Statistical Analysis Plan

Study Code	D1690C00063
Edition Number	2.0
Date	11/04/2019

DAPACARD

A double-blind, randomized, parallel group, Phase IV study to investigate the effects of DAPAgliflozin on CARDiac substrate uptake, myocardial efficiency and myocardial contractile work in type 2 diabetes patients

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Global Product Statistician

PPD

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TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
A	Peak velocity flow in late diastole caused by atrial contraction (the **A** wave)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic chemical
BMI	Body mass index
CRF	Case report form
CSP	Clinical study protocol
CI	Confidence interval
CT	Computed tomography
DAE	Adverse events leading to discontinuation of study medication
DKA	Diabetic ketoacidosis
E	Mitral peak velocity of Early filling
E/A	Peak velocity flow in early diastole (the **E** wave) to peak velocity flow in late diastole caused by atrial contraction (the **A** wave)
ECG	Electrocardiography
FGF-21	Fibroblast growth factor 21
GLSLV	Global longitudinal strain of the left ventricle
Hb	Haemoglobin
HbA1c	Glycosylated haemoglobin
HDL-C	High density lipoprotein cholesterol
IP	Investigational Product
K1	A rate constant
Kmono	A rate constant
LV	Left ventricular
LSM	Least squares mean
MFAU	Myocardial fatty acid uptake
MRI	Magnetic resonance imaging

Abbreviation or special term	Explanation
n	Number of subjects with non-missing values
NEFA	Non-esterified fatty acids
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PD	Protocol deviation
PET	Positron emission tomography
PK	Pharmacokinetic
PT	Preferred term
Q1	25th percentile
Q3	25th percentile
SAE	Serious adverse event
SOC	System organ class
SD	Standard deviation
T2D	Type 2 diabetes

AMENDMENT HISTORY

Date	Brief description of change
11 April 2019	In general: Minor updates concerning typographical errors, grammar etc.
	Section 2.1: Added the PD specification as an appendix to the SAP: "The **overall** criteria for important protocol deviations **is defined in section 2.2 and details further specified in the protocol deviations process document (Appendix 8.5)."** Rephrased two sentences regarding subject representation in datasets.
	Section 2.2.1: Changed protocol deviation criteria from - "Eligibility criteria not fulfilled (e.g. patients who were randomized in error or who developed discontinuation criteria after randomization and were not discontinued) - Study drug compliance <90% or >120% - Administration of wrong type of study drug (i.e. the one not randomized to) for the whole study period - Onset of serious disease that will influence the effects of any of the study drugs - Use of disallowed concomitant medications" to - **"Randomized but did not meet the eligibility criteria** - **Developed criteria for discontinuation of treatment but were not discontinued** - **Received wrong study drug** - **Received disallowed concomitant medication(s)** - **Suspected study drug compliance less than 90% or more than 120%** - **Severe non-compliance to the protocol** - **Other"**
	Section 2.2.1 Added "Protocol deviations will be further defined in a separate protocol deviations process document, see appendix 8.5."
	Section 3.1.3: Added LV global longitudinal strain (GLSLV), Myocardial efficiency, P-Glucose, P-Insulin, P-Glucagon, P-Glucagon/Insulin to the list of measurements

Date	Brief description of change
	Section 3.1.4: Changed from "In addition, the usage of metformin will be tabulated as part of the disease characteristics. The tabulation will be done for each treatment group and in total and include the daily metformin dosage at the time of screening visit and duration of metformin treatment." to "In addition, the **concomitant** usage of metformin will be tabulated as part of the disease characteristics. The tabulation will be done for each treatment group and in total and include the **total** daily metformin dosage at the time of screening visit and duration of metformin treatment."
	Section 3.1.7: Reformulated text regarding duration and compliance.
	Table 3.3: Removed: "Currently taking antidiabetic medication" Added: "Metformin dose"
	Table 3.4: Minor changes, related to units and footnotes. P-Glucagon/Insulin, (Ratio) (b) moved from the category "Fatty acid blood biomarkers" to the category "Glucose control biomarkers".
	Section 4.1: Added **"Minimum and maximum values will be reported to the same degree of precision as the raw data up to a maximum of 3 decimal places. Mean, first quartile, median, third quartile, and SD will be reported to one further degree of precision. Percentages will be rounded to 1 decimal place. In general, baseline will be defined as the last value prior to the date of the first dose.** **For insulin and vital status two measurements are taken with a few minutes apart. The average of those measurements will be used in the calculations.** **In general, the laboratory results from the blood biomarkers will be used for the efficacy endpoints and the clinical safety laboratory assessments will be used for the safety endpoints."**
	Section 4.1.1: Sentences about purpose and imbalance were removed. Changed which compliance intervals to present. Removed the text: "The distribution of baseline characteristics in the two treatment groups and in all patients combined will be examined. To this end"

Date	Brief description of change
	Section 4.1.2.2: The method linear regression exchanged to correlation.
	Section 4.1.2.3: Changed from "The population PK analysis will be described and presented separately from the main clinical study report." to "**The pharmacokinetic concentration data from the pre-dose blood sample at visit 4 will be listed for all patients in the PK analysis set. Further analysis may be presented separately from the main clinical study report.**"
	Section 4.1.3.1: Added "**For clinical chemistry and haematology, only fasting values will be analysed.**"
	Section 4.1.3.2: Changed "All collected AEs (which, for this study, consist of DAEs and SAEs) with start date greater or equal to the date of the randomization will be summarized using descriptive statistics (number of patients, percentage of patients)." to "All collected AEs (which, for this study, consist of DAEs and SAEs) with **onset date during the treatment period** will be summarized using descriptive statistics (number of patients, percentage of patients).".
	Section 4.1.3.2: Added "**All SAEs occurring from the time of signature of informed consent up to and including the follow-up period will be summarized by system organ class (SOC) and preferred term (PT).**".
	Section 4.2: The wording in the section 4.2 Analysis Methods has been simplified, and presentation of results has been clarified. Added: **"Any marked violations of model assumptions will be discussed in the CSR and the supporting results will be presented in appendices."**
	Section 4.2 in general: Minor updates and restructuring within the section.

Date	Brief description of change
	Section 4.2.2: Changed from: "The relationship of the response to the nuisance variable is linear within each treatment group" to: "The relationship of the response to the **baseline** variable is linear within each treatment group" Added: "**Any impact of the potential outliers and subgroups will also be investigated. Outlier as an observation with a residual that is more than three times the interquartile range above the 75th percentile or below the 25th percentile. Outliers will be identified using standardized residuals from the original ANCOVA model. If outliers are present, then additional sensitivity analyses will be performed with the outliers excluded."** Added: "**If the relationship of the response to the baseline variable is non-linear, then a suitable transformation of the response and the baseline variable (e.g., natural logarithm, square root, inverse, quadratic, etc.) may be used for analysis.**"
	Section 4.2.3: The method linear regression is changed to correlation.
	Section 4.2.3: Following has been removed in the section of Analysis of co-dependence: • The Spearman correlation analysis. • The quadratic term from the linear regression model. • The multivariate model.

1. STUDY DETAILS

1.1 Study objectives

The aim of the DAPACARD study is to explore the effect of dapagliflozin on cardiac substrate uptake, myocardial efficiency and myocardial contractile work in type 2 diabetes patients. Explicitly, the objectives of the study are as follows:

Primary objective:

To compare the changes in **global longitudinal strain of the left ventricle (GLSLV)** achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.

Secondary Objective:

To compare the changes in **myocardial efficiency (%)** achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.

Safety Objective:

To evaluate the safety and tolerability of dapagliflozin.

Exploratory Objectives:

1) To compare the changes in **wash-out in the myocardium of [11C]-Acetate** (**Kmono**, 1/min) achieved with dapagliflozin vs. placebo after 6 weeks of double-blind treatment.

2) To compare the changes in **myocardial perfusion (ml/min/g) measured by [11C]-Acetate** achieved with dapagliflozin vs. placebo after 6 weeks of double-blind treatment.

3) To compare the changes in **wash-out of [11C]-Acetate** (Kmono**,** 1/min) **in relation to myocardial perfusion** (**K1,** ml/min/g**)** achieved with dapagliflozin vs. placebo after 6 weeks of double-blind treatment.

4) To compare the changes in **myocardial fatty acid uptake** (MFAU**,** µmol/min/g) **by [18F]-FTHA** achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.

5) To compare the changes in **fatty acid uptake in liver** (µmol/min/g) **by [18F]-FTHA** achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.

6) To compare the changes in **fatty acid uptake in kidney cortex** (µmol/min/g) **by [18F]-FTHA** achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment

7) To compare the changes in **fatty acid uptake in brain** (µmol/min/g) **by [18F]-FTHA** achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.

8) To compare the changes in **Left Ventricular (LV) global radial strain** and **LV global circumferential strain** achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.

9) To compare the changes in **LV global systolic longitudinal strain rate**, **LV global diastolic longitudinal strain rate, LV global diastolic radial strain rate**, **LV global systolic radial strain rate**, **LV global diastolic circumferential strain rate** and **LV global systolic circumferential strain rate**, achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.

10) To compare the changes in **LV end-diastolic volume** (mL), **LV end-systolic volume** (mL), and **LV stroke volume** (mL) achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.

11) To compare the changes in **LV mass** (g), **LV mass/end-diastolic volume** (g/mL) and **LV ejection fraction** (%) achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.

12) To compare the changes in **Left atrial volume (min, max)** (mL), **Left atrial ejection fraction** (%) and **transmitral flow velocity indices** (**E/A** (1)**, E** (cm/s)**, A** (cm/s) and **DT** (ms)), achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.

13) To compare the changes in **blood biomarkers** (e.g. **HbA1c, Hematocrit, Hb, FGF-21, NT-proBNP**) achieved with dapagliflozin vs. placebo after 6 weeks of double-blind treatment.

14) To compare the changes from baseline in **body weight,** and **blood pressure** achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.

15) To explore **associations between change in GLSLV and change in myocardial efficiency as well as associations to changes in other exploratory end-points** with potential importance.

Pharmacokinetics objectives:

1) To evaluate the **pharmacokinetics** of dapagliflozin by a single pre-dose sample at end of study.

1.2 Study design

DAPACARD is a randomized, placebo-controlled, double-blind, parallel-group, international, multicentre, Phase IV mechanistic study. Eligible subjects with Type 2 diabetes (T2D) before randomization and fulfilling all of the inclusion criteria and none of the exclusion criteria (see clinical study protocol, CSP, Section 5, for a complete list of the inclusion and the exclusion criteria) will be randomised in a 1:1 ratio to dapagliflozin 10 mg or placebo once daily and treated for approximately six weeks.

The study includes five visits. The information collected at these visits can be briefly outlined as follows. For a complete overview of the assessments done at each visit, see Appendix 8.1 or CSP v2 Table 1.

Visit 1: Screening (day -21-0)

Demography, including birth date, sex and race / ethnicity. Vital signs, including pulse rate and blood pressure. Height and weight. Medical history, with a special attention paid to history of diabetes. Information about concomitant medications. Electrocardiogram (ECG) and echocardiogram (ECHOC) will be performed and safety information (SAE, laboratory tests) will be collected.

Visit 2: Randomization / baseline (day 1)

All the efficacy measures as listed in Section 3 will be collected. Vital signs, safety information (SAE, laboratory tests) and changes in concomitant medications will also be registered. Inclusion and exclusion criteria will again be checked.

Visit 3: Interim visit, phone (day 14 ± 4)

This is a check-up visit with a primary purpose to collect changes in concomitant medications or life style, treatment regimen compliance and safety information (SAE, DAE and symptoms of diabetic ketoacidosis [DKA]).

Visit 4: End of treatment (day 42 ± 4)

The efficacy measures will again be collected here. The safety information (SAE, DAE, DKA symptoms, laboratory values), and the possible changes in concomitant medication and life style will be captured.

Visit 5: Safety follow-up, phone (day 49 ± 4)

This is a phone visit with the purpose of capturing safety information (SAE, DAE and DKA symptoms).

1.3 Number of subjects

The sample size calculations were based on both the primary (change in GLSLV from baseline to the end of treatment) and the secondary (change in myocardial efficiency from baseline to the end of treatment) endpoints.

For the primary endpoint, the assumptions used in the sample size calculation are as follows: The between-group difference in average improvement in GLSLV is anticipated to be -2% and the standard deviation (SD) of change in GLSLV for the population under study to be 2%. The choice of these values is motivated by the literature, namely Gjesdal et al., 2016 (Gjesdal et al., 2016) and Singh et al., 2015 (Singh et al., 2015). There, the average GLSLV in patients with pre-existing cardiac abnormality (i.e. aortic stenosis or atherosclerosis), but without T2D, was estimated to be approximately -16.0%. The corresponding SD was 1.3% (Gjesdal et al., 2016, population SD) and 1.73% (Singh et al., 2015, SD of difference from baseline), of which 2% is a conservative approximation. Average GLSLV in T2D subjects with prior myocardial infarction at baseline is anticipated to be -11%, leading to a conservative approximation of expected difference of -2%.

For the secondary endpoint, the assumptions are as follows:
The between-group difference in average improvement in myocardial efficiency is anticipated to be 12.55 mmHg · L · g^{-1} with a corresponding SD of 14.2 mmHg · L · g^{-1}. This is motivated by the literature, namely Tuunanen et al., 2006 and 2007 (Tuunanen et al., 2006; Tuunanen et al., 2007), who reported the healthy subjects baseline myocardial efficiency in two different studies to be 54.3 (N=36) and 49.3 (N=8) (pooled mean of 50.21) mmHg · L · g^{-1}, with a corresponding standard deviation (SD) of 8.9 and 14.2 mmHg · L · g^{-1}, respectively. A hypothesized 25% increase in myocardial efficiency translates into 12.55 mmHg · L · g^{-1}.

Assuming 80% statistical power, a two-sided type I error rate alpha of 0.05 and a two-sample t-test as the testing procedure, leads to approximately 17 patients per group for the primary endpoint and approximately 22 patients per group for the secondary endpoint. Thus, a total of 44 evaluable subjects should be available at the end of the study. Assuming a 15% non-evaluable rate, total of 52 (26 per group) subjects will be randomized.

The 18F-FTHA examinations are exploratory and will not be performed in all the randomized patients. Instead, a minimum 40 and a maximum of 44 of the randomized patients will be scheduled for examination for 18F-FTHA uptake in heart, liver, kidney and the brain. This is due to ethical reasons and aims to limit unnecessary exposure to radioactivity. The authors in Viljanen et al. (Viljanen et al., 2009), report SD of myocardial fatty acid uptake to be 0.4 (before diet) and 0.2 (after diet) in a healthy population, leading to a pooled SD of 0.32. No information is available regarding the magnitude of the treatment effect in the planned study, but an effect of approximately 0.3-0.4 (approximately 10% relative change) is judged to be clinically relevant. Using this assumption, and the pooled estimate of the SD as a conservative approximation of the variability of measurement differences between baseline and end of treatment, leads to approximately 80-90% power with 40 randomized patients (at a two-sided alpha level 0.05 and assuming 15% non-evaluable rate).

2. ANALYSIS SETS

2.1 Definition of analysis sets

Following the CSP, the main analysis sets are defined as follows.

Analysis set	Description
Enrolled Analysis Set	The Enrolled Analysis Set will consist of all subjects who signed informed consent.
Randomized Analysis Set	The Randomized Analysis Set will consist of all randomized subjects who received at least one dose of study medication during the treatment period. In analyses of the Randomized Analysis Dataset, subjects will be summarized by the treatment group to which they were randomized (even if the treatment they received is different).
Evaluable Analysis Set	The Evaluable Analysis Set will be the primary analysis dataset and is a subset of the Randomized Analysis Set. This is also known as the Per-Protocol population. All data points after an important protocol deviation will be excluded from this analysis. Important protocol deviations are defined as deviations which could potentially affect the interpretability of the study results. The overall criteria for important protocol deviations is defined in section 2.2 and details further specified in the protocol deviations process document (Appendix 8.5). Subjects will be presented according to the randomized treatment assignment, irrespective of the treatment actually received.
Safety Analysis Set	The Safety Analysis Set will consist of all subjects who received at least one dose of study medication during the treatment period. Subjects will be presented by randomized treatment group, except if information indicates that a subject received a different treatment for the entire course of their participation in the treatment period. In this case, the safety data for such a subject will be presented according to the treatment actually received.
PK Analysis Set	The PK analysis set will include subjects for whom PK data are evaluable (with no important protocol deviations thought to significantly affect the pharmacokinetics of the drug). PK data may be reported separately from the clinical study report.

In addition, three subsets of the Evaluable Analysis Set will be defined, namely: *MRI Analysis Set*, *11C-Acetate Analysis Set* and *18F-FTHA Analysis Set.* These subsets will consist of subjects that, in addition to not having any important protocol deviations, also to a sufficient degree fulfil the measurement-specific requirements (have fasted and abstained from nicotine, alcohol and caffeine, see Section 2.2.2). Specifically:

Analysis Set	**Description**
MRI Evaluable Analysis Set	Patients in the Evaluable Analysis Set that, as per clinical judgement, sufficiently fulfilled the 4 conditions specified in Section 2.2.2 at both of the times when MRI measurements were taken.
11C-Acetate Evaluable Analysis Set	Patients in the Evaluable Analysis Set that, as per clinical judgement, sufficiently fulfilled the 4 conditions specified in Section 2.2.2 at both of the times when PET-11C-Acetate measurements were taken.
18F-FTHA Evaluable Analysis Set	Patients in the Evaluable Analysis Set that, as per clinical judgement, sufficiently fulfilled the 4 conditions specified in Section 2.2.2 at both of the times when PET-18F-FTHA measurements were taken.

The efficacy analyses will be performed using one of these three sets, the choice of a set determined by the measurement method that provided the analysed endpoint. For an exact specification of which endpoint corresponds to which set, see Table 3.4 "Source" column.

The number of patients included in the sets will be tabulated, for each treatment group separately and in total. In addition, for the Safety Analysis Set, the Evaluable Analysis Set, and the three subsets defined above, the reasons for exclusion of patients from the respective sets will be provided.

2.2 Violations and deviations

2.2.1 General protocol deviations

A protocol deviation (PD) occurs when a patient fails to adhere to pre-specified protocol eligibility criteria, and/or compliance during the course of the trial.

In this study, we will distinguish between general protocol deviations and procedure-specific deviations. General protocol deviations include all deviations except for the procedure-specific ones as defined in Section 2.2.2 and can be classified as either important or not important. Important protocol deviation is defined as a PD that "may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety or wellbeing". Important protocol deviations (IPD) will lead to exclusion of a subject

from the Evaluable Analysis Set. A non-important protocol deviation will, by itself, not lead to subject exclusion. However, a combination of non-important PDs might lead to such an exclusion, as per clinical judgement.

Important protocol deviations

Important protocol deviations include, but are not limited to:

- Randomized but did not meet the eligibility criteria
- Developed criteria for discontinuation of treatment but were not discontinued
- Received wrong study drug
- Received disallowed concomitant medication(s)
- Suspected study drug compliance less than 90% or more than 120%
- Severe non-compliance to the protocol
- Other

Protocol deviations will be further defined in a separate protocol deviations process document, see Appendix 8.5. PDs will be identified partly through programmed checks and partly through examination performed by e.g. monitors prior to database lock. A detailed list of both important and non-important protocol deviations will be provided in a separate document.

Number of patients with important protocol deviations will be tabulated for each treatment group separately and in total. No such tabulation will be made for non-important protocol deviations. However, subjects excluded from the analysis due to an important protocol deviation, or due to a combination of non-important protocol deviations, if such exist, will be listed.

2.2.2 Procedure-specific protocol deviations

These deviations refer to the fulfilment of conditions that the patients are required to adhere to when taking MRI and PET measurements. These conditions are as follows:

1) Patient should have been fasting for at least 6 hours
2) Patient should have abstained from products containing nicotine for at least 6 hours
3) Patient should have abstained from products containing alcohol for at least 6 hours
4) Patient should have abstained from products containing caffeine for at least 6 hours

A failure to fulfil at least one of these conditions might lead to removal of the patient from the respective analysis set. Whether a condition (or several) was violated to a degree that would require a patient to be excluded from the analysis will be determined by clinical judgement, and this will be done prior to database lock and study unblinding.

The number, and percentage, of patients who fail to fulfil the above criteria for any of the performed measurements (MRI, 11C-Acetate or 18F-FTHA) will be tabulated, regardless of whether a patient was, or was not, removed from the analysis due to such a failure.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Study endpoints

3.1.1 Adjudication of clinical endpoints

Adjudication will be performed only for potential events of diabetic ketoacidosis (DKA). These will be recorded in the CRF and submitted to an independent DKA Adjudication Committee (see CSP Section 8.2.6.1 for details). No other endpoints will be adjudicated.

3.1.2 Baseline demographics and patient characteristics

The values for the baseline demographics and patient characteristics, as listed below, will be obtained at the screening visit. The characteristics will be summarized descriptively, as is detailed in Section 4.1.1. The following demographics characteristics will be captured:

Table 3.1 Demographics

Demographics	Possible values / units	Measurement type	Derived
Sex	Male, Female	Categorical	No
Age	Years	Numerical	Yes
Age, categorized	<65 years ≥ 65 years	Categorical	Yes
Ethnicity	Hispanic or Latino Not Hispanic or Latino	Categorical	No
Race	White Black or African American Asian Other	Categorical	No

Also, the following patient characteristics will be captured:

Table 3.2 Patient characteristics

Patient characteristic	Possible values / units	Measurement type	Derived
Height	cm	Numerical	No
Weight	kg	Numerical	No
Weight, categorized	< 70 kg ≥ 70 - < 90 kg ≥ 90 kg	Categorical	Yes

BMI	kg/m^2	Numerical	Yes
BMI, categorized	< 25 kg/m^2 ≥ 25 and < 30 kg/m^2 ≥ 30 kg/m^2	Categorical	Yes
ECG	Normal Abnormal	Categorical	No
Pulse Rate	Beats / min	Numerical	No
Blood Pressure	mmHg	Numerical	No

The derivation of the baseline characteristics, when applicable, will be performed according to the following rules:

Patient characteristic	**Derivation principle**
Age	Derived by taking the difference between screening visit date and the date of birth. Explicitly, (1 + consent date - birth date) / 365.25
BMI	Weight / $Height^2$

The categorization of weight and BMI will be performed using the numerical values of the respective measurements.

The following measurements will be performed at randomization visit and treated as baseline characteristic:

Measurement	**Unit**	**Measurement type**	**Source**
S-Cholesterol	mmol/L	Numerical	Blood sample
S-Triglycerides	mmol/L		
S-HDL-Cholesterol Direct	mmol/L		

3.1.3 Disease history

Relevant medical and surgical history will be collected at the screening visit. History of diabetes will include information about duration of diabetes (in years, continuous and categorized), possible complications and current antidiabetic medication. Explicitly, the following diabetes history related variables will be collected:

Table 3.3 Disease history

Measurement	Possible values / units	Measurement type	Derived
Duration of Type 2 Diabetes	Years	Numerical	Yes
Duration of Type 2 Diabetes, categorized	< 3 years ≥ 3 and ≤ 10 years > 10 years	Categorical	Yes
Presence of complications	Yes No	Categorical	No
Type of complication	Retinopathy Neuropathy Autonomic Neuropathy Peripheral Nephropathy Angiopathy Other	Categorical	No
Metformin dose	≤ 500 mg > 500 and ≤ 1000 mg > 1000 and ≤ 2000 mg > 2000 mg	Categorical	No

Out of these, duration of Type 2 Diabetes will be derived as follows:

Duration of Type 2 Diabetes	Derived by taking the difference between screening visit date and the date T2D was diagnosed. Explicitly, (1 + consent date - diagnosis date) / 365.25.

Other than the history of diabetes, medical history of special interest, such as myocardial infarction and atrial fibrillation, will be registered (see Appendix 8.2 for a complete list of medical history of special interest). Additional medical and surgical history will also be collected as free text, later coded according to the version of Medical Dictionary for Regulatory Activities (MedDRA version 21.1) which is current at the time of data base lock.

In addition, the following measurements will be treated similarly to baseline patient characteristic (disease characteristics):

Measurement	Unit	Measurement type	Source
B-HbA1c	%	Numerical	Blood sample
B-HbA1c, categorized	<7% ≥7% – <8%, ≥8%	Categorical	Blood sample
LV global longitudinal strain (GLSLV)	%	Numerical	MRI
Myocardial efficiency	%	Numerical	PET-[11C]-Acetate
P-Glucose	mmol/L	Numerical	Blood sample
P-Insulin	pmol/L	Numerical	Blood sample
P-Glucagon	pmol/L	Numerical	Blood sample
P-Glucagon/Insulin	Ratio	Numerical	Blood sample

3.1.4 Prior and/or concomitant medications

Prior medications are defined as medications taken with start and stop date that fall before randomization. Concomitant medications are defined as treatments that are ongoing during the study period (i.e. after and including the randomization day). The use of prior and concomitant medications in the study will be collected as free text, later coded according to World Health Organization Drug Dictionary (WHODD).

In addition, the concomitant usage of metformin will be tabulated as part of the disease characteristics. The tabulation will be done for each treatment group and in total and include the total daily metformin dosage at the time of screening visit and duration of metformin treatment.

3.1.5 Efficacy

The efficacy endpoints in the study are changes observed in measurements listed below between the time of randomization (visit 2) and end of the 6-week treatment period (visit 4). All the endpoints are quantitative and can be viewed as measurements on a continuous scale. All the endpoints will be analysed in the same manner, described in detail in Section 4.2, which includes both a descriptive summary and a formal statistical analysis. For details about measurement procedures, see CSP Section 8.1.

In the table below, the efficacy variables are grouped according to their clinical similarity.

Table 3.4 Efficacy endpoints

Variable group	Endpoints in the group	Source
Primary		
LV global longitudinal strain (GLSLV)	GLSLV (%)	MRI
Secondary		
Myocardial efficiency	Myocardial efficiency (%)	PET-[11C]-Acetate (d)
Exploratory		
[11C]-ACETATE	Wash-out in the myocardium (Kmono) (l/min) Myocardial perfusion (mL/min/g) Wash-out in the myocardium (Kmono) / myocardial perfusion	PET-[11C]-Acetate
[18F]-FTHA	Myocardial fatty acid uptake (µmol/g/min) Fatty acid uptake in liver (µmol/g/min) Fatty acid uptake in kidney cortex (µmol/g/min) Fatty acid uptake in brain (µmol/g/min)	PET-[18F]-FTHA
LV global strain	LV global radial strain (%) LV global circumferential strain (%)	MRI
LV global systolic strain rate	LV global systolic longitudinal strain rate (s^{-1}) LV global systolic radial strain rate (s^{-1}) LV global systolic circumferential strain rate (s^{-1})	MRI
LV global diastolic strain rate	LV global diastolic longitudinal strain rate (s-1) LV global diastolic radial strain rate (s^{-1}) LV global diastolic circumferential strain rate (s^{-1})	MRI
LV volume	LV end-diastolic volume (mL) LV end-systolic volume (mL) LV stroke volume (mL) LV ejection fraction (%)	MRI
LV mass	LV mass (g) LV mass/end-diastolic volume (g/mL)	MRI
Left atrial volumes and compliance measures	Left atrial min volume (mL) Left atrial max volume (mL)	MRI

	Left atrial ejection fraction (%) E/A (I) E (cm/s) A (cm/s) DT (ms)	
Glucose control biomarkers (a)	P-Glucose (mmol/L) (c) B-HbA1c (%) (e) P-Lactate (mmol/L) P-Insulin (pmol/L) P-Glucagon (pmol/L) P-Glucagon/Insulin, (Ratio) (b)	Blood sample
Fatty acid blood biomarkers (a)	S-Free Fatty Acids, NEFA (mmol/L) P-Beta-hydroxybutyrate (umol/L)	Blood sample
Red blood cell biomarkers (a, c)	B-Erythrocyte, Volume Fraction (Ratio) B-Haemoglobin (g/L)	Laboratory, haematology/ haemostasis
Heart blood biomarkers (a)	S-N-Terminal Pro-Brain Natriuretic Peptide (pmol/L) P-Fibroblast Growth Factor 21 (ng/L) S-C-Reactive Protein (mg/L) P-high-sensitivity Troponin I (ug/L)	Blood sample
Other biomarkers (a)	S-Urate (µmol/L)	Blood sample
Vital Signs (a)	Weight (kg) Systolic Blood pressure (mmHg) Diastolic blood pressure (mmHg)	Physical examination

a No evaluation of within-group dependencies will be done for this group.
b Derived by dividing the glucagon value from the Glucose control biomarkers group with insulin value from the same group.
c Also part of the safety analysis.
d Variables obtained from MRI examination (stroke volume) and vital signs examination (blood pressure and pulse rate) on the corresponding visit are also used in calculation of myocardial efficiency.
e If data are not received in % following derivation should be applied,
HbA1c (%) = [HbA1c (mmol/mol) +24]/11

3.1.6 Safety

The safety will be assessed through collection and examination of laboratory values and adverse events.

3.1.6.1 Safety, laboratory and vital signs

The following safety measurements will be done prior to treatment initiation (screening and randomization visits) and at the end of treatment:

Measurement	Unit	Source
B-Haemoglobin	g/L	Laboratory, haematology/haemostasis
B-Erythrocyte, Volume Fraction	Ratio	
P-Creatinine	µmol/L	Laboratory, clinical chemistry
P-Bilirubin, total	µmol/L	
P-Alkaline Phosphatase (ALP)	µkat/L	
P-Aspartate transaminase (AST)	µkat/L	
P-Alanine transaminase (ALT)	µkat/L	
P-Glucose	mmol/L	
Systolic blood pressure	mmHg	Physical examination
Diastolic blood pressure	mmHg	
Pulse	bpm	

The safety measurements will be presented descriptively, as is detailed in Section 4.1.3.1. Observe that B-Haemoglobin, B-Erythrocyte, systolic blood pressure and diastolic blood pressure will also be part of the efficacy analyses.

In addition, the following safety variables will be derived:

Measurement	Possible values / units	Derivation principle
ALP, grouped	Abnormal, low Normal Abnormal, high	The classification is performed by relating the ALP measurement to the corresponding reference limits of the local labs (see Appendix 8.4).
AST, grouped	Abnormal, low Normal Abnormal, high	The classification is performed by relating the AST measurement to the corresponding reference limits of the local labs.

ALT, grouped	Abnormal, low Normal Abnormal, high	The classification is performed by relating the ALT measurement to the corresponding reference limits of the local labs.
Total bilirubin, grouped	Abnormal, low Normal Abnormal, high	The classification is performed by relating the total bilirubin measurement to the corresponding reference limits of the local labs.

3.1.6.2 Safety, adverse events

Serious adverse events (SAE) and adverse events leading to discontinuation (DAE) will be captured. All possible events of diabetic ketoacidosis (including non-serious) will also be collected.

AE type	***Definition***
AE	*An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.*
SAE	*An SAE is an AE occurring during any study phase (screening, randomization, treatment, follow-up) that fulfils one or more of the following criteria:* - *Results in death.* - *Is immediately life-threatening.* - *Requires in-patient hospitalisation or prolongation of existing hospitalisation.* - *Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.* - *Is a congenital abnormality or birth defect.* - *Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.*
DAE	*Discontinuation of Investigational Product due to Adverse Event*

AEs (for this study, SAEs and DAEs) will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the version of Medical Dictionary for Regulatory Activities (MedDRA) which is current at the time of data base lock.

For details regarding AE collection and follow-up, see CSP v2 Section 8.3.

3.1.7 Duration of exposure and treatment compliance

Compliance, as a percentage, will be calculated as 100 times the ratio of the total number of tablets taken (numerator) and the total number that should have been taken (denominator). The total number of tablets taken is the difference between total number of tablets dispensed minus total number of tablets returned over the entire randomized treatment period. The total number of tablets that should have been taken is calculated as the date of the last IP dose minus the date of first IP dose during randomized treatment period plus one (one tablet a day is the study dosing).

3.2 Management of missing data

All the analyses (both descriptive and formal) will be conducted using the available data. No imputation of values of endpoints, laboratory values, or patient characteristics will be performed. Missing start/stop dates for AE will appear as missing in the listings but will, however, be imputed for the tabulated summaries. Missing dates for T2D first diagnosed will likewise be imputed for the tabulated summaries but appear as missing, or partially missing, in the listings. Missing start/stop date of prior and concomitant medications will also be reported as missing in the listings, but imputation will be performed to allow the classification into prior and concomitant. Missing dates related to medical history (e.g. date of the most recent episode) will be reported as missing. For details in the imputation algorithms, see Appendix 8.3.

4. ANALYSIS METHODS

4.1 General principles

The SAS software version 9.4 or higher will be used for production of the statistical outputs.

For continuous measurements (e.g. age, pulse, blood pressure) the summary statistics will include number of subjects with non-missing values (n), minimum, maximum, median, mean and SD. For categorical measurements (e.g. sex, race, ethnicity) they will include frequencies and the percentage of subjects in the respective category. For the percentages, the denominator will be the number of patients in each treatment arm and in total.

Minimum and maximum values will be reported to the same degree of precision as the raw

data up to a maximum of 3 decimal places. Mean, first quartile, median, third quartile and SD will be reported to one further degree of precision. Percentages will be rounded to 1 decimal place. In general, baseline will be defined as the last value prior to the date of the first dose.

For insulin and vital status two measurements are taken with a few minutes apart. The average of those measurements will be used in the calculations.

In general, the laboratory results from the blood biomarkers will be used for the efficacy endpoints and the clinical safety laboratory assessments will be used for the safety endpoints.

4.1.1 Baseline characteristics

The baseline demographics, patient characteristics and relevant medical history will be summarized for the Evaluable analysis set.

Descriptive statistics will be tabulated for each treatment arm and in total, but no formal statistical tests of equivalence of distributions of baseline characteristics in the two treatment groups will be performed.

Medical history

The variables related to diabetes history collected at screening, as well as medical history of special interest, will be tabulated in the same manner as patient characteristics, as described above. Additional medical and surgical history of interest will be tabulated by SOC and PT.

Concomitant medications

Concomitant medications will be classified according to ATC classification/ (generic) drug name. Concomitant medications will be tabulated using the same principle as for categorical baseline characteristics (number and percentage of patients for each treatment group separately and in total). In addition, all patients with changes in medication regimen occurring during the study will be listed.

Duration of exposure and treatment compliance

Compliance will be summarized through tabulation of summary statistics (mean, SD, min, max, median, Q1, Q3) for each treatment arm separately. In addition, the number and percentage of patients with compliance below 90%, between 90 and 120%, and above 120% will also be presented. This will be done both for Evaluable Analysis Set and the Randomized Analysis Set. Duration of exposure will be summarized in a similar manner using Safety Analysis Set.

4.1.2 Efficacy

The efficacy analyses (with the exception of PK) will be performed using the Evaluable Analysis Set, as well as the three subsets of the Evaluable Analysis Set, as described in Section 2.1.

4.1.2.1 Evaluation of treatment effect

The main purpose of these analyses is to detect a systematic difference in mean for change in measurements obtained at randomization and at the end of treatment between the two treatment groups. This will be studied for primary, secondary and all the exploratory endpoints as listed in Table 3.4. Thus, for each of the endpoints, the following two-sided hypothesis will be tested:

Null hypothesis: There is no systematic difference in mean change between the two treatment groups

Alternative hypothesis: There is a systematic difference in mean change between the two treatment groups

For this purpose, a linear model with measurement difference as the dependent variable and the treatment group indicator and baseline value of the modelled endpoint as independent variables (ANCOVA) will be fitted for each of the endpoints (primary, secondary and exploratory). For details regarding modelling and presentation of results, see Section 4.2.1.

All the tests will be performed using a two-sided Type I error rate 0.05. As the nature of the study is exploratory, with no confirmatory component, no control of family-wise error rate will be performed. However, due to the large number of considered endpoints, it is likely that several of them will be found to be "significant" as a consequence of the Type I error rate allowable by the hypothesis testing procedure, even if no effect is truly present. Thus, the interpretation of the findings will be done with care, keeping in mind both whether the detected patterns are clinically meaningful and the expected number of false discoveries that might occur due to chance.

The potential effect of treatment will also be presented descriptively by tabulating summary statistics (n, minimum, maximum, mean, SD, Q1, median, Q3) for the change from baseline. These will be accompanied by similar summaries describing the distribution of all the efficacy measurements obtained at randomization and end of treatment. These summaries will be made for each treatment group separately.

4.1.2.2 Evaluation of co-dependence

The purpose of this analysis (corresponding to exploratory objective 15) is to detect, and quantify, possible dependence between the endpoints of the study. This includes, partly, detecting a possible existence of dependence within groups of endpoints as defined in Table 3.4 (primary, secondary, exploratory), and, partly, quantifying the magnitude of the dependence between the primary and secondary endpoints and the exploratory ones.

The evaluation will be done using Pearson correlation:

1) Between all the endpoints within each group as defined in Table 3.4.

2) Between the primary endpoint and the other endpoints (secondary and exploratory).

3) Between the secondary endpoint and the exploratory endpoints.

The analyses will be performed for each treatment group separately.

4.1.2.3 PK analysis

The pharmacokinetic concentration data from the pre-dose blood sample at visit 4 will be listed for all patients in the PK analysis set. Further analysis may be presented separately from the main clinical study report.

4.1.3 Safety

All the safety analyses will be performed using Safety analysis set.

4.1.3.1 Laboratory assessments and vital signs

For all laboratory assessments, descriptive statistics will be presented by treatment group and in total for both absolute values at randomization and end of treatment visits, and the change between these two visits. The statistics will include n, minimum, maximum, median, Q1, Q3, mean and SD. For ALT, AST, ALP and total bilirubin changes in evaluation (normal, below lower limit, above upper limit) between randomization and end of treatment visits will be tabulated using a shift table. If the value of a laboratory assessment obtained at randomization is missing, but there exists a corresponding value obtained at an earlier visit (i.e. screening or an unscheduled visit) this value will be used in place of the missing one.

For clinical chemistry and haematology, only fasting values will be analysed.

4.1.3.2 Adverse events

All collected AEs (which, for this study, consist of DAEs and SAEs) with onset date during the treatment period will be summarized using descriptive statistics (number of patients, percentage of patients). Such summaries will be created separately for AEs with the outcome of death, SAEs and DAEs.

The summaries will be presented by:

- SOC and PT (AEs with the outcome of death, SAE, DAE)
- PT and maximum reported intensity (SAE, DAE)
- PT and causality assessment (SAE, DAE)

Causality assessment will include “Caused by IP”, “Caused by 11C-Acetate” and “Caused by 18F-FTHA”.

In addition, key patient information for SAEs, DAEs and AEs with the outcome of death will be listed. All SAEs occurring from the time of signature of informed consent up to and including the follow-up period will be summarized by system organ class (SOC) and preferred term (PT).

All instances of DKA AEs will be listed. The listing will include the study day corresponding to the start of the AE, symptoms, DKA risk factors, intensity, outcome, a causality assessment and adjudicated results.

4.2 Analysis methods

Below, the statistical models used for the efficacy analyses, as well as presentation of results, are described.

4.2.1 Analysis of the effect of treatment

The main tool for evaluation of treatment effect in this study will be an ANCOVA model (see section 4.1.2), with treatment group as the categorical independent variable and baseline value of the respective endpoint as the covariate.

4.2.1.1 Presentation of results

Least Square Mean (LSM) change from baseline estimates, as well as the corresponding 95 percent confidence limits, will be generated from the fitted model for each treatment group. The average value of the difference in LSM between the dapagliflozin and placebo treatment groups, the corresponding 95 percent confidence interval and the p-value will also be presented.

4.2.2 Evaluation of plausibility of model assumptions

An ANCOVA model has three main assumptions, which will be checked for primary and secondary endpoints:

1) The deviations of the single data point from the expected general trend fitted by the model (residuals) follow a normal distribution

2) The relationship of the response to the baseline variable is linear within each treatment group

3) The effect of treatment is the same for all possible baseline values of the endpoint under study (no treatment-by-baseline value interaction)

The plausibility of the first and second of these assumptions will be evaluated by graphical examination of residuals using normal Q-Q-plots and scatter plots of the residuals against the baseline value of the respective endpoint. A Shapiro-Wilk normality test may also be performed. If strong deviations from normality are discovered, the p-value corresponding to the treatment effect will be obtained from an ANCOVA based on ranked response and baseline values (with the effect estimates and the corresponding CIs still based on a parametric ANCOVA).

If the relationship of the response to the baseline variable is non-linear, then a suitable transformation of the response and the baseline variable (e.g., natural logarithm, square root, inverse, quadratic, etc.) may be used for analysis.

The plausibility of the third assumption will be evaluated by expanding the ANCOVA model by including the interaction between treatment group and baseline value of the endpoint. The significance of the effect of the interaction term will be formally assessed through the statistical test based on the Wald test using a 0.1 level of significance. If the p-value from a model that includes interaction is less than 0.1, then the predicted values for each treatment will be plotted against baseline value, and the type of interaction will be assessed. If the lines do not cross, or the crossing is not too severe, then the interaction will be considered quantitative and the interaction term will be dropped from the model. Otherwise, the p-value from the model will not be reported.

Any impact of the potential outliers and subgroups will also be investigated. An outlier is an observation with a residual that is more than three times the interquartile range above the 75th percentile or below the 25th percentile. Outliers will be identified using standardized residuals from the original ANCOVA model. If outliers are present, then additional sensitivity analyses will be performed with the outliers excluded**.**

The following subgroups will be considered for the primary and the secondary endpoints: site, country, age, BMI and gender.

4.2.2.1 Presentation of results

Any marked violations of model assumptions will be discussed in the CSR and the supporting results will be presented in appendices.

4.2.3 Analysis of co-dependence

The analysis of co-dependence will be done by Pearson correlation, using Fisher transformation to produce confidence intervals as given in (PASS, Chapter 808).

Co-dependence will be examined:

- within each group as specified in Table 3.4.
- between the primary endpoint and the other endpoints (secondary and exploratory)
- between the secondary endpoint and the other endpoints (exploratory)

4.2.3.1 Presentation of results

The results of the co-dependence will be presented as the estimate of the correlation, with the corresponding 95% confidence interval as well as the p-value. Within each group, this will be presented in the form of correlation matrices. Between primary/secondary endpoints and the exploratory endpoints it will be tabulated.

5. INTERIM ANALYSES (NOT APPLICABLE)

6. CHANGES OF ANALYSIS FROM PROTOCOL (NOT APPLICABLE)

7. REFERENCES

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8. APPENDIX

8.1 Overview of the study assessments

	Screening	**Randomization Baseline**	**Interim visit** (Phone visit)	**End of treatment**	**Safety Follow-up** (Phone visit)
Visit	**1**	**2**	**3**	**4**	**5**
Day	**-21 to 0**	**1**	**14**	**42**	**49**
Informed consent	*X*				
Inclusion /exclusion criteria	*X*	*X*			
Routine clinical procedures					
Demography	*X*				
Physical examination	*X*				
Medical history and comorbid conditions	*X*				
Vital signs	*X*	*X*		*X*	
Height	*X*				
Weight	*X*	*X*		*X*	
ECG	*X*				
Echocardiogram	*X*				
Concomitant medication	*X*	*X*	*X*	*X*	
Routine safety measurements					
SAE	*X*	*X*	*X*	*X*	*X*
DAE		*X*	*X*	*X*	*X*
Diabetic ketoacidosis events		*X*	*X*	*X*	*X*
Pregnancy test (serum or urine)	*X*	*X*		*X*	
Clinical chemistry and haematology	*X*	*X*		*X*	
Blood and Urine analyses (except Safety analyses)					
HbA1c (screening)	*X*				
Biomarkers		*X*		*X*	
Urine sample		*X*		*X*	
Pharmacokinetic measurements					
Pre-dose blood sample				*X*	
Efficacy measurements					
MRI (fasting)		*X*		*X*	
CT-PET/MRI-PET (fasting)		*X*		*X*	

	Screening	Randomization Baseline	Interim visit (Phone visit)	End of treatment	Safety Follow-up (Phone visit)
Visit	**1**	**2**	**3**	**4**	**5**
Day	**-21 to 0**	**1**	**14**	**42**	**49**
Randomisation		*X*			
Study treatment dispensed (daily dosing)		*X*			
Study treatment return				*X*	

8.2 Medical history of special interest

The collected medical history of special interest will consist of the following items:

Dyslipidaemia, Hypertension, Peripheral Arterial Occlusive Disease, Angina Pectoris, Myocardial Infarction, Coronary Artery Disease, Percutaneous Coronary Intervention, Heart Failure, Valvular Heart Disease, Atrial Fibrillation, Atrial Flutter, Chronic Obstructive Pulmonary Disease, Coronary Artery Bypass, Chronic Kidney Disease, Vascular Stent

For each of the above, the presence/absence of the condition will be recorded, as well as, where applicable, whether the condition is currently treated and the dates of the most recent episode and procedure.

8.3 Imputation of missing dates

Every attempt will be made to obtain complete information about dates related to study design, e.g. date of informed consent and visit dates. In case of this information is still missing, or partially missing, at the time of database lock, the dates will not be imputed but, rather, left as unknown.

For the dates of the diagnosis of diabetes mellitus, AE start / stop date and medications start/stop dates, the following conventions will be used:

Date diabetes mellitus first diagnosed

Missing type	**Action**
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 subject will be excluded from all summaries related to duration of Type 2 diabetes.
Missing day, month and year	No imputations will occur, and the subject will be excluded from all summaries related to duration of Type 2 diabetes.
If any such imputed date falls after the consent date	The diagnosis date will be taken as equal to the consent date.

Partial date conventions for AE

Missing type	**Action**
If only the **day part** of the AE **onset date** is missing and occurs in the same month and year as the first dose of study medication	The date of first dose of study medication will be used as the onset date of the AE. Otherwise, the first day of the month will be used to complete the onset date of the AE
If the **day and month parts** of the **AE onset date** are missing and occur in the same year as the first dose of study medication	The date of the first dose of study medication will be used as the onset date of the AE. Otherwise, January 1st will be used to complete the onset date of the AE.
If the AE **onset date** is **completely** missing	The date of the first dose of study medication will be used as the onset date of the AE.
If only the **day part** of the AE **end date** is missing and occurs before or in the same month and year as the first dose of study medication	The last day of the month will be used to complete the end date of the AE.
If the **day and month parts** of the AE **end date** are missing	December 31st will be used to complete the end date of the AE.
If the **end date** of the AE is **completely** missing and the onset date of the AE occurs after the date of the first dose of study medication	Then the onset date of the AE will be used as the AE end date. Otherwise, the date of the first dose of study medication will be used as the AE end date

Concomitant medications

- 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.

8.4 Reference limits for ALT, AST, ALP and total bilirubin

Parameter	**Site**	**Reference values**				
		Male		**Female**		
		Lower limit	**Upper limit**	**Lower limit**	**Upper limit**	**Units**
AST	2201	15	45	15	35	U/L
ALT	2201	-	50	-	35	U/L
ALP	2201	35	105	35	105	U/L
Total bilirubin	2201	-	21	-	21	µmol/L
AST	7201	0.25	0.75	0.25	0.60	µkat/L
ALT	7201	0.15	1.1	0.15	0.75	µkat/L
ALP	7201	0.6	1.8	0.6	1.8	µkat/L
Total bilirubin	7201	5	25	5	25	µmol/L