Trial Statistical Analysis Plan

c18322796-01

BI Trial No.:	1245.106
Title:	A 52-week randomised, double-blind, parallel group, safety and efficacy study of empagliflozin once daily as add-on therapy to glucagon-like peptide-1 receptor agonist in Japanese type 2 diabetes mellitus patients with insufficient glycaemic control Including Protocol Amendment 1 [c03122586-02] Including Protocol Amendment 2 [c03122586-03]
Investigational Product(s):	Jardiance®, Empagliflozin
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	29 JUN 2017, SIGNED
Version:	FINAL

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical classification
BI	Boehringer Ingelheim
BIcMQ	BI-customised MedDRA query
BLQ	Below the limit of quantification
BMI	Body mass index
BRPM	Blinded report planning meeting
CT	Concomitant therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Data base lock
DBP	Diastolic blood pressure
DKA	Diabetic ketoacidosis
eCcr	Estimated creatinine clearance rate
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoT	End of treatment
FAS	Full analysis set
FFA	Free fatty acid
FPG	Fasting plasma glucose
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein

Term	Definition / description
ICH	International Conference on Harmonisation
ITT	Intention-to-treat
IRT	Interactive response tool
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LOCF-IR	Last observation carried forward including values after rescue
LLQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NCF	Non-completers considered failure
OAD	Oral antidiabetic drug
OC	Observed cases
OC-IR	Observed case including values after rescue
OR	Original results
PPS	Per protocol set
PT	Preferred term
PV	Protocol violation
Q1	First quartile
Q3	Third quartile
SBP	Systolic blood pressure
SCR	Screened patients set
SD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System organ class
TBILI	Total bilirubin
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
ULQ	Upper limit of quantification
UTI	Urinary tract infection

3. INTRODUCTION

As per ICH E9, 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 Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in 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 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

No changes in the planned analysis.

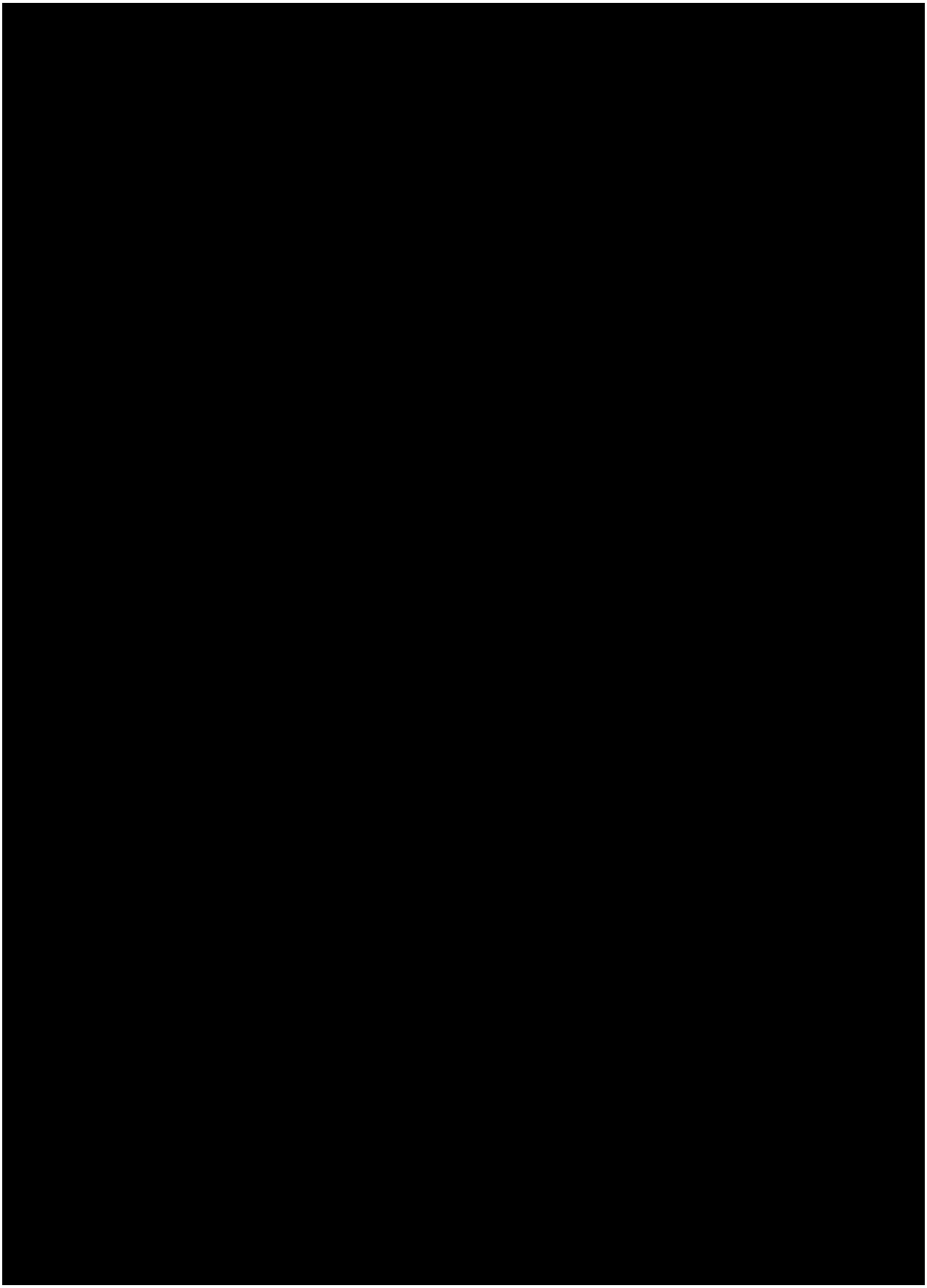
5. ENDPOINTS

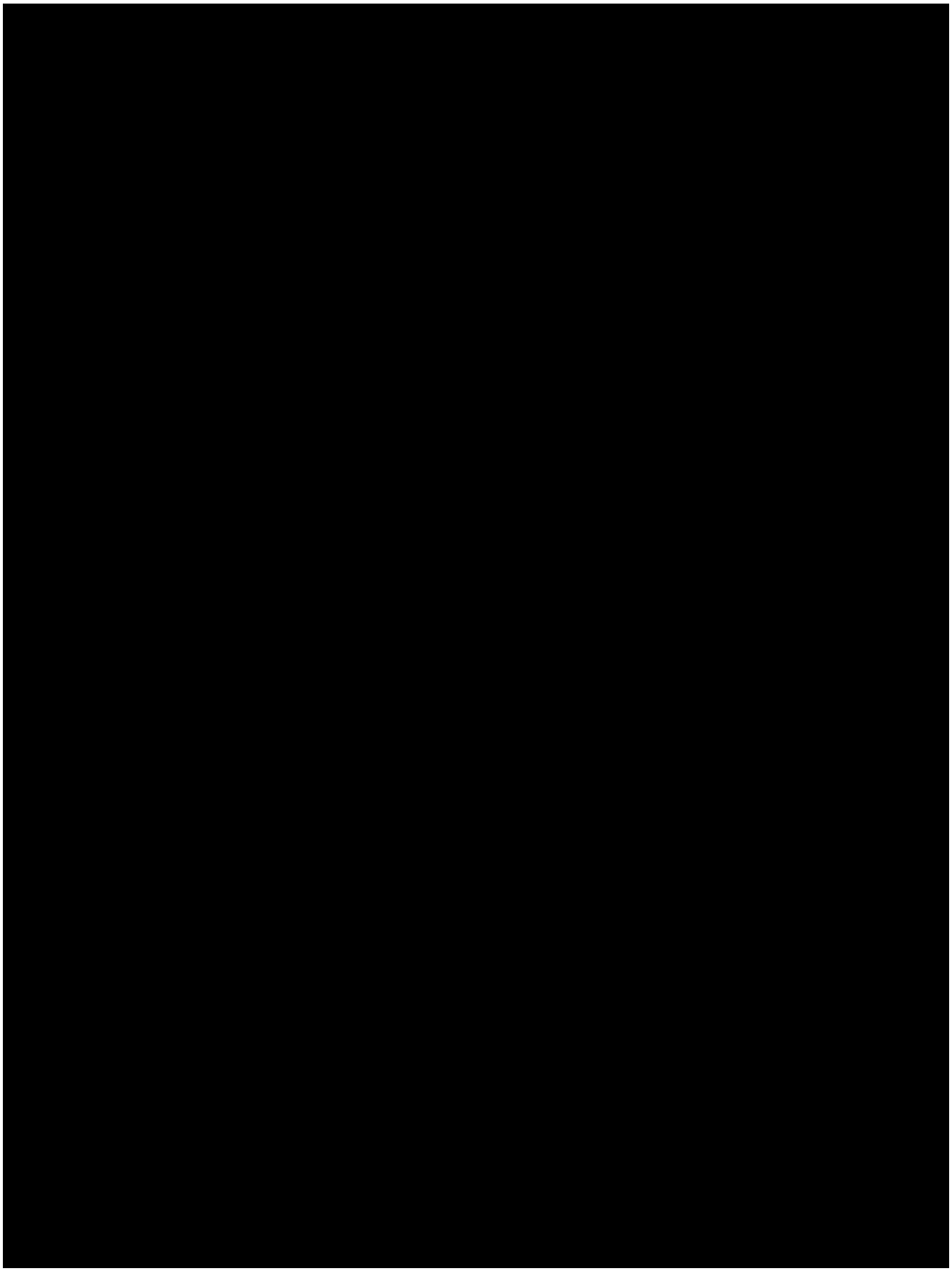
5.1 PRIMARY ENDPOINT

The primary endpoint of the trial is the proportion of patients with drug-related adverse events (AE) during 52 weeks of treatment with empagliflozin as add-on to GLP-1 RA (i.e. liraglutide).

5.2 SECONDARY ENDPOINT

The secondary endpoint is the change in HbA1c from baseline after 52 weeks of treatment of empagliflozin as add-on to GLP-1 RA (i.e liraglutide).





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For efficacy analyses, data up to 7 days after last treatment intake will be considered as on-treatment for HbA1c and waist circumference, and 1 day for all other efficacy endpoints. For safety analyses, data up to 7 days after last treatment intake will be considered as on-treatment for AEs, 3 days for safety lab measurements and 1 day for pulse rate. For further details see Table 6.7: 1. For this purpose, the following treatment regimens and study intervals will be defined in Table 6.1: 1. More detailed information is provided in the trial Analysis Data Set plan.

Table 6.1: 1 Treatment regimens / study intervals

Label	**Interval**	**Start date**	**Start time**
Screening	Screening period	Date of informed consent	00:00
Run-in*	Placebo Run-in period	Date of first administration of placebo medication	Time of first administration of placebo medication, 12:00 if missing
• Empa10 mg/ Placebo for Empa25 mg • Empa25 mg/ Placebo for Empa10 mg	Double-blind treatment period	Date of first administration of 52-week double-blind study medication	Time of first administration of 52-week double-blind study medication, 12:00 if missing
Post-treatment	Post-treatment	Date of last intake of study drug + X** +1 day	00:00
Post-study	Post-study	Last contact date +1 day	00:00

* There is switch period which consists of titration period and washout period between screening period and placebo run-in period. After screening period, patients of inclusion criterion 2-A proceed to placebo run-in period, patients of inclusion criterion 2-B proceed to washout period prior to placebo run-in period, patients of inclusion criterion 2-C proceed to titration period then washout period prior to placebo run-in period.

** The endpoint specific follow-up periods for the assignment to active treatment are presented in detail in Section 6.7.

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 assign patients to the treatment group as treated. If a patient erroneously receives the wrong trial drug, the patient will be analysed as per the first treatment received.

Additionally, the AEs with an onset during the time of the incorrect study treatment will also be tabulated and listed separately.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Violations that lead to exclusion from analysis populations are indicated as such in Table 6.2: 1.

The final decision about which patients will be excluded from analysis sets will be taken during the course of the study and finalised at the medical quality review meeting or last blinded report planning meeting (BRPM).

Table 6.2: 1 Important PVs

Category / Code		Description	Comment/Example	Exclude from	Program/ manual?*
A		**Entrance criteria not met**			
A1		**Target indication not met**			
	A1.01	No type 2 diabetes	IN1	None	Program
	A1.02	Antidiabetic background therapy not as required	IN2 *detect manually for cleaning*	None	Program
A2		**Inclusion criteria not met**			
	A2.01	HbA1c out of range	HbA1c out of range for IN2(A), IN2(B), or IN2(C) by >0.2%	None	Program
	A2.02	Age out of range	IN3	None	Program
	A2.03	BMI out of range	IN4	None	Program
A3		**Exclusion criteria violated**			
	A3.01	Uncontrolled FPG level	EX1 *detect manually for cleaning*	None	Program
	A3.02	Additional background therapy	EX2 *detect manually for cleaning*	None	Program
	A3.03	Relevant concomitant diagnoses	EX3, 7	None	Program
	A3.04	Bariatric or other relevant gastrointestinal surgery within the past two years	EX6	None	Program
	A3.05	Blood dyscrasias or any disorders causing hemolysis or unstable red blood cell count	EX8	None	Program
	A3.06	Indication of liver disease	EX4	None	Program
	A3.07	Contraindication to liraglutide or empagliflozin	EX9, 10	None	Program
	A3.08	Treatment with protocol excluded anti-obesity drugs	EX12 *Forbidden CTs list will be reviewed for cleaning*	None	Program + CT list
	A3.09	Renal insufficiency or renal impairment (assessed by eGFR)	EX5	None	Program
	A3.10	Treatment with protocol excluded systemic steroids or recent change in thyroid hormone dose	EX13 *Forbidden CTs list will be reviewed for cleaning*	None	Program + CT list

*For "Program", ADS will be created by program. For "manual", ADS will be created by important excel spread sheet.
CT: Concomitant therapy, IRT: Interactive response tool, DBL: Data base lock, FAS: Full analysis set, TS: Treated set, eCRF: electronic case report form

Table 6.2: 1 (cont'd) Important PVs

Category / Code		Description	Comment/Example	Exclude from	Program/ manual?*
	A3.11	Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial	EX16 (Medical judgement), depending on the type of drug given in the prior trial (only if investigational drug interferes with glucose metabolism).	None	Program
	A3.12	Specific exclusion criterion for pre-menopausal women violated	EX14	None	Program
	A3.13	Relevant alcohol or drug abuse and other conditions affecting study compliance	EX15	None	Program
	A3.14	Any other clinical condition unsafe for participation that would jeopardise patient safety while participating in this clinical trial	EX17	None	Program
	A3.15	Liraglutide dose prior to or during placebo run-in period not as required	EX11	None	Program
B		**Informed Consent**			
	B1	Informed consent not given	Date of informed consent missing, or No signature on patient's "Declaration of Informed Consent" *Patient's data will not be used at all.*	All	Program
	B2	Informed consent too late	Date of informed consent not obtained prior to any study related procedure.	None	Program
C		**Trial medication and randomisation**			
C1		**Incorrect trial medication taken**			
	C1.01	No study medication taken	Patient randomised but no study medication taken.	TS	Program
	C1.02	Incorrect trial medication taken	Wrong medication taken for more than 20% of the overall treatment duration. Can only be finally judged after DBL since unblinding information is required.	None	Manual
C2		**Randomisation not followed**			
	C2.01	Treated without randomisation	Patient was treated, but not randomised according to IRT.	None	Program

*For "Program", ADS will be created by program. For "manual", ADS will be created by important excel spread sheet.
CT: Concomitant therapy, IRT: Interactive response tool, DBL: Data base lock, FAS: Full analysis set, TS: Treated set, eCRF: electronic case report form

Table 6.2: 1 (cont'd) Important PVs

Category / Code		Description	Comment/Example	Exclude from	Program/ manual?*
C3		**Non-compliance**			
	C3.01	Non-compliance with study drug intake	Overall study treatment compliance outside 80% and 120% (exclusive) or study treatment compliance below 80% in the last visit interval.	None	Program
	C3.03	Last treatment more than 7 days prior to next visit	Last treatment more than 7 days prior to next visit.	None	Manual
C4		**Medication code broken**			
	C4.01	Medication code broken without just cause	Medication code was broken for no valid reason.	None	Manual
D		**Concomitant medication**			
	D2	**Prohibited medication use**			
	D2.01	Use of prohibited medication during treatment period	Review of eCRF for prohibited medication. *Forbidden CTs list will be reviewed*	None	Manual + CT list
E		**Missing data**			
	E1.01	No baseline HbA1c value	No valid baseline HbA1c value	FAS	Program
G		**Trial specific**			
G3		**Other trial specific violation**			
	G3.13	Prohibited antidiabetic medication	More than 14 days of insulin treatment or any duration of other antidiabetics	None	Program
	G3.17	Change of background antidiabetic therapy	Increase with/without AE or decrease with reason "Other" during double blind treatment period	None	Program
I		**Other safety related violations**			
I1		**Violations regarding ECG**			
	I1.01	First ECG after drug intake and ECG-related adverse event at baseline		None	Manual
	I1.02	ECG Missing at a visit where ECG was planned		None	Manual
I2		**Pregnancy monitoring**			
	I2.01	Pregnancy		None	Program
	I2.02	Pregnancy test not done for woman of child bearing potential for at least one visit before treatment discontinuation		None	Program
I4		**Misuse of study drug**			
	I4.02	Administration of unsealed medication kit		None	Manual

*For "Program", ADS will be created by program. For "manual", ADS will be created by important excel spread sheet.
CT: Concomitant therapy, IRT: Interactive response tool, DBL: Data base lock, FAS: Full analysis set, TS: Treated set, eCRF: electronic case report form

6.3 PATIENT SETS ANALYSED

The following analysis sets will be defined for this trial.

Screened set

The screened set (SCR) will consist of all patients who were screened for the trial with informed consent given and completed at least one screening procedure at visit 1.

Randomised set

The randomised set (RS) will consist of all patients in the screened set who were randomised to study drug, regardless of whether any study drug was taken.

Treated set

The treated set (TS) will consist of all patients who were randomised and treated with at least one dose of the study drug. The assignment of patients to treatment group will be based on the first study drug intake in the double-blind treatment period.

Full analysis set

The full analysis set (FAS) will consist of all patients in TS who were treated with at least one dose of the randomised study drug and had a baseline HbA1c assessment. The assignment of patients to treatment groups will be based on the randomised study drug at time of randomisation.

Table 6.3: 1 Patient sets analysed

Class of endpoint	SCR	TS	FAS
Secondary efficacy endpoints			OC, OC-IR, LOCF
Other continuous efficacy endpoints			OC, LOCF
Other binary efficacy endpoints			NCF
Primary safety endpoints		OR	
Other safety endpoints		OR, OC-IR, LOCF-IR	
Disposition	OR		
Demographic			OR
Baseline endpoints			OC

OR: Original results, LOCF-IR: Last observation carried forward including values after rescue, OC-IR: Observed case including values after rescue, NCF: Non-completers considered failure

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 efficacy endpoints of this trial, depending upon the type of the endpoint (see Table 6.3: 1).

Original result (OR) analysis

OR analysis implies the analysis of data exactly as observed, no time windowing as described in Section 6.7. OR analysis will be performed on endpoints that are either not affected by patients' rescue medication use (see Section 5.4.2) or if it is not meaningful to apply any imputation rule on them for replacing the missing values.

Observed cases (OC) analysis

For all efficacy endpoints, it is planned to analyse only the available data that are observed while patients are on treatment. In other words, missing data will not be replaced in the OC analysis. The time window as described in Section 6.7 is to be considered in the OC approach. For all efficacy endpoints, this OC-technique will set to missing for all values measured after the first day of taking rescue medication (see Section 5.4.2).

For lipid parameters, it is planned to analyse by using OC- technique but including the original observed values after taking rescue medication. That is called OC including values on rescue medication (OC-IR).

Last observation carried forward (LOCF)

For quantitative endpoints, missing values will be replaced by the last observed measurement on treatment. If the patient has no on-treatment value, baseline value will be carried forward. This method tends to result in more conservative estimates than an OC-analysis. The values measured after taking rescue medication during the treatment period will be set to missing, and these missing values will be imputed by LOCF approach.

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

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.

Let:

D_0 = date of a visit with a missing endpoint value;

D_1 = date of the next-visit (with end-point value non-missing) after the visit with a missing endpoint;

D_{-1} = date of the previous-visit (with end-point value non-missing) before the visit with a missing endpoint;

E_i = endpoint values for visits D_{-1}, D_0, D_1 for i=-1, 0 and 1)

Then the missing endpoint value can be interpolated as:

$$E_0 = E_{-1} + ((E_1 - E_{-1}) \times (D_0 - D_{-1}) / (D_1 - D_{-1})).$$

For lipid parameters, it is planned to analyse by using LOCF- technique but including the original observed values after taking rescue medication. That called LOCF including values on rescue medication (LOCF-IR).

Non-completes considered failure (NCF)

For binary endpoints, a conservative method to replace missing values is to consider them as “failures”. Missing data due to early discontinuation will be replaced as “failure” up to the planned final visit. The values measured after taking rescue medication will be replaced as “failure”.

For binary endpoints that are derived from quantitative endpoints, 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.

Safety and other variables

Missing safety data will not be replaced, but an analysis of the changes from baseline to the last available value under treatment and the minimum and maximum post baseline will be determined for quantitative safety laboratory variables.

Missing dates and times

Missing or partial date information for AEs will be replaced according to general Boehringer Ingelheim (BI) rules described in the BI guidance for "Handling of missing and incomplete AE dates" (1).

If the date of first drug administration is missing but the patient has been 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 is in the same month. If randomisation is 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 in the morning.

As a general rule, a missing drug stop date will be imputed according to the following principles.

- If an End of treatment (EoT) visit is documented, it should be the date of the EoT visit.
- If the date is incomplete with only month and year and the EoT visit is missing, it should be the first day of the following month.
- If the patient is lost to follow-up, it should be the date of the last visit + 1 or the longest treatment duration based on drug supply + 1 day.
- If the patient dies during the course of the trial and no additional information about drug stop date are available, the date of death will be used as drug stop date assuming that the patient takes the medication until the day of death.
- All other cases need to be assessed by the trial team on an individual basis, trying to use the points above as guidance.

If only the year of birth is known, the day and month of birth will be imputed as 01 January. For other incomplete date information always 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.

For partial start and stop dates for concomitant therapies and additional antidiabetic drugs, the following derivations will be used to impute "worst case" values.

- If the day of the end date is missing then end date is set to last day of the month.

- If the day and month of the end date are missing then end date is set to 31st December of the year.
- If the day of the start date is missing then the start date is set to first day of the month.
- If the day and month of the start date are missing then the start date is set to 1st January of the year.
- All other cases need to be assessed by the team on an individual basis, using the above points as guidance.

Values below/above limits of quantifications

For biomarkers (insulin, glucagon) we will replace the values which are below the lower limit of quantification (LLQ) with 2/3 times LLQ. This is approximately the median of the expected "true" value if the biomarker follows a normal distribution. We will replace the values which are above the upper limit of quantification (ULQ) with 3/2 times ULQ. With this approach even a change of the method with different limit of quantifications can be handled within a trial. The number of below the LLQ will be included in the biomarker table.

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 study medication.

Measurements taken prior to the first intake of randomised study medication will be considered pre-treatment values. These pre-treatment values will be assigned to a visit according to the nominal visit number as record on the eCRF or provided by the laboratory.

The date and clock time of the first drug administration will be used to separate pre-treatment from on-treatment values. Measurements taken after the first intake of randomised study drug 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 study drug for efficacy analyses and to the first study drug taken for safety analyses.

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

Table 6.7: 1 Endpoint specific follow-up period for the assignment to active treatment

Endpoint	Last day of assignment to treatment phase (days after study drug stop date)
Efficacy	
HbA1c	7
FPG	1
Body weight	1
Blood pressure	1
Insulin and glucagon	1
Waist circumference	7
Safety	
Adverse events	7
Safety laboratory measurements	3
Pulse rate	1

On-treatment efficacy and safety 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 study drug (usually this is at Visit 7).

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 is endpoint dependent (see Table 6.7: 1).

Table 6.7: 2 Time windows for on-treatment HbA1c, body weight, and waist circumference measurements scheduled for each on-treatment visit

Visit number	Visit label	Planned days	Time window (actual days on treatment) Start	End[A]
7	Baseline	0	NA	1 [B]
9	Week 8	56	2	98
11	Week 20	140	99	196
13	Week 36	252	197	308
15	Week 52/EoT	364	309	Study drug stop date + X days

[A] In case of premature discontinuation of the study drug a Visit 15 has to be performed. If such a Visit 15 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 15 will end X days after the study drug stop date, including Day X. The definition of X is endpoint specific, cf. Table 6.7: 1. As visit 16 is optional, no time window for this visit is planned.

[B] Only values taken prior to the start of treatment with randomised study drug can be considered baseline values. Time windows will be used for assignment of measurements to scheduled visits.

Table 6.7: 3 Time windows for on-treatment FPG, vital sign, and safety lab measurements scheduled for each on-treatment visit

			Time window (actual days on treatment)	
Visit number	Visit label	Planned days	Start	End[A]
7	Baseline	0	NA	1[B]
8	Week 4	28	2	42
9	Week 8	56	43	70
10	Week 12	84	71	112
11	Week 20	140	113	168
12	Week 28	196	169	224
13	Week 36	252	225	280
14	Week 44	308	281	336
15	Week 52/EoT	364	337	Study drug stop date + X days

[A] In case of premature discontinuation of the study drug a Visit 15 has to be performed. If such a Visit 15 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 15 will end X days after the study drug stop date, including Day X. The definition of X is endpoint specific, cf. Table 6.7: 1. As visit 16 is optional, no time window for this visit is planned.

[B] Only values taken prior to the start of treatment with randomised study drug can be considered baseline values. Time windows will be used for assignment of measurements to scheduled visits.

Table 6.7: 4 Time windows for on-treatment biomarkers measurement and bone markers scheduled for each on-treatments visit

			Time window (actual days on treatment)	
Visit number	Visit label	Planned days	Start	End[A]
7	Baseline	0	NA	1[B]
15	Week 52/EoT	364	2	Study drug stop date + X days

[A] In case of premature discontinuation of the study drug a Visit 15 has to be performed. If such a Visit 15 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 15 will end X days after the study drug stop date, including Day X. The definition of X is endpoint specific, cf. Table 6.7: 1. As visit 16 is optional, no time window for this visit is planned.

[B] Only values taken prior to the start of treatment with randomised study drug can be considered baseline values. Time windows will be used for assignment of measurements to scheduled visits.

Repeated and unscheduled efficacy and safety measurements will be assigned to the nominal visits and listed in the Clinical Trial Report (CTR) Appendix 16.2 according to the time windows described above. Only one observation per time window will be selected for analysis at an on-treatment visit – the value will be selected which is the closest to the protocol-planned visit day. If there are two observations that 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. If an observation is available on the last day of treatment, this observation will be preferably selected over any later observation that is still within the time window (not applicable for standard laboratory summaries). If there are multiple values within the time window of the last visit, including a value on the last day of drug intake, the value on the last day of drug intake is used as the value of the last visit.

7. PLANNED ANALYSIS

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.

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.

Disposition of the patient population participating in the trial will be analysed by treatment groups on the SCR and presented in the CTR as a frequency-distribution. Reason for not randomising screened patients will be tabulated on the SCR.

The frequency of patients in different analysis sets will also be analysed for each treatment group.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive analysis of the demographic variables and baseline characteristics described in Section 5.4.1 will be presented on the FAS.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the CTR using the FAS.

CT will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3) and preferred name at baseline and on-treatment on the FAS. Separate summaries of use of antihypertensives, acetylsalicylic acid (ASA), or lipid lowering drugs at baseline by preferred name will be presented on the FAS.

Antidiabetic medication introduced on treatment will be summarised on the FAS.

Concomitant diseases will be summarised by MedDRA system organ class (SOC) and preferred term (PT) on the FAS. Relevant diabetic medical history will also be presented on the FAS.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the CTR. The number and percentage of patients with overall compliance for the study drug will be summarised on the FAS. The overall compliance will be calculated as a weighted average of reported

compliance. 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).

7.4 PRIMARY ENDPOINT

The primary endpoint of this trial is the frequency of patients with drug-related AE during 52 weeks of treatment. Frequency tabulation and descriptive statistics will be used to assess the safety by summarizing drug-related AE during 52 weeks of treatment by treatment group (Empagliflozin 10 mg or 25 mg) based on TS. More details are given in Section 7.8.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary endpoint

[redacted]

Mixed model repeated measures (MMRM)

Restricted maximum likelihood-based MMRM will be performed on FAS (OC) with the following model.

HbA1c change from baseline
= overall mean + treatment + baseline HbA1c + baseline renal function + visit + treatment-by-visit interaction + baseline HbA1c-by-visit interaction + error

In the above MMRM model, “treatment”, “baseline renal function”, “visit” and “treatment-by-visit” interaction are fixed classification effects, “baseline HbA1c” and “baseline HbA1c-by-visit” interaction are covariates.

The term “baseline HbA1c” refers to the last HbA1c assessment prior to the administration of any randomised medication (HbA1c values at Visit 7) and not to the HbA1c measurement used for the stratification in the randomisation.

“Baseline renal function” is a classification variable derived from the categorization of eGFR at baseline as specified in Section 5.4.1 and Table 6.4: 1. For modeling purpose, eGFR categories <90 and ≥90 are used in the model.

Unstructured covariance structure will be used to model the within-patient correlation due to repeated measurements. If the model fails to converge, the following covariance structure

will be tested: compound symmetry, variance components and Toeplitz. The covariance structure, with which the model converges and provides the best fit as determined by Akaike information criterion (AIC), will be used for final analysis. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

Because the change in HbA1c from baseline at each on-treatment visit is used as the outcome variable in the MMRM model, the above model is also used to evaluate the HbA1c change from baseline overtime.

Only the available data which are observed whilst patients are on treatment will be included in the analysis. Missing data are handled implicitly by the above statistical model, rather than by using any imputation. This approach will also additionally set to missing all values measured after the use of restricted antidiabetic medication during the trial (see Section 4.2.2 in CTP).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse events

AEs will be coded using the most recent version of the Medical dictionary for regulatory Activities (MedDRA) coding dictionary.

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. For this purpose, AE data will be combined in a 2-step procedure into AE records.

In a first step, multiple AE occurrence data on the eCRF will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level terms are reported for the occurrences
- The occurrences are 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. Hypoglycaemic events are only collapsed if they occur within 12 hours of each other. The 12 hour period will begin with the first hypoglycaemia onset time. If another event occurs outside this initial 12 hour window a new period for the collapsing will begin.)
- Treatment is not changed between the onset of the occurrences or treatment is changed between the onset of the occurrences, but no deterioration is observed for the later occurrence

In a second step, AE episodes will be condensed into AE records provided that the episodes have been reported with the same term on the respective MedDRA level and that the episodes are assigned to the same treatment. For further details on summarisation of AE data, please refer to the guideline “Handling and summarisation of AE data for CTRs and integrated summaries” (2).

7.8.1.1 Assignment of AEs to treatment

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake till last drug intake + residual effect period (7 days for this trial) will be assigned to the randomised treatment. All AEs occurring before first drug intake will be assigned to ‘screening’ and all AEs occurring after the residual effect period will be assigned to ‘post-treatment’.

7.8.1.2 Analysis of other significant AEs

Other significant AEs will be reported and summarised according to ICH E3 (3).AEs classified as “other significant” will include those non-serious AEs with:

- “action taken = discontinuation” or “action taken = reduced”, or
- Marked haematological and other lab abnormalities or lead to significant CT as identified by the Clinical Monitor/Investigator at a medical quality review meeting or BRPM.

7.8.1.3 AE summaries

An overall summary of AEs will be presented.

The frequency of patients with AEs will be summarised by treatment, primary SOC and PT. AEs will also be reported by intensity. Separate tables will be provided for patients with drug-related AEs, for patients with AEs leading to discontinuation, for patients with serious AEs, for patients with other significant AEs and for patients with AESI.

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

7.8.1.4 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 as described in CTP, Section 5.3.3. On the basis of this information the hypoglycaemic event will be classified as:

- asymptomatic hypoglycaemia: event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤3.9 mmol/L (70 mg/dL),
- documented symptomatic hypoglycaemia with a measured plasma glucose concentration ≥3.0 mmol/L and ≤3.9 mmol/L (≥54 mg/dL and ≤70 mg/dL): event accompanied by typical symptoms of hypoglycaemia,
- documented symptomatic hypoglycaemia with a measured plasma glucose concentration <3.0 mmol/L (<54 mg/dL): event accompanied by typical symptoms of hypoglycaemia but no need for external assistance,
- severe hypoglycaemic episode: event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.
- symptomatic hypoglycaemia and plasma glucose concentration >3.9 mmol/L (70 mg/dL)
- symptomatic hypoglycaemia and plasma glucose concentration not measured

The frequency of patients with hypoglycaemia according to investigator's judgement will be summarised by primary SOC and PT.

Confirmed hypoglycaemic AE is defined as hypoglycaemic AE with glucose value available and below 70 mg/dL or where assistance is required.

Summaries of confirmed hypoglycaemic AEs will include total number of hypoglycaemic AEs (asymptomatic and symptomatic), severity and intensity of the worst episode, action taken, minimum glucose level of worst episode, time to onset of first episode, and number of episodes per patient (asymptomatic and symptomatic).

Subgroup analyses of hypoglycaemic AEs with respect to age category, rescue therapy and renal function will be performed.

Summary table will include rate of confirmed hypoglycaemic AEs by severity, by age categories, and by renal function. For subgroup of age categories and renal function, time at risk for each group will be used.

Time to the onset of the first hypoglycaemia will be analysed by Kaplan-Meier estimates. The Kaplan-Meier analysis will be performed based on confirmed AEs.

Different summaries will be shown for the number of patients with hypoglycaemia (symptomatic, asymptomatic reported as AE, or asymptomatic reported as non-AE), severity of the worst episode, minimum glucose level of worst episode, time to onset of first episode, and number of episodes per patient in the CTR, Appendix 16.1.9.2.

7.8.1.5 Adverse event of special interest (AESI)

Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)

The frequency of patients with metabolic acidosis will be summarized by type and treatment group. Patients with DKA will be retrieved based on narrow BI-customised MedDRA query (BIcMQ) for DKA.

Decreased renal function/Hepatic injury

The frequency of patients with the protocol defined renal and hepatic events (See CTP, Section 5.3.6.1) will be summarised by primary SOC and PT as AESIs. The renal and hepatic events are identified through the AE being flagged as AESI on the eCRF.

AE frequency tables will also 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

Events involving lower limb amputation

The frequency of patients with events leading to lower limb amputation will be summarized by type and treatment group.

7.8.1.6 Analysis of urinary tract infections (UTI) / genital infections

UTIs / genital infection will be tabulated based on the official BIcMQ.

The frequency of patients with UTIs / genital infections based on BIcMQ will be summarised by primary SOC and PT. The frequency tables by sex will also be provided for the UTIs / genital infections.

UTIs / genital infections will be summarised by intensity (mild, moderate, severe), age group, time of occurrence (in the first 3 months of treatment or after), time to onset of first event (0 to ≤3 months, >3 months), duration (<7 days, 7-14 days, >14 days), treatment for the event (no treatment, therapy assigned, hospitalisation), whether leading to discontinuation of treatment, and the number of episodes per patient.

Subgroup analyses of UTIs / genital infections with respect to age group, sex, baseline HbA1c, and history of UTI / genital infections will be performed.

In the analysis of the number of episodes of UTI and genital infection, AEs will be collapsed within each BIcMQ regardless of PT with the collapsing following the description at the start of Section 7.8.1 but the condensing will not be conducted in order to maintain multiple episodes per patient.

Kaplan-Meier time to event analyses will also be presented for the UTIs and genital infections.

7.8.1.7 Analysis of complicated UTI

Complicated UTI includes serious AEs of narrow BIcMQ UTI, all events of sub-BIcMQ pyelonephritis and all events of preferred term Urosepsis. Frequency of patients with complicated UTI will be summarized.

7.8.1.8 Analysis of volume depletion

Volume depletion will be tabulated on the basis of the BIcMQ for overall summary and by age group and renal function based on baseline eGFR.

7.8.1.9 Analysis of adjudicated events

Hepatic events will be adjudicated by an external expert committee. The patients with adjudicated hepatic events will be summarized by treatment and relationship with the trial medication.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (4). Baseline for safety laboratory parameters will be the last available measurement before the start of randomised study drug. Laboratory measurements taken up to 3 days after the last administration of randomised study drug will be considered as on-treatment. For continuous safety laboratory parameters, standardised and normalised values will be derived as well as the differences from baseline. The process of standardisation and normalisation as well as standard analyses for safety laboratory data is described in the BI guideline (4). All analyses considering multiple of times upper limit of normal (ULN) will be based on original and not normalised data.

General laboratory evaluation

Descriptive statistics with normalised values will be provided by treatment group for baseline, on-treatment values and for changes from baseline. 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. Frequency tables for categorical laboratory values categorised by value at baseline and last value on treatment will be shown. Frequency tables will summarise the number of patients with potentially clinically significant abnormalities. In addition, descriptive statistics with normalised values and frequency for categorical laboratory values will be provided for overtime in the CTR, Appendix 16.1.9.2.

General laboratory evaluation will also be provided for bone markers.

Hepatic laboratory parameters

To support analyses of liver related adverse drug effects, patients with following alterations of hepatic laboratory parameters at randomisation at Visit 7 are of special interest:

- An elevation of AST and/or ALT ≥3xULN combined with concomitant or subsequent total bilirubin ≥2xULN in a 30 day period after AST/ALT elevation and/or
- Marked peak aminotransferase (ALT, and/or AST) elevations ≥5xULN

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(TBILI) but have 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 TBILI ≥2xULN” or “ALT and/or AST ≥5xULN”.

Summaries will be presented for patients with elevated liver enzymes. Details on patients with elevated liver enzymes will also be listed.

Renal laboratory parameters

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 creatinine clearance (Ccr) and glomerular filtration rate (GFR) will be estimated according to the two formulas:

- Cockcroft-Gault formula [mL/min]:
  eCcr = (140 – age) x (weight [kg]) x (0.85 if female) / (72 x serum creatinine [mg/dL])
- Japanese equation [mL/min/1.73m²]: eGFR (mL/min/1.73m^2) = 194 x [serum creatinine (mg/dL)]$^{-1.094}$ x [age]$^{-0.287}$ x [0.739 if patient is female]

Age will be considered as a discrete variable for the above calculations, and the age will be from the same visit as the other variables. The weight used in the calculations will be that from the same visit, if available. If a value is not available, an interpolated value from the previous and subsequent visits will be used. If no subsequent value is available an LOCF approach will be used. Baseline values will not be interpolated.

For the analysis of eGFR and for the covariates in the statistical modelling, the values calculated from the above 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 PVs based on renal function, the central laboratory values will be used.

Staging of the eGFR will be categorized according to the following staging:

Table 7.8.2: 1 Japanese equation eGFR staging

Stage	eGFR [mL/min/1.73m²]	Description
1	≥90	Normal renal function
2	60 to <90	Mild renal impairment
3	30 to <60	Moderate renal impairment
4	<30	Severe to end-stage renal impairment

Staging of the eCcr will be categorized according to the following staging:

Table 7.8.2: 2 Cockcroft-Gault eCcr staging

Stage	eCcr [mL/min]	Description
1	≥90	Normal renal function
2	60 to <90	Mild renal impairment
3	30 to <60	Moderate renal impairment
4	<30	Severe renal impairment and beyond (e.g., End-stage renal disease)

Descriptive statistics will be created for creatinine and eGFR values over time. Descriptive statistics for eCcr will be presented in the CTR, Appendix 16.1.9.2. These data will be used to create plots of the parameters over time. Subgroups tables of these descriptive statistics at Week 52 will also be presented for age subgroups.

A summary will also be created representing the number of patients with creatinine on treatment ≥2 x baseline and greater than the upper limit of normal.

A shift table from baseline to last value on treatment for eGFR (Japanese equation) will be provided in the CTR, Section 15 and eCcr (Cockcroft-Gault) will be provided in the CTR, Appendix 16.1.9.2.

In addition, urine albumin and urine albumin / creatinine ratio will be summarised in the CTR. Urine creatinine does not have a reference range and it is determined to calculate the albumin / creatinine ratio. Only the albumin / creatinine ratio will be analysed as for urine creatinine, no normalised values can be derived. In cases where urine albumin values are reported to be below the quantification limits (e.g. <3 mg/L), the albumin / creatinine ratio is determined as missing and will not be replaced by estimated values.

Four summaries will be presented for the descriptive statistics of urine albumin/creatinine ratio by baseline value (normal (<30mg/g), microalbuminurea (30-<300 mg/g) and macroalbuminurea (≥300 mg/g)), descriptive statistics of urine albumin by baseline value (<20mg/L, 20-<200mg/L and ≥200mg/L) and frequency of transitions from baseline based on the before mentioned categories.

Serum lipid parameters/free fatty acid (FFA)

Lipid parameters (Total cholesterol, HDL, LDL, LDL/HDL ratio, Non-HDL, and Triglycerides) and FFA will be analysed using descriptive statistics and MMRM modelling. Descriptive statistics will be shown over time for the TS (LOCF-IR and OC-IR) including change from baseline and percent change from baseline. For each lipid parameter, separate MMRM models will be fitted on the TS (OC-IR) for both change from baseline and percentage change from baseline. The MMRM models will include “baseline lipid” and “baseline HbA1c” as continuous covariates and “treatment”, “baseline renal function”, “visit” and “treatment-by-visit” interaction as fixed effects.

Blood ketone body

Descriptive statistics will be created for blood ketone bodies (total ketone bodies, acetoacetic acid, 3-hydroxybutyric acid) over time.

7.8.3 Vital signs

Only descriptive statistics of pulse rate are planned for this section of the CTR.

7.8.4 ECG

No analysis will be conducted. Any clinically significant new findings in the ECG measurement after the first screening ECG will be considered as AEs.

8. REFERENCES

1	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
2	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", version 5.0; IDEA for CON.
3	*CPMP/ICH/137/95*: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
4	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**29-JUN-17**	[redacted]	None	This is the final TSAP without any modification