Boehringer Ingelheim

Trial Statistical Analysis Plan

c08863148-01

BI Trial No.:	1245.107
Title:	A 52-week randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of empagliflozin once daily, as add-on to insulin in Japanese patients with Type 2 Diabetes Mellitus with insufficient glycaemic control Including Protocol Amendment [c03122592-02]
Investigational Product:	Jardiance®, Empagliflozin
Responsible trial statistician:	Phone: , Fax:
Date of statistical analysis plan:	26 SEP 2017 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
ALQ	Above Limit of Quantification
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical classification
BC	Body composition (set)
BI	Boehringer Ingelheim
BICMQ	BI-customized MedDRA query
BLQ	Below the limit of quantification
BMI	Body mass index
BRPM	Blinded report planning meeting
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 prressure
DI	Disposition index
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
eCcr	Estimated creatinine clearance rate
ECG	Electrocardiogram
eCCr	Estimated creatinine clearance
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EMA	European medicines agency
EoT	End of treatment
FAS	Full analysis set

Term	Definition / description
FPI	Fasting plasma insulin
gCV	Geometric coefficient of variation
gMean	Geometric mean
HbA_{1c}	Glycated haemoglobin
HCRU	Health care resource utilisation
HOMA-IR	Homeostatic model assessment - insulin resistance
HOMA-IS	Homeostatic model assessment - insulin secretion
ICH	International Conference on Harmonisation
INN	International non-proprietary names
IPV	Important protocol violation
IRC	Independent Review Committee
ITT	Intention to treat
IVRS	Interactive Voice Randomisation System
IWRS	Interactive Web Randomisation System
LOCF	Last observation carried forward
LQ	Limit of quantification
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model Repeated Measures
MQRM	Medical Quality Review Meeting
NCF	Non-completers considered failure
O*C	Oracle Clinical
OC	Observed case
OC-IR	Observed cases, including values after rescue
OLS	Open label set
OR	Original results
PK	Pharmacokinetics
PPG	Postprandial glucose
PPS	Per protocol set

Term	Definition / description
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
RS	Randomised set
SBP	Systolic blood pressure
SCR	Screened set
SD	Standard deviation
SDL	Subject data listing
SMQ	Standardised MedDRA query
SOC	System Organ Class
SSC	Special search category
SUB	Sub-searches
TBL	Total bilirubin
TOC	Table of contents
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
UTI	Urinary tract infection
WHO	World Health Organisation

3. INTRODUCTION

As per International Conference on Harmonisation (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 Trial statistical analysis plan (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, randomisation.

SAS® Version 9.2 or later version will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP have already been outlined in the CTP. There are no changes compared to the planned analysis of the study.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint in this study is the change from baseline in HbA_{1c} after 16 weeks of treatment. Throughout the study protocol, the term "baseline" refers to the last observation prior to the administration of any randomised study medication.

5.2 SECONDARY ENDPOINT

The secondary endpoint is proportion of patients with drug-related adverse events during 52 weeks of treatment.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

There will be four treatment phases in this trial: screening, study treatment phase (with 10 mg or 25 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. Note that the term "treatment regimen" can also cover time periods with no active treatment.

Table 6.1: 1 Treatment regimens / study intervals

Label	**Interval**	**Start date**	**Start time**
Screening	Screening	Date of informed consent	00:00
Placebo/ Empagliflozin 10mg/ Empagliflozin 25mg	Treatment	Date of first administration of study medication	Time of first administration of study medication 12:00 if missing
Post-treatment	Post-treatment	Date of last intake of study drug +1 day	00:00
Post-study	Post-study	Date of trial completion (in termination page of eCRF) + 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 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. The only exception will be drug-related adverse events (AE) which will be analysed based on the actual treatment taken at the time of the AE onset. Additionally, the AEs with an onset during the time of the incorrect study treatment will also be listed separately.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Not all important protocol violations (IPV) will generate exclusion from the per protocol population. Violations that lead to exclusion from analysis populations are indicated as such in Table 6.2.1

The decision about which IPV could generate exclusion from analysis sets will be taken during the course of the study and finalised at the last blinded report planning meeting (BRPM).

Table 6.2: 1 Important Protocol Violations

Category / Code		Description	Comment/Example	Excluded from
A		**Entrance Criteria Not Met**		
A1		**Target indication not met**		
	A1.01	No type 2 diabetes	INC1 checked	PPS
	A1.02	Antidiabetic background therapy not as required	INC2 checked	PPS
A2		**Inclusion criteria violated**		
	A2.01	HbA_{1c} out of range	HbA_{1c} out of range for inclusion by more than 0.2% for insulin alone: [7.5%, 10%] at Visit 1 for insulin with 1 OAD: [7.0%, 9.5%] at Visit 1 [7.5%, 10%] at Visit 4	PPS
	A2.02	Age out of range	INC6 checked and calculated date checked	None
	A2.03	BMI out of range	INC7 checked	None
	A2.06	Fasting serum C-peptide levels out of range	INC3 checked	None
A3		**Exclusion criteria violated**		
	A3.01	Uncontrolled FPG level	EXC1 checked	None
	A3.02	Additional background therapy	EXC2 checked	PPS
	A3.03	Relevant concomitant diagnoses	EXC3, EXC7 checked	None
	A3.04	Bariatric or other relevant gastrointestinal surgery within the past two years	EXC6 checked.	PPS
	A3.05	Blood dyscrasias or any disorders causing hemolysis or unstable red blood cell	EXC8 checked	PPS
	A3.06	Indication of liver disease	EXC4 checkedParameters above 3 ULN at screening or during run-in period	None
	A3.07	Contraindication to any of the drugs in the study regimen	EXC9 checked	None
	A3.08	Treatment with protocol excluded anti-obesity drugs	EXC11 checked	PPS
	A3.09	Renal insufficiency or renal impairment (assessed by eGFR)	EXC5 checked: eGFR < 45mL/min/1.73m^2 during screening or run-in period	PPS
	A3.10	Treatment with protocol excluded systemic steroids or change in thyroid hormone dose	EXC12 checked	PPS
	A3.11	Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial	EXC15 checked, review at MQRM/BRPM to determine efficacy impact (Medical judgement), depending on the type of drug given in the prior trial (only if investigational drug interferes with glucose metabolism).	PPS Final decision at the DBL meeting
	A3.12	Specific exclusion criterion for pre-menopausal women violated	EXC13 checked	None

Category / Code		Description	Comment/Example	Excluded from
	A3.13	Relevant alcohol or drug abuse and other conditions affecting study compliance	EXC14 checked	None
	A3.14	Any other clinical condition unsafe for participation that would jeopardize patient safety while participating in this clinical trial	EXC16 checked.	None
	A3.26	Known allergy or hypersensitivity to insulin or empagliflozin	EXC10 checked	None
B		Informed Consent		
	B1	Informed consent not available	INC8 checked, No signature, or Inform consent date missing Patient's data will not be used at all	All
	B2	Informed consent too late	INC8 checked Inform consent date > Visit 1 date/date of any study procedure	None
C		Trial medication and randomisation		
C1		Incorrect Trial Medication Taken		
	C1.01	No study medication taken	Patient randomised according to IRT but no medication taken according to eCRF or IRT	TS
	C1.02	Incorrect trial medication taken	Wrong medication taken for more than 20% of the treatment duration up to Visit 10 or for more than 20% of the last visit interval before the primary endpoint assessment (different medication than the patient was randomised to taken i.e. drug kit recorded in eCRF from different treatment group than drug kit assigned by IRT) Can only be judged after DBL since unblinding information is required	PPS
C2		Randomisation not followed		
	C2.01	Treated without randomisation	Patient treated according to eCRF but not randomised according to IRT.	PPS
C3		Non-compliance		
	C3.01	Non-compliance with drug intake	During the treatment period, overall study treatment compliance up to Visit 10 outside 80% and 120% (exclusive) or study treatment compliance below 80% in the last visit interval up to Visit 10.	PPS
	C3.03	Last treatment more than 7 days prior to next visit	Last treatment prior to Visit 10 was more than 7 days prior to next visit.	PPS

Category / Code		Description	Comment/Example	Excluded from
	C4.01	Medication code broken without just cause	Medication code was broken prior to Visit 10 for no valid reason. [manual check. Final decision at the DBL meeting based on medical judgement. This decision will overwrite the programmed result.]	PPS Final decision at the DBL meeting
		Concomitant Medication		
D2		Prohibited medication use		
	D2.01	Use of prohibited medication	Review of eCRF for prohibited medication. If first prohibited medication was taken prior to Visit 10 then exclude from PPS. If first prohibited medication was taken between Visit 10 and end of treatment then do not exclude from PPS. [manual check. Final decision at the DBL meeting based on medical judgement. This decision will overwrite the programmed result.]	PPS/None
D3		Mandatory medication not taken		
	D3.01	Background antidiabetic therapy not taken as specified in the protocol	- Changes in insulin total daily dose outside +/-10% or +/-2U range from baseline prescribed dose before Visit 10 for more than 7 consecutive days and not for rescue (exclude from PPS). If the change in insulin consists of several records of consecutive changes, it will be considered "not for rescue" only if none of the records are checked at “Yes” for “Rescue medication” in eCRF.	PPS
E		Missing data		
	E1.01	No baseline HbA1c value	No valid baseline HbA1c value	FAS
I2		Pregnancy monitoring		
	I2.01	Pregnancy	Positive pregnancy test or manual iPV	None
	I2.02	Pregnancy test not done for woman of child bearing potential for at least one visit before treatment discontinuation		None

6.3 PATIENT 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 study drug, regardless of whether any study drug was taken.

- TS – Treated set
  All patients randomised and treated with at least one dose of study drug. The TS is the basis for safety analyses.

- FAS – Full analysis set
  All patients randomised, treated with at least one dose of study drug, and with a baseline HbA_{1c} value. The FAS is the basis for the ITT analysis.

- PPS – Per-protocol set
  All patients in the FAS without IPV leading to exclusion. See Table 6.2:1.

In Table 6.3: 1 the data sets which are to be used for each category class of endpoint are illustrated.

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

Class of endpoint	SCR	TS	FAS	PPS
Primary endpoint (at week 16)			LOCF-16, OC-16	LOCF-16
Safety endpoints		OR, OC-IR^		
Disposition	OR			
Demographics			OR	
Baseline efficacy			OC-16	

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

Similarly, note that patient set PPS is only applicable to analysis performed at week 16.

Note that the number of patients with available data for an endpoint may differ. For details, see Section 6.6 “Handling of missing data”.

6.5 POOLING OF CENTRES

Centres will not be pooled.

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).

Original result (OR) analysis

Original result 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 or if it is not meaningful to apply any imputation rule on them for replacing the missing values.

Observed cases analysis at week 16 (OC-16)

For efficacy endpoints at week 16, 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-16 analysis will be performed and missing data in this analysis will not be replaced.

This OC-16 technique will set all values measured after rescue medication taken to missing.

The criterion for rescue medication for this analysis types is based on the definition of rescue medication for the analysis of efficacy endpoints at week 16, as described in Section 5.3.3.1. It includes changes in insulin above and/or below the range +/- 10% or +/- 2U from the baseline prescribed dose for 8 consecutive days or more.

As insulin dose can be adjusted after Visit 10, values collected after visit 10 will also be set to missing for the OC-16 technique.

Observed cases analysis at week 52 (OC-52)

For efficacy endpoints at week 52, a similar OC technique will be used but considering a different criteria for setting values measured after rescue medication to missing.

The criterion for rescue medication for OC-52 is based on the definition of rescue medication for the analysis of efficacy endpoints at week 52, as described in Section 5.3.3.1. As insulin adjustments are allowed between visit 10 and visit 19, changes in insulin use will not be considered rescue therapy. This applies to data recorded in all parts of the study (including visits 5-10).

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

In addition, for lipids, the OC-technique will also be adapted without setting the values measured after any rescue medication taken to missing (whether this is change in insulin use or not), and using the original observed values instead.

For analyses at week 16, the OC-IR technique will set values to missing after the visit 10 date.

Last observation carried forward (LOCF-16, LOCF-52 and LOCF-IR)

An alternative method for quantitative endpoints is to replace missing values due to early discontinuation of a patient by her/his last observed measurement. This method tends to result in more conservative estimates than an OC-analysis.

The last observation 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.

If a patient is on rescue medication after Visit 5 and before Visit 6, then all the on-treatment visits will be set to missing and the baseline HbA_{1c} value will be carried forward to populate the missing on-treatment values in HbA_{1c}.

Missing values within a course of measurements 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 missing endpoint;

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

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

In general, 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.

As for the OC techniques, two approaches will be used for the criteria of rescue medication, whether we are analysing efficacy endpoints at week 16 or at week 52 (see Section 5.3.3.1 for more details):

- LOCF-16 will be based on the definition of rescue medication for the analysis of efficacy endpoints at week 16
- LOCF-52 will be based on the definition of rescue medication for the analysis of efficacy endpoints at week 52

For the LOCF-16 technique, as insulin dose can be adjusted after Visit 10, values collected after visit 10 will also be set to missing, and the missing values will be imputed by LOCF.

Another technique, LOCF including values on rescue medication (LOCF-IR), will be used, when values measured after initiation of rescue medication are not set to missing. For analyses at week 16, the values after the visit 10 date will be set to missing prior to LOCF-IR imputation.

Missing data will only be imputed up to the planned visit to be reached by all randomised patients (week 16 for LOCF-16, week 52 for LOCF-52).

Non-completers considered failure (NCF-16 and NCF-52)

For binary endpoints, like a treat to target response of HbA_{1c}<7.0%, 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 to be reached by all patients.

For binary endpoints that are derived from quantitative endpoints (e.g. HbA_{1c}), 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 HbA_{1c}).

The values measured after rescue medication was taken during the active treatment period by the patients will be set to "failures". Two approaches will be used for the criteria of rescue medication, whether we are analysing endpoints at week 16 or at week 52 (see Section 5.3.3.1 for more details):

- NCF-16 will be based on the definition of rescue medication for the analysis of efficacy endpoints at week 16. For the NCF-16 technique, as insulin dose can be adjusted after Visit 10, values collected after visit 10 will be set to missing.

- NCF-52 will be based on the definition of rescue medication for the analysis of efficacy endpoints at week 52

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

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 [1].

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 8:00 o'clock in the morning.

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

- If the date is completely missing and an end of treatment (EoT) visit or a Visit 19 is documented, it should be the minimum of these two dates.

- If the date is incomplete with only month and year, it should be the first day of the following month, or the minimum between end of treatment (EoT) visit and Visit 19 (if they are documented).

- If the patient is lost to follow-up it should be the date of the last visit + the longest treatment duration based on drug supply + 1 day.

- If a patient died 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 took 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.

c) Missing dates for concomitant and other antidiabetic therapies

For partial start and stop dates for concomitant therapies (CT) 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 the 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 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 trial team on an individual basis, using the above points as guidance

d) Missing Visit 10 date

The visit 10 date is used as a cut-off date in several situations:

- for the definition of several iPVs, in order to identify violations leading to exclusion from PPS
- for the definition of OC-16 and LOCF-16 imputation techniques, where values collected after visit 10 date are set to missing
- for summaries of AEs at week 16

For these analyses, if a patient skipped visit 10 (e.g. attended visit 11 or visit 12 as the next visit) and visit 10 date is missing as a result, then the planned visit 10 date will be used instead, i.e. 112 days from start of study drug.

e) Other dates

Only the year of birth will be collected in the eCRF, and 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.

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 drug will be considered pre-treatment values. These pre-treatment values will be assigned to a visit according to the nominal visit number as recorded on the electronic case report form (eCRF) or as 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	
HbA_{1c}	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 5). Reasons to base the time windows on the actual treatment start date rather than the randomisation date are:

- If first intake of study drug 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 study drug after the randomisation, the time window for the first on-treatment visit could include times the patient was not yet on study drug.

The time window for the first visit after randomisation starts on the day after the first intake of study drug. This maximises the number of measurements used in by visit analyses and provides consistency with the LOCF approach, 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 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
5	Baseline	0	NA	1[A]
6	Week 2	14	2	21
7	Week 4	28	22	42
8	Week 8	56	43	70
9	Week 12	84	71	98
10	Week 16	112	99	126
11	Week 20	140	127	154
12	Week 24	168	155	182
13	Week 28	196	183	210
14	Week 32	224	211	238
15	Week 36	252	239	266
16	Week 40	280	267	294
17	Week 44	308	295	322
18	Week 48	336	323	350
19	Week 52	364	351	Study drug stop date + X[B] days
End of treatment (EoT) visit	For patients who prematurely discontinue treatment, the end of treatment (EoT) visit should be the last on-treatment visit. That visit will be assigned to a scheduled visit (above) according to the time window it falls into. The time window will end X[B] days after the study drug stop date.			

A: only values taken prior to the start of treatment with randomised study drug can be considered baseline values.

B: the definition of X is endpoint specific, cf. Table 6.7: 1.

For examinations that are not planned at every on-treatment visit, the time windows will be defined according to the same algorithm, based on the midpoint between the planned visit days of such an examination.

Repeated and unscheduled efficacy and safety measurements will be assigned to the nominal visits and listed in the SDL 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 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. 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.

Note: for LOCF imputation, the last observed on-treatment value will be carried forward, 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 IPVs, also summarised by whether the IPV led to exclusion from the PPS, will be presented by treatment group for the randomised set. 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 non-missing values), mean, standard deviation (SD).

For end-of-text tables, the set of summary statistics is: N (number of patients with non-missing values) / Mean / SD / Min / Q1 (lower quartile) / Median / Q3 (upper quartile) / Max.

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline “Reporting of Clinical Trials and Project Summaries” [5].

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.

Treatment comparisons:

In all specified statistical analyses, treatment comparisons will be made between each randomised empagliflozin group (10 and 25 mg) and placebo.

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, height (cm), smoking history and alcohol status, duration of diabetes (categories based on years), renal impairment (eGFR and eCCr) and type of insulin therapies. Categories for baseline characteristics are defined in Section 6.4.

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

HbA_{1c} (%), HbA_{1c} categories, fasting plasma glucose (mg/dL), weight (kg), weight categories, waist circumference (cm), blood pressure, blood pressure categories and mean daily glucose.

Both 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 Anatomical-Therapeutic-Chemical classification level 3 (ATC3) and preferred name. Summaries will be presented for concomitant therapies taken during randomised treatment and those taken at baseline. Separate summaries of use of antihypertensives, ASA or lipid lowering drugs at baseline by preferred name will be presented.

Prescribed background medication daily dose at baseline will be presented for total daily insulin.

Concomitant diseases will be summarised by MedDRA system organ class and preferred term. Relevant diabetic 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 outside 80% and 120% (exclusive) 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

The primary analysis is at 16 weeks and will be performed on the full analysis set (FAS) with LOCF-16 being the implemented imputation rule.

For further information on the imputation rule see Section 6.6.

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 (as explained in Section 7.8.2).

7.4.1 Primary efficacy analysis

The primary analysis is an analysis of covariance (ANCOVA) comparing the change from baseline in HbA_{1c} after 16 weeks of treatment. All randomised treatment groups will be included in the same analysis. The statistical model will be:

Change from baseline in HbA_{1c} after 16 weeks = overall mean + baseline HbA_{1c} + treatment + baseline renal function + type of insulin therapies + random error

This model includes effects accounting for the following sources of variation: 'baseline HbA_{1c}', 'baseline renal function', 'type of insulin therapies' and 'treatment'. 'Treatment', 'baseline renal function', and 'type of insulin therapies' are fixed classification effects and 'baseline HbA_{1c}' is a linear covariate. Note that baseline renal function refers to the eGFR categorization (>=60 mL/min/1.73 m2, <60 mL/min/1.73 m2). Such categorization is applicable to the analysis of other endpoints as well.

The random error is assumed to be normally distributed with mean 0 and unknown variance. The primary analysis will be performed on the FAS with treatment assignment as randomised.

A hierarchical testing sequence will be used as defined in the protocol.

7.5 SECONDARY ENDPOINT

Refer to Section 7.8 for the analysis of secondary endpoint.

7.7 EXTENT OF EXPOSURE

A descriptive statistics table of the extent of exposure with mean, SD, median and range of the number of days a patient was on treatment will be provided for the treated set.

This table 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. This will also be defined as a protocol violation.

Frequencies 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 weeks, >4 to 10 weeks, >10 to 16weeks, >16 to 24 weeks, >24 to 32 weeks, >32 to 42 weeks, >42 to 52 weeks, >52 weeks

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

AEs will be coded using the most recent version of the MedDRA coding dictionary.

The analyses of adverse events 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 this purpose, AE data will be combined in a 2-step procedure into AE records.

In a first step, AE occurrences, i.e. AE entries on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- 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. 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 collapsing will begin.)

- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

In a second step, AE episodes will be condensed into AE records provided that the episodes were reported with the same term on the respective MedDRA level and that the episodes are assigned to the same treatment. For further details on summarization of AE data, please refer to the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' [2].

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. That means that all adverse events occurring between first drug intake till 7 days after last drug intake will be assigned to the randomised treatment. 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 with 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 criterion [3]. Thus, AEs classified as 'other significant' will include those non-serious and non-significant adverse events with:

(i) 'action taken = discontinuation' or 'action taken = reduced', or

(ii) Marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review meeting (MQRM) or BRPM.

7.8.1.3 AE summaries

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. AEs will also be reported by intensity. Separate tables will be provided for patients with other significant adverse events, for patients with adverse events of special interest (AESI), for patients with serious adverse events, for patients with AEs leading to discontinuation, and for patients with drug-related AEs.

The system organ classes will be sorted according to the standard sort order specified by EMA, preferred terms will be sorted by frequency (within system organ class).

The following AE summaries will also be provided at week 16, including data up to visit 10 date only: AE overall summary, the frequency of patients with AEs summarised by treatment, primary system organ class and preferred term, frequency of patients with AEs reported by intensity, patients with other significant adverse events, patients with adverse events of special interest (AESI), patients with serious adverse events, patients with AEs leading to

discontinuation, patients with drug-related AEs, and analyses of hypoglycaemic events (as described in Section 7.8.1.4).

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. 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

Different tables will be shown for (i) patients with investigator defined asymptomatic or symptomatic hypoglycaemia reported as AE or non-AE, and (ii) patients with confirmed hypoglycaemic adverse events, i.e. hypoglycaemic adverse events that had a plasma glucose concentration ≤ 70 mg/dL or required assistance.

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 and the impact of treatment on the occurrence of hypoglycaemia will be explored using logistic regression with model involving treatment and continuous baseline HbA_{1c}. Time to the onset of the first hypoglycaemia will be analysed by Kaplan-Meier estimates. The logistic regression and Kaplan-Meier analysis will be performed on confirmed events.

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 category (CKD staging), background medication and age group.

In the number of episodes analysis, hypoglycaemic events will be collapsed 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.

7.8.1.5 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
- Metabolic acidosis, ketoacidosis and DKA
- Events involving lower limb amputation

Events of these AESIs are identified through the AE being flagged by the investigator as an AESI on the case report form (CRF).

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

Metabolic acidosis, ketoacidosis and DKA

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

Events involving lower limb amputation

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

The following specific adverse events will be tabulated by treatment group.

- Genital infections (the applicable BICMQ at the time of the analysis)
- Urinary tract infections (the applicable BICMQ at the time of the analysis)

Specific adverse events of UTIs and genital infections will additionally be summarised by age group, baseline HbA_{1c}, intensity (mild, moderate or severe), whether leading to discontinuation of treatment, time of occurrence (in the first 3 months of treatment or after), duration (<7 days, 7-14 days and >14 days), sex, by how the event was treated (no treatment, therapy assigned, hospitalisation) and the number of episodes per patient. In the number of episodes analysis of UTI and genital infection AEs will be collapsed within each BIcMQ regardless of preferred term 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 UTI and genital infections specific adverse events.

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.

An additional specific adverse events of volume depletion will be tabulated.

Volume depletion: the applicable BICMQ at the time of the analysis

7.8.1.6 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.

7.8.1.7 Analysis of adjudicated events

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

7.8.1.8 AEs while patients taking wrong medication

A listing will be provided for AEs that had onset while a patient was taking the wrong medication.

7.8.2 Laboratory data

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 are described in the BI guidance for the Display and Analysis of Laboratory Data [4]. All analyses considering multiple of times upper limit of normal (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, analysis of patients with AST and/or ALT≥3xULN with concomitant or subsequent TBILI≥2xULN in a 30 day period after AST/ALT elevation will also be performed.

The start of the 30 day time span is triggered by either liver enzyme elevation above the defined thresholds. Patients who fulfil one of the criteria for ALT/AST or total bilirubin elevations above and 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 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 given by the laboratory, not on normalised values with BI standard reference ranges. The creatinine clearance and glomerular filtration rate will be estimated according to the two formulas and stored in the trial databases:

- Cockcroft-Gault formula (mL/min):
  eCcr = (140 – age) x (weight in kg) x (0.85 if female) / (72 x creatinine (mg/dL))
- Japanese formula (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 from the same visit.

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 IPVs 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 following eGFR staging.

Table 7.8.2: 1 eGFR staging (by Japanese formula)

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 prepared with respect to the following categorisation and a shift table will be supplied for eCcr as well.

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)

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

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 as defined for the new XLAB macro. 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.

Urine creatinine does not have a reference range and 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 BLQ (e.g. <3 mg/L) the albumin / creatinine ratio is determined as missing and will not be replaced by estimated values. Four additional 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) and transitions from baseline based on the aforementioned categories. Similar analyses will be provided for urin albumin with the following categories (<20mg/L; 20-<200mg/L; ≥200mg/L).

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

General laboratory evaluation will also be provided for bone markers.

7.8.3 Vital signs

Other than the analysis of SBP and DBP as efficacy endpoints only descriptive statistics are planned for the summary of pulse rate (bpm), change from baseline in pulse rate over time up to week 52.

7.8.4 ECG

12-lead ECG measurements will be taken at baseline (visit 5), visit 8, visit 10, visit 13, visit 16 and visit 19. ECG-findings before first intake of trial drug will be considered as baseline condition. Any clinically significant new findings in the ECG measurement after the first screening ECG were to be reported by the investigator as AEs and will be analysed as planned in Section 7.8.1.

7.8.5 Creatinine and eGFR time curve analysis

Descriptive statistics will be created for creatinine and eGFR values over time by treatment and presented in tables. Descriptive statistics for eCcr will be presented in Section 16.1.9.2. These data will be used to create plots of the parameters over time. Subgroups tables of these descriptive statistics over time will also be presented for age subgroups.

7.8.6 Lipid parameter and FFA analyses

Lipid parameters and FFA will be analysed using descriptive statistics and MMRM modelling. Descriptive statistics will be shown over time for the treated set (LOCF-IR and OC-IR) including change from baseline and percent change from baseline. For each lipid parameter and FFA, separate MMRM models will be fitted on the treated set (OC-IR) for both change from baseline at week 52 and percentage change from baseline at week 52 as dependent variables. The MMRM models will include ‘baseline lipid’ (only for lipid parameters), ‘baseline FFA’ (only for FFA) and ‘baseline HbA1c’ as continuous covariates and ‘baseline eGFR (Japanese formula)’, ‘type of insulin therapies’, ‘treatment’, ‘visit’ and ‘treatment by visit interaction’ as fixed effects.

7.8.7 Ketone bodies analyses

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

8. REFERENCES

1 *001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", version 2.0; IDEA for CON.

2 *001-MCG-156:* "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON

3 *CPMP/ICH/137/95:* “Structure and Content of Clinical Study Reports”, ICH guideline topic E3, current version; Note For Guidance on Structure and Content of Clinical Study Reports

4 *001-MCG-157:* "Display and Analysis of Laboratory Data", current version, in: IDEA for CON.

5 *001-MCG-159:* “Reporting of Clinical Trials and Project Summaries”, current version, in: IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YYYY)	Author	Section changed	Brief description of change
Final	26-SEP-2017		None	This is the final TSAP without any modification