TRIAL STATISTICAL ANALYSIS PLAN

c35189692-01

BI Trial No.:	1245-0218
Title:	A randomised, double-blind, placebo-controlled, parallel group, 52 weeks phase IV trial to evaluate efficacy and safety of oral, once daily empagliflozin in elderly Japanese patients with type 2 diabetes mellitus and insufficient glycaemic control Including protocol version 1.0 [c3096609-01]
Investigational Product(s):	Jardiance®, empagliflozin
Responsible trial statistician(s):	[redacted] Address: [redacted] Tel: [redacted]
Date of statistical analysis plan:	09 MAY 2022 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical classification
BI	Boehringer Ingelheim
BIcMQ	BI-customized MedDRA query
BMI	Body mass index
CEC	Clinical event committee
CRF	Case report form
CT	Concomitant therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DBP	Diastolic blood pressure
DKA	Diabetic ketoacidosis
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
ECG	ECG Electrocardiogram
EDMS	Electronic Document Management System
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EMA	European medicines agency
EOT	End of treatment
EOS	End of study
FAS	Full analysis set
[redacted]	[redacted]
FPG	Fasting plasma glucose
HbA1c	Glycated haemoglobin
ICH	International Conference on Harmonisation
iPD	Important protocol deviation
IRT	Interactive response technology
ITT	Intention to treat
LLT	Lowest Level Term
LOCF	Last observation carried forward
MDRD	Modification of diet in renal disease

Term	Definition / description
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MMRM	Mixed-effect Model Repeated Measures
[redacted]	[redacted]
MQRM	Medical Quality Review Meeting
NCF	Non-completers considered failure
OC	Observed case
OC-IR	Observed cases, including values after rescue
OR	Original results
PK	Pharmacokinetics
PPS	Per protocol set
PT	Preferred term
PD	Protocol deviation
Q1	Lower quartile
Q3	Upper quartile
REML	Restricted maximum likelihood
RS	Randomised set
SBP	Systolic blood pressure
SCR	Screened set
SD	Standard deviation
SDG	Standardized Drug Groupings
SMQ	Standardised MedDRA query
SOC	System Organ Class
TMF	Trial Master File
TOC	Table of contents
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
WHO	World Health Organisation

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the CTP, including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in the CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.4 or a later version will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Descriptions in the CTP related to statistical analysis will be changed as follows:

- [redacted]
- [redacted]
- [redacted]
- Descriptive statistics on the impact of COVID-19 on study visits as well as trial medication intake will be provided if any.
- The definition of iPDs will be specified in the DV domain instead of the TSAP prior to DBL.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint is defined in the CTP Section 2.1.2.

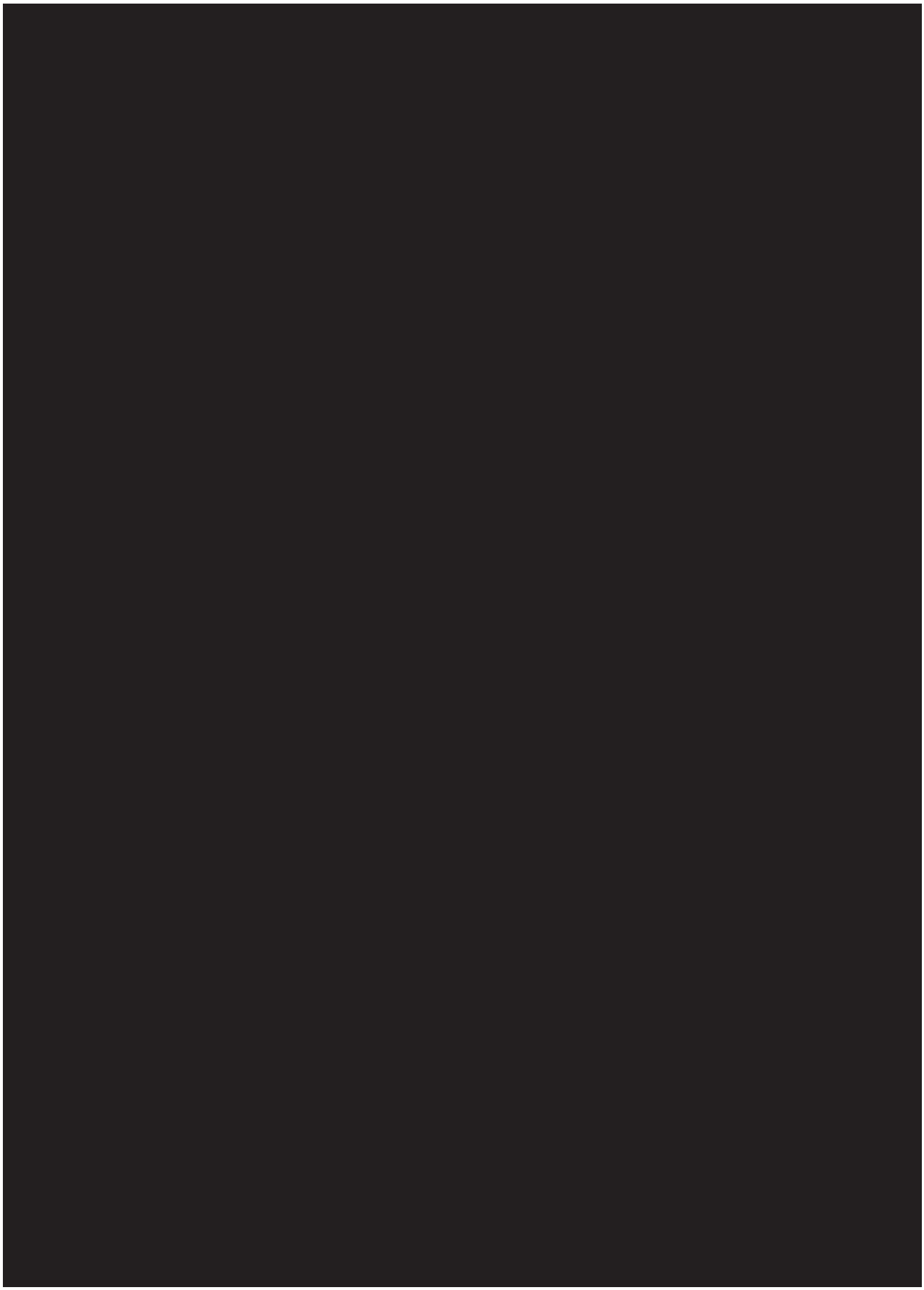
5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

Secondary endpoints are listed in the CTP Section 2.1.3.



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

There will be 5 treatment study phases in this trial: screening, placebo run-in, study treatment phase (with either 10 mg Empagliflozin or matching placebo), post-treatment and post-study. The purpose of the definitions below is to describe all the different study/treatment intervals, in which a patient can lie during the course of the trial.

Table 6.1: 1 Treatment regimens / study intervals

Label	Interval	Start date	Start time
Screening	Screening	Date of informed consent	00: 00
Run-in	Run-in	Date of first administration of run-in medication	Time of first administration of run-in medication 12:00 if missing
Placebo/Empagliflozin 10mg	Treatment	Date of first administration of trial medication	Time of first administration of trial medication 12:00 if missing
Post-treatment	Post-treatment	Date of last intake of trial medication + 1 day	00:00
Post-study	Post-study	Last contact date + 1 day	00:00

For efficacy and safety analyses, measurements will still be considered on-treatment during a follow-up period specific to each parameter. These follow-up periods are defined in Table 6.7: 1.

The efficacy analyses will follow the intention-to-treat (ITT) principle in assigning patients to treatment groups, i.e. patients will be analysed as randomised.

Safety analyses will be run on the treated set (TS). Patients will be shown under the randomised treatment. Safety analyses will also assign patients to the treatment group as randomised. In the exceptional case that a patient took the wrong treatment, adverse events may occur while being on the wrong treatment. Analyses of this data are described in Section 7.8.1.7.

6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation (PD) is important, if it affects the rights or safety of the study patients, or if it can potentially influence the primary outcome measurement in a non-negligible way (4).

The documentation of the iPD categories, definition and how to handle iPDs in the analysis are done in the DV domain and stored within the TMF in EDMS.

6.3 SUBJECT SETS ANALYSED

The following analysis sets will be defined for this trial.
SCR - Screened patients set
All patients screened for the trial, with informed consent given and who completed at least one screening procedure at Visit 1.

RS - Randomised set
All patients from the screened set who were randomised to trial medication, regardless of whether any trial medication was taken.

TS – Treated set
All patients randomized and treated with at least one dose of trial medication. The TS is the basis for safety analyses.

FAS - Full analysis set
All patients randomised, treated with at least one dose of trial medication, and with a baseline and at least one on-treatment HbA1c value. The FAS is the basis for the ITT analysis.

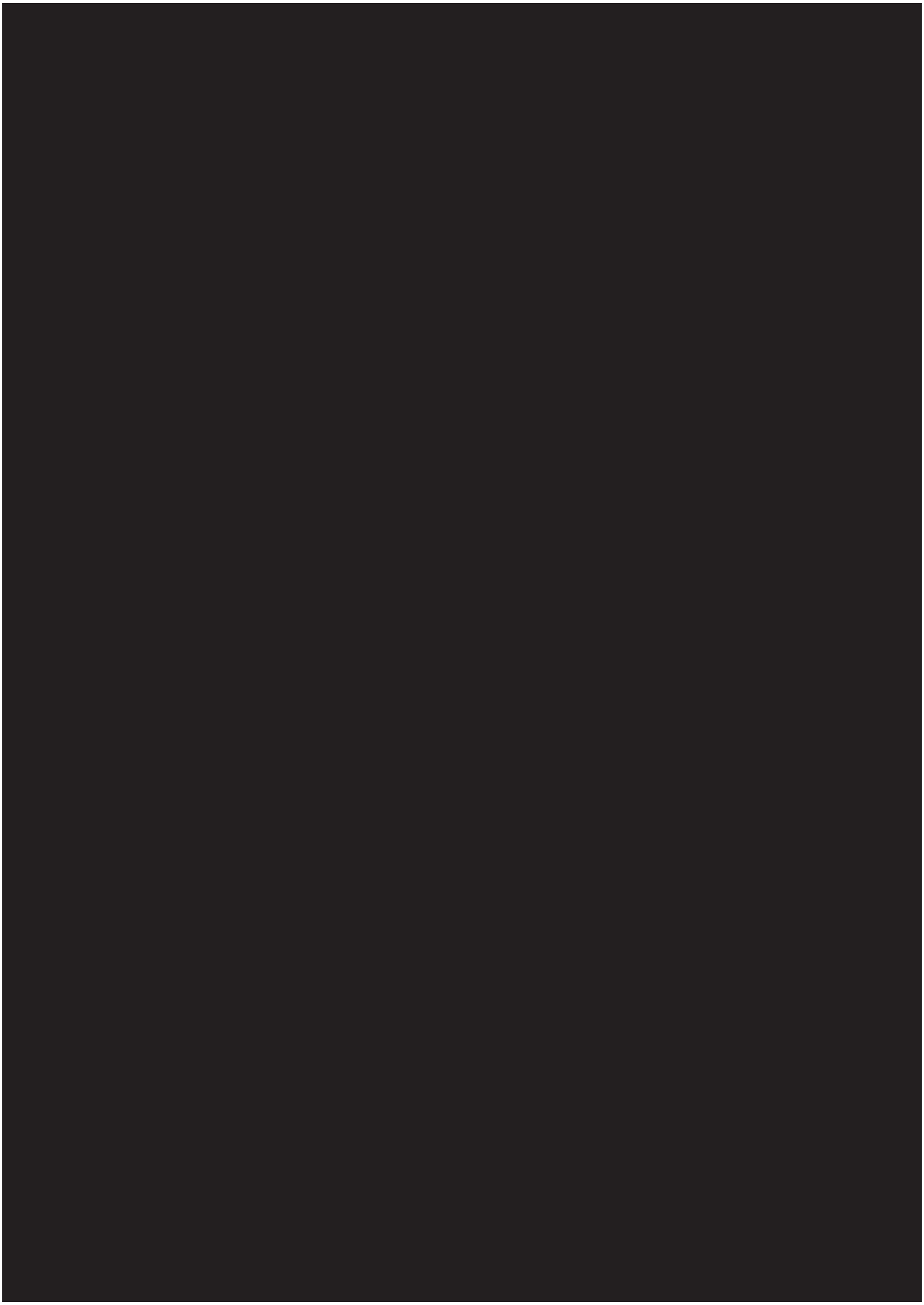
PPS - Per-protocol set
All patients in the FAS without iPD leading to exclusion.

In Table 6.3: 1 the data sets which are to be used for each category class of endpoint are illustrated. Note that the number of patients with available data for an endpoint may differ. For details, see Section 6.6 “Handling of missing data and outliers”.

Table 6.3: 1 Summary of which data sets will be used for which class of endpoints

Class of endpoint	TS	FAS	PPS
Primary endpoint		OC, OC-IR, LOCF	OC
Subgroup analyses of primary endpoint		OC	
Further endpoints (binary)		NCF	
Further endpoints (continuous)		OC, OR#	
Safety endpoints	OR, OC-IR^		

#OR results will only be presented for time to first rescue medication and number of patients with rescue.
^OC-IR will be used for secondary endpoints and laboratory measurements.



6.5 POOLING OF CENTRES

This section is not applicable, because centre is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Based on the different reasons of patients' data missing for different endpoints, various methods will be used to assess the impact of missing data on the efficacy endpoints of this trial, depending upon the type of the endpoint (see Table 6.3: 1).

6.6.1 Definition of rescue therapy for censoring

For some of the imputation methods defined below, values after rescue medication will be set to missing. In this context, the following two situations are defined as use of rescue medication:

- Additional antidiabetic medication used for ≥7 consecutive days
- Increased in dose of background medication for ≥7 consecutive days

This approach will be used when considering which data to exclude from the OC and LOCF analyses. For this definition of rescue therapy no statistical analysis will be conducted. For the definition of rescue therapy as a further endpoint, please refer to Section 5.3.2.

6.6.2 Imputation methods

6.6.2.1 Original result (OR) analysis

Original result analysis implies the analysis of data exactly as observed. OR analysis will be performed on endpoints that are either not affected by patients' rescue medication use or if it is not meaningful to apply any imputation rule on them for replacing the missing values.

6.6.2.2 Observed cases (OC) analysis

For all efficacy endpoints, it is planned to analyse only the available data that were observed while patients were on treatment, i.e., excluding the missing data. In other words, OC analysis will be performed and missing data in this analysis will not be replaced. Also, all values measured after rescue medication will be handled as missing (rescue medication as defined in Section 6.6.1).

The OC-technique represents the primary data selection tool that will be used for the primary analysis in this trial. Subsequent handling of missing data will be performed via a likelihood based method, and in the case of the primary analysis, will use the MMRM model.

6.6.2.3 Observed cases analysis including values on rescue medication (OC-IR)

For some endpoints the OC-technique will also be adapted without setting the values measured after rescue medication taken to missing, and using the original observed values instead. This is also done as a sensitivity analysis of the endpoint with OC as the imputation rule and will be called Observed Cases including values on rescue medication (OC-IR).

6.6.2.4 Last observation carried forward (LOCF)

An alternative method for quantitative endpoints is to replace missing values due to early discontinuation of a patient by her/his last observed measurement on treatment.

The last observation on-treatment need not necessarily be a value selected as a visit value if multiple measurements were performed within a time window for a visit. In this case the last on-treatment value within the time window will be carried forward, while the visit value can be the value that was observed closest to the planned visit date or the first value observed in the time window. See Table 6.7: 2 for further details.

For example, if a patient is on rescue medication after Visit 3 and before Visit 4, then all the on-treatment visits will be set to missing and the HbA1c value from baseline will be carried forward to populate the missing on-treatment values in HbA1c.

Missing values within a course of measurements on treatment will be interpolated based on the last observed value before the missing visit and the first observed value after the missing visit. This is independent from the selection of a value as the picked visit value to be used in the descriptive analysis by visit.

The missing endpoint value can be interpolated as E0 = E-1 + ((E1 - E-1) x (D0 - D-1) / (D1 - D-1)), where
D0 = date of a visit with a missing endpoint value,
D1 = date of the next-visit (with end-point value non-missing) after the visit with missing endpoint,
D-1 = date of a previous-visit (with end-point value non-missing) before the visit with missing endpoint, and
Ei = endpoint values for visits D-1, D0 and D1 for i = -1, 0 and 1.

The values measured after rescue medication was taken during the active treatment period by the patients will be set to missing; and these missing values will be imputed by LOCF technique.

Missing data will only be imputed up to the planned visit to be reached by all randomised patients (Week 52).

6.6.2.5 Non-completers considered failure (NCF)

For binary endpoints, like a treat to target response of HbA1c < 7.0%, a method that missing values are replaced as “failures” will be considered. Missing data due to early discontinuation per the completer definition will be replaced as “failure” (i.e., HbA1c >= 7.0%) up to the

planned final visit to be reached by all patients. In addition, values obtained after rescue medication will also be handled as “failure”.

For binary endpoints that are derived from quantitative endpoints (e.g. HbA1c), missing values within a course of measurements on treatment will be replaced on the basis of the corresponding imputed value of the underlying quantitative endpoint (e.g. interpolation for HbA1c).

6.6.3 Safety and other variables

Missing safety data will not be replaced.

6.6.4 Missing dates and times

a) Missing AE dates
Missing or partial date information for AEs will be replaced according to general BI rules described in the BI guidance for “Handling of missing and incomplete AE dates” (5).

b) Missing drug administration dates
If the date of first drug administration is missing but the patient was randomised, the date of the first drug administration will be set to the date of randomisation.

If the date of first administration is partially missing with the month and year present, the day will be set to the date of randomisation if randomisation was in the same month. If randomisation was in the month prior to the first drug administration the missing day will be imputed as the first day of the month. A missing time of first drug administration will be imputed as 12:00 o'clock noon, missing administration times at on-treatment visits will be imputed by 08:00 o'clock in the morning.

If the date of trial medication stop is partially or completely missing, use the minimum of the following dates:

- End of treatment visit date, if available
- Date of death
- Trial completion (last contact date)
- Longest extrapolated treatment duration (assuming 1 tablet/day)
- (in case for partially missing date) Last day of the year/month given as partial date

In case of a partially missing date, if the imputed date is before the first day of the month/year given as the partial date, the first day of the month/year will be used. All other cases need to be assessed by the trial team on an individual patient basis, using the points above as guidance.

c) Missing dates for concomitant and other antidiabetic therapies
For incomplete date information, the midpoint of the possible interval will be used. If only the year is present, the day and month will be imputed as 01 July, if year and month is present the day will be imputed as 15. If the year is missing, the date will be considered missing.

If this leads to contradictions for the start or end date of a concomitant therapy (e.g. imputed end date before documented start date), a partial end date will be imputed as the end of the interval or a partial start date will be imputed as the start of the interval in the database to resolve this contradiction.

All other cases or conflicting cases resulting from these imputation rules need to be assessed by the trial team on an individual patient basis.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

With regard to efficacy and safety endpoints, the term “baseline” refers to the last observed measurement prior to administration of any randomised trial medication. Measurements taken prior to the first intake of randomised trial medication will be considered pre-treatment values. Since the protocol specifies that all measurements are taken at Visit 3 before any intake of trial medication, all measurements at the first day of drug intake are assumed to qualify as baseline assessments.

Measurements taken after the first intake of randomised trial medication will be considered on-treatment values if they have been obtained up to end of the parameter specific follow-up period as defined in Table 6.7:1 below and will be assigned to the randomised trial medication for efficacy and safety analyses.

Measurements taken after the end of the endpoint specific follow-up period and after the last intake of trial medication will be considered post-treatment values.

On-treatment efficacy, safety, health related and QoL measurements will be assigned to visits based on time windows around the planned visit dates. These time windows are defined based on the planned number of days after the date of first administration of trial medication (see Table 6.7: 2).

Table 6.7: 1 Endpoint specific assignment to active treatment

Endpoint	**Last day of assignment to treatment phase**

	(days after trial medication stop date)
Efficacy	
HbA1c	7
Safety	
Adverse events	7
Safety laboratory measurements	3
Pulse rate	1
FPG	1
Chair stand test	7
Grip strength	7
Body composition	7
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Reasons to base the time windows on the actual treatment start date rather than the randomisation date are:

- If first intake of trial medication shows a large delay by e.g. more than one week after the date of randomisation, a measurement taken four weeks after randomisation rather reflects the drug effect after three weeks than after four weeks and thus may underestimate the treatment effect at this visit.
- With large delays of the introduction of trial medication after the randomisation, the time window for the first on-treatment visit could include times the patient was not yet on trial medication.

The time window for the first visit after randomisation starts on the day after the first intake of trial medication. This maximises the number of measurements used in by visit analyses, but may lead to an underestimation of the treatment effect at the first visit for parameters that react slowly on treatment.

The midpoint between two on-treatment visits defines the end of a time window, with the midpoint being included in the time window of the preceding visit. The end of the time window of the last on-treatment visit (EOT) is endpoint dependent (cf. Table 6.7: 1).

Table 6.7: 2 Time windows for on-treatment efficacy measurement scheduled for each on-treatment visit

			Time Window (actual days on treatment)	
Visit number	Visit label	Planned days	Start	End[A]

3	Baseline	1	NA	1[B]
4	Week 4	29	2	57
5	Week 12	85	58	127
6	Week 24	169	128	211
7	Week 36	253	212	309
8	Week 52/EOT	365	310	Trial medication stop date + X days

A. In case of premature discontinuation of the trial medication a Visit 8 has to be performed. If such a Visit 8 falls into the time window of a previous visit, measurements will be assigned to this previous visit and the visit value will be determined as described below. In this case the time window for the visit that includes Visit 8 will end X days after the trial medication stop date, including Day X. The definition of X is endpoint specific, cf. Table 6.7: 1. No time window for optional visit is planned.
B. Only values taken prior to the start of treatment with randomised trial medication can be considered baseline values. Time windows will be used for assignment of measurements to scheduled visits.

Only one observation per time window will be selected for analysis at an on-treatment visit - the value will be selected which is closest to the protocol planned visit day. If there are two observations which have the same difference in days to the planned day or if there are two observations on the same day, the first value will be used.

Note: For LOCF imputation, the last observed on-treatment value will be carried forward within the applicable period, whether or not it was selected in the previous time window. For interpolation only selected values are to be used. For more details on LOCF refer to Section 6.6.

7. PLANNED ANALYSIS

Disposition of the patient population participating in the trial will be analysed by treatment groups and presented in the clinical trial report as a frequency-distribution.

A frequency of patients with iPDs, also summarised by whether the iPD led to exclusion from the PPS, will be presented by treatment group for the RS. The frequency of patients in different analysis sets will also be analysed for each treatment group.

For in-text tables presenting descriptive analysis of the endpoints and other variables (analysed in original scale), the set of summary statistics is: N (number of patients with nonmissing values), mean, SD.

For end-of-text tables, the set of summary statistics is: N (number of patients with nonmissing values) / Mean / SD / Min / Q1) / Median / Q3 / Max.
Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline “Standards for Reporting of Clinical Trials and Project Summaries” (6).

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are actually missing values. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not.

In all specified statistical analyses, treatment comparisons will be made between randomised empagliflozin group and placebo.

Descriptive statistics on the impact of COVID-19 on study visits as well as trial medication intake will be provided if any.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive analysis of the following demographic variables measured at baseline will be presented:

Sex, age (in years), age groups, BMI (kg/m^2), BMI categories, history of hypertension(Yes / No), height (cm), duration of diabetes (categories based on years), renal impairment (eGFR using MDRD formula), HbA1c (%) and HbA1c categories. Categories for baseline characteristics are defined in Section 6.4.

Demographic and baseline characteristics tables will be presented for the FAS. A summary of the number of patients in each randomisation strata per treatment will also be shown. This will be based upon the data received from the IRT provider.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report using the FAS.
Concomitant medication use will be summarised by WHO ATC level 3 (ATC3) and preferred name. Summaries will be presented for concomitant therapies taken during randomised

treatment, taken at baseline and those newly introduced during ramdomised treatment. Separate summaries of use of acetylsalicylic acid (ASA), antihypertensives or lipid lowering drugs at baseline by preferred name will be presented. The following codes from the SDGs will be used to define ASA, antihypertensives and lipid lowering drugs:

- ASA: 50000019
- Antihypertensives: 0000000049
    - Adrenergic receptor agonists: 0000000051
    - Adrenergic receptor antagonists: 0000000050
    - Angiotensin converting enzyme (ACE) inhibitors: 0000000053
    - Angiotensin II receptor antagonists: 0000000054
    - Calcium channel blockers: 0000000769
    - Renin inhibitors: 0000000095
    - Other antihypertensives: 0000000055
- Lipid lowering drugs: 6000000014
    - Niacin: 6000000008
    - Fibrates: 6000000009
    - Statins: 0000000096
    - Ezetimibe: 50000014
    - PCSK9: 50000011
- Other lipid lowering drugs: 6000000010

Concomitant diseases will be summarised by MedDRA SOC and PT. Relevant medical history by treatment group will also be presented. Both summaries will be presented using the FAS.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. The number and percentage of patients with overall compliance will be reported. The sum of all reported compliance over the planned visits (disregarding run-in) will be divided by the total duration (until last visit where medication is returned) to derive the overall compliance. The FAS will be considered.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

The primary analysis will be performed on the FAS (OC). The primary analysis is an REML-based MMRM approach comparing the change from baseline in HbA1c after 52 weeks of treatment. All randomised treatment groups will be included in the same analysis.

The primary analysis model will be: HbA1c change from baseline at each on-treatment visit = baseline HbA1c + age + baseline renal function + sex + visit by treatment interaction + random error,
where ‘baseline renal function’, ‘sex’ and ‘visit by treatment interaction’ are fixed classification effects, and ‘baseline HbA1c’ and ‘age’ are linear covariates.

In all modelling, the variable 'baseline renal function' will be defined as last eGFR value before first intake of study treatment categorised according to the CKD staging. Note that baseline renal function refers to the eGFR categorization (>=60 mL/min/1.73 m^2, <60 mL/min/1.73 m^2). Such categorization is applicable to the analysis of other endpoints as well.

For each patient, the error terms from all the visits represent the within-patient variability, and are assumed to follow a multivariate normal distribution with an unstructured covariance matrix. If an unstructured (co)variance structure fails to converge, the following structures will be tested: compound symmetry, variance components and Toeplitz. The (co)variance structure converging to the best fit, as determined by Akaike's information criterion, will be used. This rule will also be used for other MMRM analyses unless otherwise stated.

The treatment effect will be estimated on the basis of the least square mean treatment difference at week 52 extracted from the primary analysis model.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals).

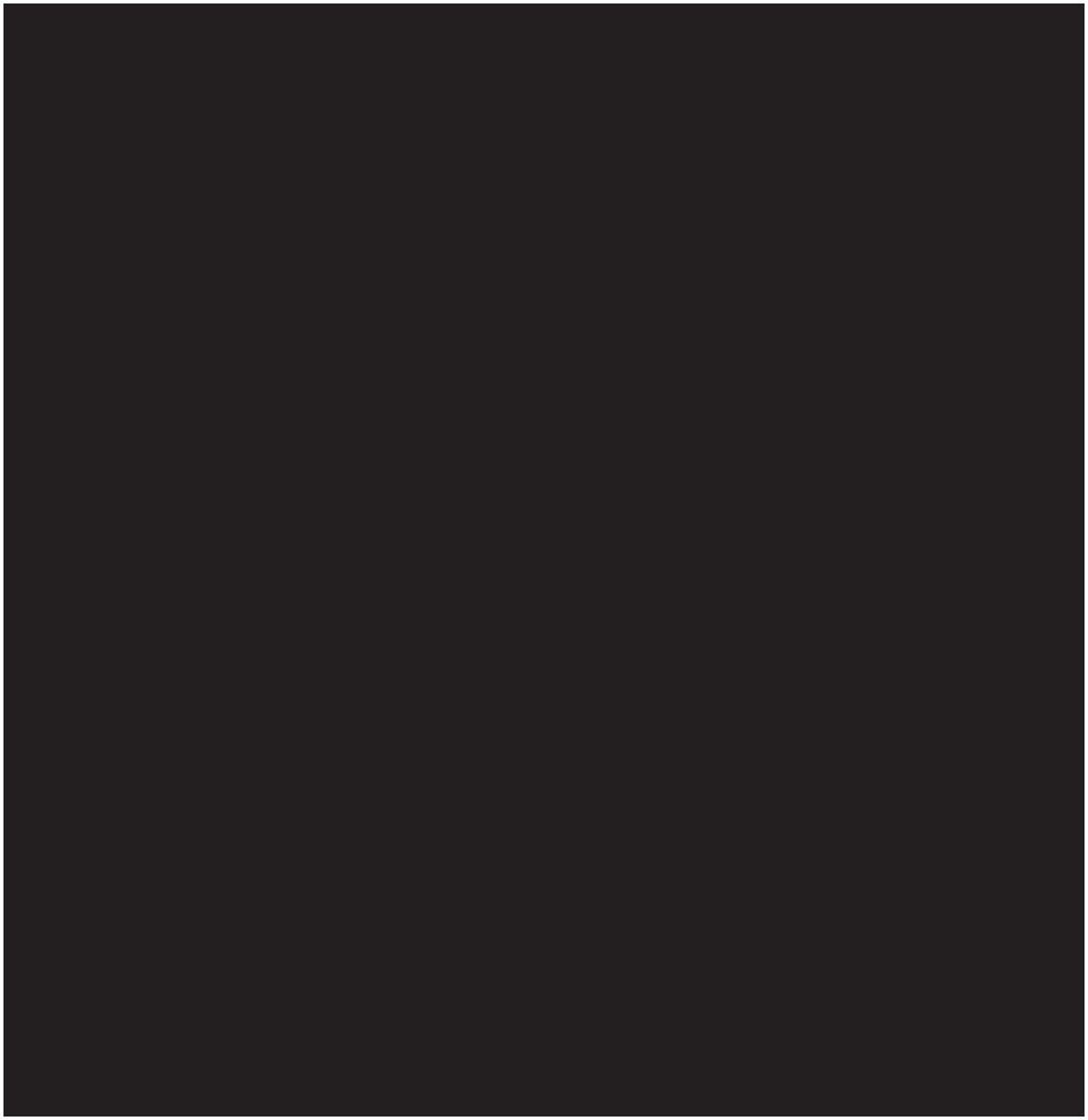
7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

Not applicable.

7.5.2 (Other) Secondary endpoint(s)

Refer to Section 7.8.5 for the analyses of secondary endpoints.



7.7 EXTENT OF EXPOSURE

A descriptive statistics table with mean, SD, median and range of the number of days a patient was on treatment will be provided for the TS. The tables will also provide the sum total of the time (in years) that all patients pooled together were on treatment. A separate listing will be created of any patients that switched treatment at any time indicating exposure to each treatment. A frequency table of number and percent of patients belonging to each categorical range of exposure weeks will be provided as well. The following are the categories of exposure-ranges (in weeks):
0 to <4, 4 to <12, 12 to <24, 24 to <36, 36 to <51 and >=51.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse Events

AEs will be coded using the latest version of the MedDRA coding dictionary at DBL. The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs (NOT the number of AEs). For analysis of multiple AE occurrences, data from the eCRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (including LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest and also additional information of specific AEs or AESIs.
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarization of AE data, please refer to the guideline “Analysis and Presentation of Adverse Event Data from Clinical Trials” (7).

7.8.1.1 Assignment of AEs to treatment

The analysis of adverse events will be based on the concept of treatment emergent adverse events. This means that all adverse events occurring between first drug intake until 7 days after last drug intake will be assigned to the first treatment received. All adverse events occurring before first drug intake will be assigned to 'pre-treatment' and all adverse events occurring after last drug intake + 7 days will be assigned to 'post-treatment'.

7.8.1.2 AE summaries

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary SOC and PT.

AEs will also be reported by intensity. Separate tables will be provided:

- for patients with adverse events of special interest (AESI),
- for patients with serious adverse events,
- for patients with AEs leading to discontinuation,
- for patients with AEs leading to death,
- for patients with drug-related AEs.

The SOCs will be sorted according to the standard sort order specified by EMA, and PTs will be sorted by frequency (within SOC).

7.8.1.3 Analysis of hypoglycaemic events

The investigator will record for each AE whether it represents a hypoglycaemic event and, if so, record additional information to assess the intensity of the hypoglycaemic event. On the basis of this information the hypoglycaemic event will be classified as:

- confirmed hypoglycaemic adverse event are defined as hypoglycaemic adverse events that had a glucose concentration ≤ 70 mg/dL or required assistance.
- severe hypoglycaemia: event requiring assistance.
- hypoglycaemia event with blood glucose level <54 mg/dL (<3.0 mmol/L), even if asymptomatic.
- symptomatic hypoglycaemia, independent of the blood glucose value (this includes cases when the blood glucose was not measured during the event, but hypoglycaemia was diagnosed based on the clinical presentation).

The number of patients with hypoglycaemia according to investigator's judgement will be tabulated by treatment group. A subgroup analysis of confirmed events with respect to age category, rescue therapy and renal function will be performed.

The impact of treatment on the occurrence of hypoglycaemia will be explored using logistic regression model involving treatment and continuous baseline HbA1c. Time to the onset of the first hypoglycaemia will be estimated by Kaplan-Meier method. The logistic regression and Kaplan-Meier analysis will be performed on confirmed events as for all hypoglycaemia tables.

Summaries of hypoglycaemic events will include total number of hypoglycaemic events, descriptive hypoglycaemic event rate, number of episodes per patient, severity and intensity of the worst episode, action taken, minimum glucose level of worst episode, and time to onset of first episode. Hypoglycaemic events will also be summarised by baseline eGFR using MDRD formula, background medication and age group.

Different tables will be shown for (i) patients with investigator defined asymptomatic or symptomatic hypoglycaemia reported as AE, (ii) patients with confirmed hypoglycaemic adverse events, i.e. hypoglycaemic adverse events that had a plasma glucose concentration ≤ 70 ml/dL or required assistance, and, (iii) patients with minor, confirmed hypoglycaemic adverse events, defined as a hypoglycaemic event that had a plasma glucose concentration ≤ 70 mg/dL but did not require assistance.

7.8.1.4 AEs of special interest (AESI)

The protocol defines the following adverse events that for analysis purposes will be considered as AESIs:

- Decreased renal function
- Hepatic injury
- Diabetic ketoacidosis (DKA)
- Events leading to lower limb amputation

Events of these AESIs are identified through the AE being flagged by the investigator as an AESI on the CRF.

AE frequency tables will be created for renal and hepatic events based on narrow SMQs.
Renal: 20000003 Acute renal failure
Hepatic: 20000008 Liver related investigations, signs and symptoms (SMQ)
20000009 Cholestasis and jaundice of hepatic origin (SMQ)
20000010 Hepatitis, non-infectious (SMQ)
20000013 Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions

The frequency of patients with DKA will be summarised based on the applicable BIcMQ at the time of the analysis.

The frequency of patients with events leading to lower limb amputation will be summarised.

In addition, muscle weakness will be tabulated by treatment group, which will be defined by the PTs of Sarcopenia, Muscular weakness, Muscle atrophy, Muscle fatigue and Myopathy.

7.8.1.5 Events qualifying for external adjudication by the Clinical Event Committee (CEC)

An independent external CEC regularly reviews events and evaluates whether pre-specified criteria for these adjudication endpoints are met. Details on composition of the CEC, responsibilities and clinical event definitions are provided in a separate CEC Charter.

The CEC will be provided with additional, specified background material on the patients with these events and perform an assessment of the events.

Adjudication assessments will be incorporated to the database. Frequency tables will be provided for the PTs in the specified SMQs of events and for the adjudication endpoints. Tables will be provided for events qualifying for adjudication and then separately the events that were confirmed or non-assessable.

7.8.1.6 Analysis of adjudicated events

DKA and hepatic events will be adjudicated by an external expert committee. The patients with adjudicated hepatic events will be summarized.

7.8.1.7 AEs while patients taking wrong medication

A listing will be provided for AEs that occurred while a patient was taking the wrong medication. If such a patient is identified, an additional adverse event table that assigns the adverse events to the actual treatment taken will be presented. A patient who took both the assigned treatment and at least one tablet of the wrong treatment, will be counted as at risk in both treatment groups for the respective relevant time. The table will include all adverse events by SOC and PT.

7.8.1.8 COVID-19 related analyses

The subgroup of patients with SARS-COV-2 infection will be analysed. SARS-COV-2 infections will be defined by the narrow BIcMQ SARS-COV-2 infection. All analyses will be repeated using the broad instead of the narrow BIcMQ.

An overview of adverse events will be presented for this subgroup of patients. Additionally, the number of patients with adverse events, the number of serious AEs and AEs leading to discontinuation of study treatment will be presented by treatment, primary SOC and PT.

A listing will be prepared presenting all SARS-COV-2 infections.

7.8.2 Laboratory data

For continuous safety laboratory parameters, standardised and normalised values will be derived as well as the differences to baseline. The process of standardisation and normalisation as well as standard analyses for safety laboratory data are described in the BI guidance for the "Handling, Display and Analysis of Laboratory Data" (8). All analyses considering multiple of times ULN will be based on original and not normalised data.

The frequency of the number of patients with AST/ALT elevations ≥ 3xULN, ≥ 5xULN, ≥ 10xULN, and ≥ 20xULN will be displayed.

To support analyses of liver related adverse drug effects, patients with AST and/or ALT ≥ 3xULN with concomitant or subsequent TBILI ≥ 2xULN in a 30 day period after AST/ALT elevation are of special interest.

The start of the 30 day time span is triggered by each liver enzyme elevation above the defined thresholds. Patients who fulfil one or two of the criteria for ALT/AST or total bilirubin elevations above and has no information available for the remaining parameter(s) at the same time-point or within the 30 day time window will not be listed under "ALT and/or AST ≥ 3xULN with Total Bilirubin ≥ 2xULN".

Patients with elevations as described will be summarised and stratified by Alkaline phosphatase < 2xULN and ≥ 2xULN.

All calculations for the grading of renal function will be based on the originally measured laboratory values and the ULNs given by the laboratory, not on normalised values with BI standard reference ranges. The glomerular filtration rate will be estimated according to the MDRD formula (please see Table 6.4: 1) and stored in the trial databases.

For the analysis of eGFR and for the covariates in the statistical modelling, the values calculated by the MDRD formula using the serum creatinine values from the central laboratory will be used, not the eGFR values provided by the central laboratory. For the assignment of iPDs based on renal function the central laboratory values will be used.

To support analysis of renal function, eGFR throughout the trial will be categorised according to the MDRD staging shown in Table 7.8.2: 1.

Table 7.8.2: 1 MDRD staging

Stage	eGFR [mL/min/1.73m^2]	Description
1	≥ 90	Normal renal function
2	60 to < 90	Mild renal impairment
3A	45 to < 60	Moderate renal impairment A
3B	< 45	Moderate renal impairment B to end-stage renal impairment

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (see DM&SM: "Handling, Display and Analysis of Laboratory Data") (8).

Baseline for safety laboratory parameters will be the last available measurement before the start of randomised trial medication. Laboratory measurements taken up to 3 days after the last administration of randomised trial medication will be considered as on-treatment.

Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range at baseline and the last measurement on treatment. Descriptive statistics will be provided by treatment group for baseline, on-treatment values and for changes from baseline. Frequency tables will summarise the number of patients with potentially clinically significant abnormalities. Details on patients with elevated liver enzymes will be listed. Summaries will also be presented for patients with elevated liver enzymes.

A summary will also be created representing the number of patients per treatment group that experienced a doubling in creatinine on treatment compared to baseline that was out of the normal range.

Only patients with at least one available on-treatment value will be included in the analysis of an individual laboratory parameter. All individual data will be presented in listings.

A shift table from baseline to last value on treatment for eGFR using MDRD formula will also be provided.

7.8.3 Vital signs

Vital signs (SBP, DBP and pulse rate) will be taken at Screening (Visit 1) through EOT (Visit 8). Only descriptive statistics are planned for the summary of vital signs for baseline, on-treatment and change from baseline by visit. Descriptive statistics will also be shown graphically for SBP and DBP.

7.8.4 ECG

12-lead ECG measurements will be taken at baseline (Visit 3) and EOS (Visit 9). ECG-findings before first intake of trial medication will be considered as baseline condition. Any clinically significant new findings in the ECG measurement after the first ECG will be considered as AEs and analysed as planned in Section 7.8.1.

7.8.5 Others

Time curve analysis
Descriptive statistics will be presented in tables for creatinine, eGFR, haematocrit, haemoglobin and weight over time by treatment. Presented values will be used to create plots of the parameters over time.

In addition, tables of descriptive statistics for creatinine, eGFR values will also be presented for age subgroups.

Secondary endpoints analyses
Secondary endpoints in this trial only provide one post-baseline assessment (no repeated measurements). ANCOVA will be performed to compare the change from baseline in each of the continuous secondary endpoints at week 52 on the TS (OC-IR).

The statistical model will be: Change from baseline in secondary endpoint after 52 weeks = baseline secondary endpoint + age + sex + treatment + BMI + baseline HbA1c + random error.

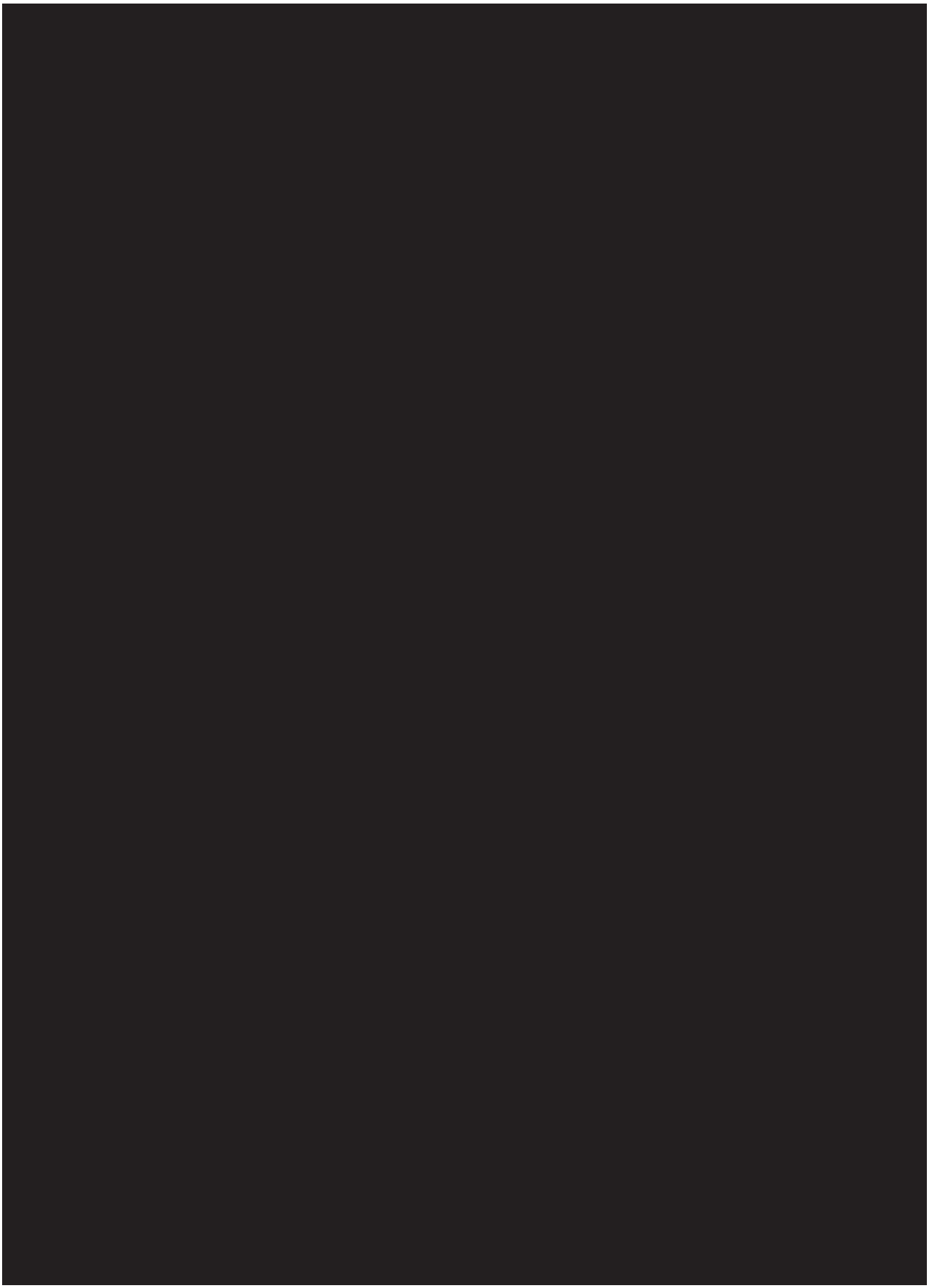
In addition, descriptive statistics will be provided by visit including actual values and change from baseline values in the abovementioned secondary endpoints at Week 52. Descriptive statistics will also be presented with boxplots in each group both at baseline and at Week 52.

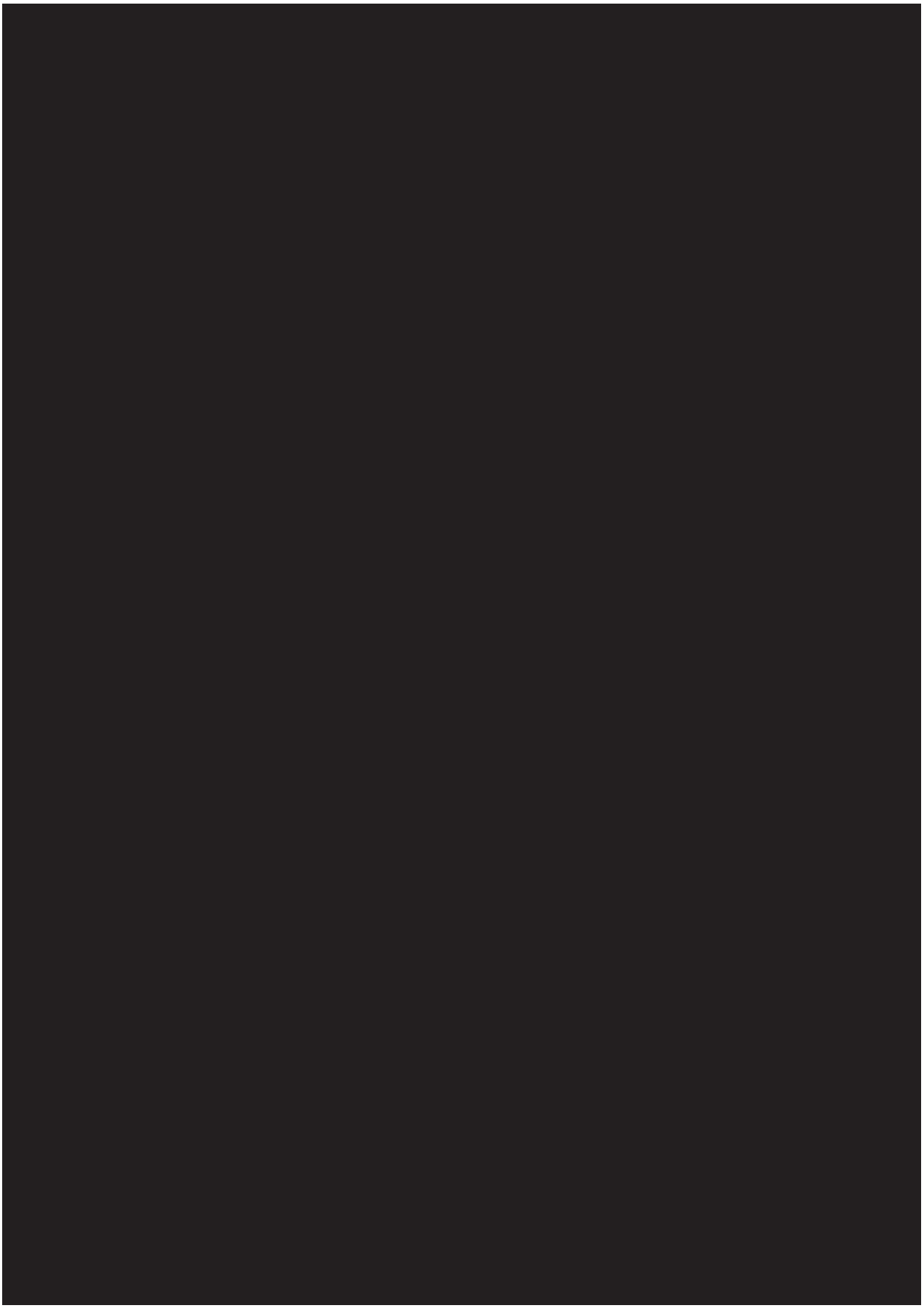
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study/Follow-up visit and all data has been entered and cleaned as defined in the “Data Ready to be Unblinded and/or Final Trial Closure Notification” (RUN) form.

9. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
[redacted]	[redacted]
[redacted]	[redacted]
4.	*001-MCS-40-413: Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", IDEA for CON.*
5.	*BI-KMED-BDS-HTG-0035: "Handling of missing and incomplete AE dates", current version; KMED.*
6.	*BI-KMED-BDS-HTG-0045: "Standards for Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.*
7.	*BI-KMED-BDS-HTG-0041: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED.*
8.	*BI-KMED-BDS-HTG-0042: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.*
[redacted]	[redacted]





11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**09-MAY-22**	[redacted]	None	This is the final TSAP

APPROVAL / SIGNATURE PAGE

Document Number: c35189692 **Technical Version Number:1.0**

Document Name: 8-01-tsap

Title: A randomised, double-blind, placebo-controlled, parallel group, 52 weeks phase IV trial to evaluate efficacy and safety of oral, once daily empagliflozin in elderly Japanese patients with type 2 diabetes mellitus and insufficient glycaemic control

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	10 May 2022 06:53 CEST
Approval-Project Statistician		10 May 2022 07:58 CEST
Approval-Team Member Medicine		10 May 2022 08:11 CEST
Approval-Medical Writer		10 May 2022 09:33 CEST
Approval-Clinical Trial Leader		12 May 2022 03:14 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed