calculation of descriptive statistics
- For repeated measurements obtained at the designated Baseline visit, the latest value (which may be scheduled or unscheduled) will be defined as the Baseline provided that this occurred prior to the first dose of dapagliflozin. Repeated measurements designated Baseline will be used in descriptive statistics rather than the planned measurement they replace
- For repeated measurements obtained at any time point after the first dose of dapagliflozin, the first value of any repeated measurements will be used in the calculation of changes from Baseline and for the descriptive statistics. Unscheduled and repeated measurements will not be included in the descriptive statistics at time points after the first dose of dapagliflozin.

5.3.3 Statistical significance level

All statistical tests will be two-sided and will be performed at the 5% level of significance. No multiplicity adjustments will apply. However, it is acknowledged that the issue of false positives is very relevant in this study, as the number of tested hypotheses is large. This issue

will be taken into consideration when interpreting the results, keeping in mind both the expected number of false positives (i.e. rejections of a hypothesis when no effect is in fact present) and clinical feasibility of the pattern of seemingly detected effects.

5.3.4 Software

All statistical analyses and production of tables, figures and appendices will be performed using SAS software version 9.3 or later.

5.3.5 Missing and censored data

In general, missing data will not be imputed. The only exceptions to this rule are missing dates for start or stop of an adverse event, missing dates of start and end of concomitant medications and missing dates for onset of a historical medical condition. For details on imputation rules regarding dates, see Appendix D.

5.3.6 Laboratory data reported above or below a threshold

Any laboratory variables with results from the laboratory given as '<xx', '>xx', '≤xx' or '≥xx' in the database will be imputed with the absolute value of the number without the sign (e.g., < 2.2 will be imputed as 2.2) for the descriptive statistics, changes from baseline and derivation of any derived variables dependent on this value. Graphical displays will also make use of this convention. Observed value results will be listed as is without any imputation.

5.3.7 Center pooling strategy

It is planned to recruit subjects in different centers. The data from different sites will be pooled for all analyses.

5.3.8 Coding dictionaries

All AEs and medical history will be coded for analysis according to the Medical Dictionary for Regulatory Activities (MedDRA)® coding dictionary, using the latest version available. Prior and concomitant medication will be coded according to the World Health Organisation Drug Dictionary Enhanced + Herbal Dictionary March 2017. Medical procedures will not be coded.

5.3.9 Study population characteristics

5.3.9.1 Patient disposition

An overall disposition will be listed and summarised descriptively, with the descriptive summary done per group and organized by population type (e.g. patients enrolled into study).

All disposition summary tables will be based on the Enrolled Set and the percentages will be based on the number of patients in the Medication Dispensed Set. No percentages will be presented for the number of patients enrolled or for the number of patients in the Run-in Set.

5.3.9.2 Protocol deviations

Protocol deviations will be handled in accordance with PAREXEL SOPs.

Deviations from the protocol will be assessed as "not important" or "important". Important deviations from the protocol may lead to the exclusion of patients from the Evaluable Patients Set and include the following:

- Violation of inclusion and/or exclusion criteria;
- Dosing deviations (e.g., non-compliance);
- Patients receiving prohibited concomitant medications;
- Other procedural and study conduct deviations recorded by the clinical unit on the protocol deviation log.

Compliance will be calculated as specified in Section 5.3.14. Patients will be considered non-compliant for a given interval(s) if the compliance is more than 120% or less than 80%.

Only important protocol deviations (as agreed and documented at the DRM prior to database hardlock) will be reported in the relevant table and listing.

The complete set of criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study-specific protocol deviation specification document.

All important protocol deviations will be listed and summarised by group based on the Medication Dispensed Set. Percentages for the summary will be based on the number of patients in the Medication Dispensed Set for each study group respectively.

Patients and data excluded from the Evaluable Subjects Set will be listed, including the reasons for exclusions. These listings will be based on the Medication Dispensed Set.

5.3.10 Demographics, medical history and baseline data

Demographics (including Screening height, weight, age, gender, ethnicity and race) will be listed by patient based on the Safety Set. Demographic characteristics (age, gender, race, and ethnicity) and patient characteristics (Screening height and weight) will be also summarised based on the Safety Set, by group. The denominator for the percentages will be the number of patients in the Safety Set for each group.

Medical history data will be listed by patient, based on the Safety Set and summarised by group, system organ class (SOC) and preferred term (PT) based on the Safety Set.

Percentages for the summary will be based on the number of patients in the Safety Set for each study group respectively. Surgical history will be listed by patient, based on the Safety Set, showing the procedure and the date of the procedure.

The following additional listings will be presented, based on the Safety Set:

- For patients with T2DM:
  - the date of first diagnosis
  - duration of T2DM
- For patients with renal impairment:
  - date of first diagnosis
  - duration of renal impairment
  - most likely aetiology as detailed in Appendix A.
  - if applicable, chronic glomerulonephritis type as detailed in Appendix A.

The disease duration will be calculated as follows:

- (1 + informed consent date - diagnosis date) / 365.25.

See Appendix D for details the handling of missing or incomplete diagnosis dates.

The following additional baseline characteristics will be summarised, where applicable:

- Duration of T2DM and duration of renal impairment, summarised by:
  - Continuous summary (years)
  - Categorical summary (years): n (%): < 3, ≥3 - ≤ 10, > 10
- HbA1c
  - Continuous summary (%)
  - Categorical summary (%): n (%): <6, ≥6 - <6.5, ≥ 6.5 - <7, ≥ 7 - <8, ≥ 8 - <9, ≥ 9 - <10
- eGFR (mL/min/1.73 m^2)
  - Continuous summary
  - Categorical summary: n (%): < 30, ≥ 30 - <45, ≥ 45 - <60, ≥ 60 - <90, ≥ 90
- UACR (mg/g)
  - Continuous summary
  - Categorical summary: n (%): < 30, ≥30 - ≤300, > 300 - < 2200, ≥2200
- Fasting insulin (uU/ml), continuous summary

5.3.11 Pregnancy testing

Pregnancy testing results will be listed for each female patient, based on the Safety Set.

5.3.12 Prior and concomitant medication

Missing dates/times for prior/concomitant medications will be handled as described in Appendix D.

Prior and concomitant medication will be listed by patient based on the Safety Set (a flag for Evaluable Subjects will be included). The listing will include the information detailed in collected in the eCRF as well as the preferred term, anatomical therapeutic chemical class and classification as prior or concomitant (or both where applicable).

Prior and concomitant medications will be summarised by group, separately for prior and concomitant medications, based on the Safety Set. Percentages will be based on the number of patients in the Safety Set for each group.

5.3.13 Exposure to investigational product

Exposure to dapagliflozin will be listed for each patient, based on the Safety Set. The date and time (where available) of administration, as well as the duration of exposure will be included in the listing.

Duration of exposure is defined as the number of days exposed to study drug and calculated as (last dosing date – first dosing date) + 1.

The duration of exposure will be summarised by descriptive statistics.

5.3.14 Compliance to investigational product

Compliance will be calculated and expressed as a percentage. Based on the tablet counts, the percentage treatment compliance will be calculated as the number of tablets taken (dispensed minus returned) relative to expected number of taken tablets:

- 100 x (number of tables taken / expected number of taken tablets)

The expected number of tablets taken will be calculated as:

- (number of tablets taken daily) × (number of days between visits, until treatment is completed or permanently discontinued).

The following intervals will be considered for the calculation of compliance:

- Overall: based on Day 1 to Day 14; this will only be calculated for patients completing the treatment period (Day 1 – Day 14);
- Start of Treatment: based on Day 1 to Day 4;
- Maintenance Treatment: based on Day 5 to Day 11;
- End of Treatment: based on Day 12 to Day 14.

Based on drug accountability obtained from the eCRF, the compliance for the overall period will be tabulated. The compliance will also be listed by patient including results for both drug accountability obtained from eCRF and patient diaries. The safety set will be used.

5.3.15 Food and fluid consumption

Details regarding food and fluid consumption will be listed by patient based on Safety Set.

5.3.16 Efficacy analysis and reporting, general approach

Unless otherwise specified, all listings and individual patient figures in this section will be based on the Evaluable Subjects Set; all tables and mean figures in this section will be based on the Evaluable Subjects Set.

5.3.16.1 Statistical models

For each efficacy variable, and each patient group, two models will be constructed. The first will be used to estimate the change from baseline to ST, and from baseline to ET. The second will be used to estimate the change from end of treatment to follow-up.

Model 1

Due to the likely dependence between within-patient observations, the first model will be a linear mixed effect model with time (ST and ET), the baseline value of the variable and the interaction between the two as fixed effects. The within-patient dependence is incorporated through covariance matrix of the residuals, which is assumed to be unstructured. Least squares mean (LSM) estimates of average effect at each one of the two time points will be obtained from the model and tabulated, together with the 95% confidence intervals (CI) and p-values.

Kenward-Rogers method will be used for approximation of degrees of freedom for the tests from which the p-values are obtained.

Explicitly, the following SAS code will be used for the first model:

```
PROC MIXED DATA = <DATA>;
        BY <GROUP>;
        CLASS <TIME> <USUBJID>;
        MODEL <CHANGE> = <TIME> <BASE> <TIME> * <BASE> / DDFM =
        KENWARDROGER;
        REPEATED <TIME> / TYPE = UN SUBJECT = <USUBJID>;
        LSMEANS <TIME> / CL ALPHA = 0.05;
RUN;
```

where <GROUP> is the variable representing the patient group, <CHANGE> refers to the variable containing the change versus the baseline for each patient, <TIME> refers to the

time-point, <USUBJID> refers to the variable containing the patient numbers, <BASE> refers to the baseline value; <TIME> * <BASE> refers to the interaction term.

In case on non-convergence of the model the following alternative will be explored in order, as required:

Each of the groups and each of the timepoints will be considered separately by fitting a linear regression model with change between baseline to the specific timepoint (ST, ET) as the response and the baseline value of the modelled endpoint as a single covariate. Similarly, to the original model, the estimated expected change from baseline for a patient with an average baseline value (which can be seen as a form of LSM), as well as the 95% CI and p-value, will be tabulated.

Explicitly, the following SAS code will be used:

```
PROC MIXED DATA = <DATA>;
    BY <GROUP> <TIME>;
    CLASS <GROUP>;
    MODEL <CHANGE> = <BASE>  <GROUP>;
    LSMEANS <GROUP>/ CL ALPHA = 0.05;
RUN;
```

With variable names as above.

Model 2

The model for the change between the ET and the FU timepoints will be a linear regression model. This model will be constructed for each group separately and include the baseline value of the studied endpoint as a single covariate. Similarly, to the back-up option for Model 1, the estimated expected change between ET and FU for a patient with an average baseline value, as well as the 95% CI and p-value, will be tabulated.

This will be done using the following SAS code:

```
PROC MIXED DATA = <DATA>;
    BY <GROUP>;
    CLASS <GROUP>;
    MODEL <CHANGE> = <BASE>  <GROUP> ;
    LSMEANS <GROUP> / CL ALPHA = 0.05;
RUN;
```

Here, <CHANGE> refers to the change between ET and FU.

The approach described above will be applied for the analyses of all endpoints, with the exception of PK (discussed separately in Section 5.3.16.5).

The formal analyses will be accompanied by listings, tables with summary statistics and Box plots. The summary tables for the values observed at each measurement timepoint will be presented for each group separately, in general including mean n, SD, median, minimum, maximum, as well as the first and third quartiles. For the change from baseline, the summary will include n, median, minimum and maximum.

5.3.16.2 24-hour urine data

A listing of urine sample collection, showing each collection day's start and stop date/time, urine sodium amount excreted, urine glucose concentration, urine glucose amount excreted, urine volume and UACR, will be presented.

A separate listing will be presented showing the by-patient arithmetic mean of the urine sodium amount excreted, urine glucose amounts excreted urine volume and UACR taken across the following summary periods:

- Baseline: Day -3 up to and including Day -1;
- Start of Treatment (ST): Day 2 up to and including Day 4 and for UACR ST: Day4;
- End of Treatment (ET): Day 12 up to and including Day 14;
- Follow-up (FU): Day 15 up to and including Day 17.

The following by-patient changes will be derived for each urine sodium amount excreted, urine glucose amount excreted, urine volume and UACR:

- ST average versus the BL average
- ET average versus the BL average;
- FU average versus the ET average.

Changes in urine sodium amount excreted, urine glucose amount excreted, urine volume and UACR will be listed, for each of the change types specified above.

Each of the average summary periods (Baseline, ST, ET and FU), as well as the individual study day values, will be summarised for urine sodium amount excreted, urine glucose amount excreted, urine volume and UACR, by group.

Calculated by-patient changes, for each of the change types defined above (i.e., each of the defined intervals/days where changes are calculated), will be summarised by group and time-point.

Box-plots for each change type versus time-point will be presented, with all groups overlaid on the same plot and separate plots for each of urine sodium amount excreted, urine glucose amount excreted, urine volume and UACR.

5.3.16.3 24-hour blood pressure monitoring

The results of systolic and diastolic blood pressure will be listed for each of the intervals over which this is collected over the 24-hour period.

The following by-patient averages will be derived and listed for systolic and diastolic blood pressure, for each of the collection days as specified in Section 5.1.5.3:

- Daily average defined as the average over the entire 24 hours collection;

CCI [redacted]

The following rules will apply with regards to incomplete blood pressure measurements:

- Daily average: a minimum of 40 valid data points will be required for the calculation of the daily average; otherwise, no Daily average will be calculated.

CCI [redacted]

The above rules are based on the following sampling frequencies and the requirement that 50% of data be non-missing:

- a sampling frequency of every 15 minutes (= 0.25 hours) during the day, which would result in ~16/0.25 = 64 data points over a 16 hour period is time-period;
- a sampling frequency of every 30 minutes (= 0.5 hours) during the night, which would result in ~8/0.5 = 16 data points over an eight hours period;
- 64 + 16 = 80 data points over the whole 24-hour period;

For each patient, CCI [redacted] will be derived and listed for systolic and diastolic blood pressure.

Changes in the daily average CCI [redacted], will be derived and listed. The following changes will be derived:

- Change from Baseline (Day -1) to ST (Day 4);
- Change from Baseline (Day -1) to ET (Day 13);
- Change from ET (Day 13) to FU (Day 18).

Daily averages, CCI [redacted] and the corresponding changes will be summarised by group and time-point.

Boxplots for daily averages, CCI [redacted] will be presented, with all groups overlaid on the same plot and separate plots for systolic and diastolic blood pressure, CCI [redacted].

5.3.16.4 Measurements for plasma volume estimates

The total plasma volume will be estimated based on results from a noncompartmental analysis of the plasma ICG-time profile. The derivation of the plasma volume estimates will be conducted by AstraZeneca and details regarding the estimation techniques will be documented separately. The plasma volume estimates will be provided to PAREXEL for further analysis and reporting as described below.

Presentation of ICG

The bolus dose of ICG (in mg) administered will be derived based on the administered volume (mL) and the confirmed strength (5 mg/mL) of the ICG solution:

- bolus dose administered (mg) = volume administered (mL) x 5 mg/mL.

The details of the bolus dose of ICG administered for each study day will be listed, including the dose volume and the date/time of the ICG injection and bolus dose.

The plasma ICG concentrations will be listed by patient and time-point, including the date/time of the sample; and will be summarised using geometric mean, 10^{th} and 90^{th} percentiles by group and time-point.

Presentation of plasma volume

Changes in the estimated plasma volume will be derived. The following changes will be calculated:

- Change from baseline (Day 1, pre-dose) to ST (Day 4);
- Change from baseline to ET (Day 14);
- Change from ET (Day 14) to FU (Day 18).

The estimated plasma volume for each patient and study day will be listed and summarised by study period and group, including changes specified above. Box plots for the estimated plasma volume versus study period by group will be presented.

5.3.16.5 Pharmacokinetic concentrations

All PK presentations will be based on all available data.

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. In addition, plasma concentrations of dapagliflozin will be listed by patient and time-point.

Plasma dapagliflozin concentrations will be summarised by group and time-point. Where possible, the following descriptive statistics will be presented: n, geometric mean, [geometric mean x geometric SD], [geometric mean / geometric SD], geometric CV%, median, minimum and maximum.

In all cases, the geometric mean is calculated as follows:

- Geometric mean = $\exp[M_L]$,

where M_L is the mean of natural log-transformed values, and 'exp' refers to the natural exponential function.

The geometric CV% is calculated as follows:

- Geometric CV% = $100 \times \text{sqrt}[\exp(S_L^2) - 1]$,

where S_L is the SD of natural log-transformed values, and 'sqrt' refers to the square root function.

The geometric SD is calculated as follows:

- Geometric SD = $\exp[S_L]$,

where S_L is defined as above.

The PK profiles will also be illustrated by figures for average PK profile over time on a linear and a semi-logarithmic scale.

5.3.16.6 Censored data for pharmacokinetic evaluation

For the listings, plasma concentrations that are NQ will be listed as "BLQ" – no imputations or substitutions will be performed for the listings. For descriptive statistics, plasma concentrations that are NQ will be handled as described below.

Any dapagliflozin plasma concentration data reported as not quantifiable (NQ), below the limit of quantification (BLQ), "<x.xx" or similar will be handled as follows for the descriptive statistics:

- At a time-point where less than or equal to 50% of the values are NQ, all NQ values will be set to the lower limit of quantification (LLOQ), and all descriptive statistics will be calculated.
- At a time-point where more than half of the values (but not all) are NQ, the geometric mean, [geometric mean x geometric SD], [geometric mean / geometric SD] and geometric coefficient of variation (CV)% will be set to Not Determined ("ND"). The maximum value will be reported from the individual data, and the minimum and median will be shown as "BLQ" – below the limit of quantification.
- If all values are NQ at a time-point, no descriptive statistics will be calculated for that time-point. Not applicable ("NA") will be written in the field for geometric CV% and "BLQ" will be written in all other statistics.
- The number of BLQ values (n below LLOQ) and the number of data points (n) will be reported for each time-point.

5.3.16.7 Bioimpedance spectroscopy

The BIS examination will consist of two parts: an evaluation at Baseline, ST, ET and FU, similar to other efficacy endpoints, and acute changes evaluation at ET, aiming to examine the changes between a pre-dose measurement and measurements 1, 2 and 4 hours post-dose. The measurements obtained during BIS, and for which the analyses will be performed, are CCI [redacted], extracellular fluid (in litre and %), CCI [redacted]

Part 1

Changes in the BIS results will be derived. The following changes will be calculated:

- Change from Baseline (Day 1, pre-dose) to ST (Day 4);
- Change from Baseline (Day 1, pre-dose) to ET (Day 14, 1 h post-dose);
- Change from ET (Day 14, 1 h-post-dose) to FU (Day 18).

The BIS results for each patient, as well as corresponding changes, will be listed. Results will also be summarised by time-point and group, including changes specified above, similarly to other efficacy endpoints.

Corresponding box plots for the BIS results versus study period will be presented, with each group overlaid on the same plot. The statistical model from Section 5.3.16.1 will be used to analyse the changes more formally, with results presented as described in Section 5.3.16.1.

Part 2

CCI [redacted]

[redacted]

CCI [redacted].

CCI [redacted]

CCI [redacted]

[redacted]

Following variables will also be listed:

- Systolic daily average, CCI [redacted]

- Diastolic daily average, CCI [redacted], CCI [redacted]
- Plasma volume
- Extracellular fluid (litres and percent), CCI [redacted]
- 24-hr urinary volume
- Sodium excretion (24-hr urine)

5.3.18 Safety analysis

All safety TLFs will be based on the Safety Set unless otherwise specified.

5.3.18.1 Adverse events

Adverse events will be summarized by SOC and PT. Adverse events will be assigned to a study phase (Screening, treatment or follow-up) based on the start date/time of the AE.

Adverse events with missing start and/or end dates and/or times (if applicable) will be handled as described in Appendix D.

All AEs will be listed for each patient. A listing showing AE onset and resolution date/time will be presented. Relationship to dapagliflozin (causally related or not causally related) will also be listed.

An overall summary (number of patients and percentage of patients) of all AEs will be presented by group. The summary will include the following categories:

- Number and percentage of patients with AEs
- Number and percentage of patients with AEs judged as causally related to dapagliflozin in the opinion of Investigator;
- Number and percentage of patients with AEs leading to death;
- Number and percentage of patients with SAEs (including outcomes = death);
- Number and percentage of patients with any related SAEs (including outcomes = death);
- Number and percentage of patients with AEs leading to permanent discontinuation of dapagliflozin;
- Number and percentage of patients with SAEs leading to permanent discontinuation of dapagliflozin;
- Number and percentage of patients with hypoglycaemia AEs;
- Number and percentage of patients with hypoglycaemia AEs leading to permanent discontinuation of dapagliflozin;

The AE overall summary as detailed above will be repeated for event counts.

Adverse related to hypoglycaemia events are specified by the following PTs:

- Blood glucose decreased
- Hypoglycaemia
- Hypoglycaemia unawareness
- Hypoglycaemic coma
- Hypoglycaemic encephalopathy
- Shock hypoglycaemic
- Hypoglycaemic seizure
- Hypoglycaemic unconsciousness

Summaries (patient counts and percentages) of AEs by group, SOC and PT will be presented for the following:

- All AEs by group;
- All AEs by group and investigator's assessment of causality;
- All AEs by group and maximum reported intensity;
- Serious AEs by group;
- Adverse events leading to permanent discontinuation of dapagliflozin, by group.

The denominator for summaries will be the number of patients in the Safety Set for each group.

An AE summary showing the number of events by group and PT will be presented for all on-treatment AEs and SAEs.

An additional summary of all non-serious AEs which occur in at least 5 percent of patients in any group will be presented, the events categorized by SOC and PT, and group. In addition to the number and percentage of patients that experience at least one event, the number of events will also be presented.

All potential events of diabetic ketoacidosis (DKA) will be recorded in the eCRF and submitted to an independent DKA Adjudication Committee. Patients with AEs and SAEs recorded on the DKA eCRF page will be listed.

Patients with DKA events reviewed by the adjudication committee will be listed.

Key information for adverse events leading to death, SAEs and discontinuation will be listed separately. These listings will include group, reported term, PT, date of the event, time from start of treatment up to the onset of the event, causality and outcome. Additional details will be presented as required.

5.3.18.2 Clinical laboratory

Clinical chemistry and haematology

Safety laboratory measurements (clinical chemistry and haematology/haemostasis as specified in Section 5.1.3.2) will be listed by patient and time-point, including the date/time of the sample, changes from baseline and flags for measurements outside the reference range. The listing will include all repeated and unscheduled measurements.

Descriptive statistics will be presented by group, time-point and visit for observed values and changes from baseline.

Baseline is defined as the results from assessments performed at pre-dose on Day 1.

Urinalysis

The results for qualitative and quantitative urinalysis (as specified in Section 5.1.3.2) will be listed separately.

5.3.18.3 Hy´s Law

Number and percentage of patients with potential Hy's Law will be presented per treatment group. Potential Hy's Law is an increase in serum Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN, irrespective of serum Alkaline Phosphatase (ALP), at any point during the study following the start of the IMP.

5.3.18.4 Vital signs

Vital signs measurements will be listed by patient and time-point including the date/time of the assessment and changes from baseline. Descriptive statistics will be presented by group and time-point for both observed values and changes from baseline.

Baseline is defined as the results from assessments performed at pre-dose on Day 1.

5.3.18.5 Physical examination

Abnormal physical examination findings post-baseline will be recorded as AEs.

5.4 Partial Analysis

A partial analysis based on all patients from Group 2, will be conducted. The partial analysis will include all the evaluations originally planned to be conducted, and reported, for all three groups simultaneously.

6. APPENDICES

Appendix A Demographic and baseline variables

Below is a detailed list of the following demographic and background information that will be recorded at the Screening visit:

Demographic characteristics:

- Date of birth (year only)
- Age (years)
- Gender (male / female)
- Race (White, Black or African American, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Vital signs

- Height (reported in centimetres [cm])
- Weight at Screening (reported in kilograms [kg])
- Supine blood pressure (diastolic and systolic ([mmHg])
- Pulse (beats/min)

Disease history

- Medical history, including the condition and start and end date [or status as "Ongoing"] of the condition
- Surgical history, including the procedure and the date of the procedure
- For patients with impaired renal function:
    - date of first renal impairment diagnosis
    - most likely aetiology from among the following: cystic kidney disease; diabetic nephropathy; ischaemic/hypertensive nephropathy; chronic glomerulonephritis; renal artery stenosis; chronic pyelonephritis (infectious); chronic interstitial nephritis; obstructive nephropathy; unknown; other: specified

- if applicable, chronic glomerulonephritis type from among the following: immunoglobulin A nephropathy; focal segmental glomerulosclerosis; membranous nephropathy; minimal change; lupus nephritis; other primary or secondary glomerulonephritis CKD diagnosis: specified

- For patients with T2DM, date of first T2DM diagnosis

Screening lab results

- Screening results for HbA1c and eGFR; eGFR to be based on the serum creatinine level and CKD-EPI method, and recorded directly on the eCRF

Appendix B Efficacy Variables

Group	Measurements
Blood	
CCI	
CCI	
CCI	
CCI	
PK	- Concentrations of dapagliflozin
Urinalysis	
Spot urine sample for urinary albumin and creatinine	- Albumin, creatinine
CCI	
U-albumin, U-glucose and U-blood (Dipstick)	- Albumin, glucose, blood
CCI	
24-hr urine (a)	- Sodium excretion, sodium concentration, glucose excretion, glucose concentration, 24-hr urinary volume, UACR CCI
Other	-
24-hr blood pressure	- Systolic daily average, CCI

	- Diastolic daily average, CCI [redacted]
Plasma volume	Plasma volume
Bioimpedance spectroscopy	- CCI [redacted] Extracellular fluid (litres and percent), CCI [redacted] - CCI [redacted]
Vital signs	- CCI [redacted]

(a) The measurement consists of an average of three (alt, four) measurements taken on consecutive days

With the exception of PK and hourly BIS, the endpoints of the study are within-patient differences in the listed measurements between ST and Baseline measurements, between ET and baseline measurements and between FU and ET measurements. For PK, the endpoint is the concentrations of dapagliflozin at the time-points at which a PK sample was obtained. For BIS, the following additional endpoints will be considered: at Visit 8, the difference between 1, 2 and 4 hr measurements and the pre-dose measurement.

Explicitly, the different study endpoints are defined as detailed below.

Appendix C General rounding rules

All data will be listed according to the number of decimal places presented in the original data, with the exception of data for which the original number of decimals exceeds four decimal places; in these cases, the data will be presented to three significant figures.

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all subjects fulfil certain criteria, the percentage value will be displayed as 100
- For values where the absolute frequency is zero, there will be no percentage displayed at all
- All other percentage displays will use 2 decimal places

Percentages displayed based on continuous data (e.g., percentage changes from baseline) will be displayed to 2 decimal places.

When reporting descriptive statistics, the following rules will apply in general:

- n will be an integer
- Mean, geometric Mean, SD, geometric SD, median, Q1 and Q3 will use 1 decimal place more than the original data
- Minimum and maximum will be reported using the same number of decimal places as the original value
- If no subjects have data at a given time point, for example, then only n=0 will be presented. If n<3, then only n, minimum and maximum will be presented. If n=3, then only n, mean, median, minimum and maximum will be presented. The other descriptive statistics will be left blank.
- P-values will be presented to four decimal places (p-values that are smaller than 0.0001 will be presented as '<0.0001')
- An extra digit of precision will be added (four significant digits at most) for reporting of the least-squares (LS) means and bounds of all confidence intervals (CIs) within inferential analyses

A maximum of four significant figures will apply to all summary statistics.

Appendix D Missing data

Missing data for adverse events

If an onset date is incomplete, the derived onset date will be calculated using the following algorithm:

- Calculate a surrogate date as the first non-missing valid date from the following list (in order of precedence):
  - First active study medication date
  - Informed consent date
  - Visit date corresponding to the visit at which the event was reported

If a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing. Any AEs with unknown intensity, causality or seriousness will be regarded as unknown for the tabulations.

There will be no imputation of AE data for the data listings – all data will be listed as recorded in source.

Missing data for prior/concomitant medications

Missing start or end dates and times of medications other than dapagliflozin and ICG will be handled as follows for the purposes of the classification as prior or concomitant:

- If the reported start date is missing or invalid and the informed consent date is not missing or invalid, then the imputed start date is set equal to the informed consent date. If the consent date is missing or invalid and the birth date is not missing or invalid, then the imputed start date is set equal to the birth date. If the start date, the consent date and the birth date are all invalid or missing, then the imputed start date is set equal to missing.
- If the reported start date is partially entered, then the imputed start date is set equal to the earliest possible reported start date based on the partial entered reported start date.
- If the reported end date is missing, continuing, unknown or invalid, then the imputed end date is set equal to the most recent database extraction date.

- If the reported end date of the medication is partial, then the imputed end date is set equal to the last possible reported end date based on the partial entered reported end date.

Imputed dates will not appear on the listings.

Missing data for diagnosis date

If the date of disease diagnosis is partially missing, the following rules will take effect:

- Missing day, but month and year are present: the day will be imputed as the 15th day of the month.

- Missing day and month, but year is present: the day and month will be imputed as 30 June of the year (provided that the imputed date is less than the consent date).

- Missing year, but day and month are present: No imputations will occur, and the patient will be excluded from all summaries related to duration of disease.

- Missing day, month and year: No imputations will occur, and the patient will be excluded from all summaries related to duration of disease.

- If any such imputed date falls after the consent date, then the diagnosis date will be taken as equal to the consent date.

These durations, even if partially imputed, will be listed. However, only the portion of the date of diagnosis actually observed, rather than imputed dates, will be displayed in listings.

Missing data for efficacy evaluation

There will be no imputation of missing efficacy data. Data will be used as far as is available and listed as reported without imputation.

Missing data for safety evaluation

Apart from the missing date/time imputation for adverse event assessments, there will be no imputation of missing safety data. Data will be used as far as is available and listed as reported without imputation.

7. AMENDMENT TO THE STATISTICAL ANALYSIS PLAN

7.1 Amendment :Version Final 3.0

7.1.1 Rationale for the amendment

This SAP was amended following Astrazeneca comments after Dry Run.

7.1.2 List of changes

Change #1

STATISTICAL ANALYSIS PLAN

The following text was added:

The SAP describes Group 1 as it was originally planned in the latest version of the CSP. it was decided that no Group 1 subjects will be enrolled onto this study (please see reference in Action log on the 22nd of March 2019), so no statistical outputs will contain Group 1 information.

Change #2

Study Design (Section 2)

- **Baseline measurement (Baseline)** is the measurement obtained before initiation of treatment, typically during Visit 4. For 24-hr blood pressure, the baseline measurement is the measurement obtained the day before Visit 4.
- **Short treatment measurement (ST**) is the measurement obtained after the patient has been in the study for a short time, typically on Visit 5.
- **End of treatment measurement (ET)** is the measurement obtained on the visit corresponding to the last day of the treatment period, namely Visit 8, unless the patient attended an early termination visit. CCI [redacted] in the 24-hr urine, the end of treatment measurement is the measurement obtained the day before Visit 8.
- **Follow-up measurement (FU)**. Is the measurement obtained after the end of the treatment period, namely Visit 9. CCI [redacted]
- The exception from the rules outlined above is the 24-hr urine, the collection of which will take place on consecutive days, rather than on one single day. In this case, Baseline, ST, ET and FU measurements used in the analyses will be the averages of these consecutive samples. Explicitly, Baseline is the average of

measurements obtained on day -3 to day -1, ST the average of measurements obtained on day 2 to day 4, ET the average of measurements obtained on day 12 to day 14 and FU the average of measurements obtained on day 15 to day 17.

Was changed to:

- **Baseline** is the measurement obtained before initiation of treatment, typically during Visit 4. For 24-hr blood pressure, the baseline measurement is the measurement obtained the day before Visit 4.
- **Start of Treatment (ST**) is the measurement obtained after the patient has been in the study for a short time, typically on Visit 5.
- **End of treatment (ET)** is the measurement obtained on the visit corresponding to the last day of the treatment period, namely Visit 8, unless the patient attended an early termination visit. For 24-hr blood pressure, CCI CCI [redacted], the end of treatment measurement is the measurement obtained the day before Visit 8.
- **Follow-up (FU)** is the measurement obtained after the end of the treatment period, namely Visit 9. CCI [redacted]

The exception from the rules outlined above is the 24-hr urine, the collection of which will take place on consecutive days, rather than on one single day. In this case, Baseline, ST, ET and FU used in the analyses will be the averages of these consecutive samples. Explicitly, Baseline is the average of measurements obtained on day -3 to day -1, ST the average of measurements obtained on day 2 to day 4, ET the average of measurements obtained on day 12 to day 14 and FU the average of measurements obtained on day 15 to day 17.

Change #3

CCI [redacted]

CCI

Change #4

24-hour urine data (Section 5.3.16.2)

A listing of urine sample collection, showing each collection day's start and stop date/time, urine sodium amount excreted, urine glucose concentration, urine glucose amount excreted, urine volume and UACR, will be presented.

A separate listing will be presented showing the by-patient arithmetic mean of the urine sodium amount excreted, urine glucose amounts excreted urine volume and UACR taken across the following summary periods:

- Baseline: Day -3 up to and including Day -1;
- Short of Treatment (ST): Day 2 up to and including Day 4;
- End of Treatment (ET): Day 12 up to and including Day 14;
- Follow-up (FU): Day 15 up to and including Day 17.

The following by-patient changes will be derived for each urine sodium amount excreted, urine glucose amount excreted, urine volume and UACR:

- ST average versus the BL average
- ET versus the BL average;
- FU average versus the ET average.

Was changed to:

A listing of urine sample collection, showing each collection day's start and stop date/time, urine sodium amount excreted, urine glucose concentration, urine glucose amount excreted, urine volume and UACR, will be presented.

A separate listing will be presented showing the by-patient arithmetic mean of the urine sodium amount excreted, urine glucose amounts excreted urine volume and UACR taken across the following summary periods:

- Baseline: Day -3 up to and including Day -1;
- Start of Treatment (ST): Day 2 up to and including Day 4 and for UACR ST:Day4;
- End of Treatment (ET): Day 12 up to and including Day 14;
- Follow-up (FU): Day 15 up to and including Day 17.

The following by-patient changes will be derived for each urine sodium amount excreted, urine glucose amount excreted, urine volume and UACR:

- ST average versus the BL average
- ET average versus the BL average;
- FU average versus the ET average.

.

Change #5

24-Hour blood pressure monitoring (Section 5.3.16.3)

- CCI [redacted].

Was changed to:

CCI [redacted]

Change #6

Bioimpedance spectroscopy (Section 5.3.16.7)

The BIS examination will consist of two parts: an evaluation at Baseline, ET, ST and FU, similar to other efficacy endpoints, and a short-term evaluation at ET, aiming to examine the changes between a pre-dose measurement and measurements 1, 2 and 4 hours post-dose. The measurements obtained during BIS, and for which the analyses will be performed, are CCI [redacted], extracellular fluid (in litre and %), CCI [redacted]

Part 1

Changes in the BIS results will be derived. The following changes will be calculated:

- Change from baseline (Day 1, pre-dose) to ST (Day 4);
- Change from baseline (Day 1) to ET (Day 14, 1 h post-dose);
- Change from ET (Day 14, 1 h post-dose) to FU (Day 18).

The BIS results for each patient, as well as corresponding changes, will be listed. Results will also be summarised by time-point and group, including changes specified above, similarly to other efficacy endpoints.

Corresponding box plots for the BIS results versus study period will be presented, with each group overlaid on the same plot. The statistical model from Section 5.3.16.1 will be used to analyse the changes more formally, with results presented as described in Section 5.3.16.1.

Part 2

CCI [redacted].

Was changed to:

The BIS examination will consist of two parts: an evaluation at Baseline, ST, ET and FU, similar to other efficacy endpoints, and acute changes evaluation at ET, aiming to examine the changes between a pre-dose measurement and measurements 1, 2 and 4 hours post-dose. The measurements obtained during BIS, and for which the analyses will be performed, are CCI extracellular fluid (in litre and %), CCI

Part 1

Changes in the BIS results will be derived. The following changes will be calculated:

- Change from Baseline (Day 1, pre-dose) to ST (Day 4);
- Change from Baseline (Day 1, pre-dose) to ET (Day 14, 1 h post-dose);
- Change from ET (Day 14, 1 h post-dose) to FU (Day 18).

The BIS results for each patient, as well as corresponding changes, will be listed. Results will also be summarised by time-point and group, including changes specified above, similarly to other efficacy endpoints.

Corresponding box plots for the BIS results versus study period will be presented, with each group overlaid on the same plot. The statistical model from Section 5.3.16.1 will be used to analyse the changes more formally, with results presented as described in Section 5.3.16.1.

Part 2

CCI

Change #7

Partial Analysis (Section 5.4)

A partial analysis based on all patients from Group 2 and Group 3, but none from Group 1, will be conducted. The partial analysis will include all the evaluations originally planned to be conducted, and reported, for all three groups simultaneously.

Was changed to:

A partial analysis based on all patients from Group 2, will be conducted. The partial analysis will include all the evaluations originally planned to be conducted, and reported, for all three groups simultaneously.