Trial Statistical Analysis Plan

c14640701-02

BI Trial No.:	1245.69
Title:	A Phase III, randomised, double blind, placebo-controlled, parallel group, efficacy, safety and tolerability trial of once daily, oral doses of **E**mpagliflozin as **A**djunctive to in**S**ulin th**E**rapy over 52 weeks in patients with Type 1 Diabetes Mellitus (EASE-2) Including Protocol Amendment 2 1245.69 [c03024901-03]
Investigational Product(s):	Empagliflozin
Responsible trial statistician:	 Phone : Fax:
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Version:	Revised

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2 LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical classification
AUC	Area under the curve
BHB	Beta-hydroxybutyrate
BI	Boehringer Ingelheim
BIcMQ	BI-customised MedDRA query
BMI	Body mass index
CEC	Clinical event committee

Term	Definition / description
CRF	Case report form
CSII	Continuous subcutaneous insulin infusion
CT	Concomitant therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBP	Diastolic blood pressure
DKA	Diabetic Ketoacidosis
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DST	Daylight saving time
ECG	Electrocardiogram
eCRF	Electronic case report form
e-diary	Electronic diary
EMA	European medicines agency
eGFR	Estimated glomerular filtration rate
EoT	End of treatment
FAS	Full analysis set
FPG	Fasting plasma glucose
GI	Genital infection
HbA_{1c}	Glycated haemoglobin
HCRU	Health care resource utilisation
HLT	High level term
ICH	International Conference on Harmonisation
IPV	Important protocol violation
ITT	Intention to treat
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
MAGE	Mean amplitude of glucose excursions
MDG	Mean daily glucose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention to treat
MMRM	Mixed model for repeated measures

Term	Definition / description
NCF	Non-completers considered failure
O*C	Oracle Clinical
OC	Observed cases
OC-AD	Observed cases – all data
OC-H	Observed cases – excluding anti-hypertensives
OC-OffT	Observed cases – off-treatment
OC-P	Observed cases – excluding paracetamol
OR	Original results
PG	Plasma glucose
PK	Pharmacokinetics
PPS	Per protocol set
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
SMQ	Standardised MedDRA query
SOC	System Organ Class
SSC	Special search category
TBL	Total bilirubin
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
UTI	Urinary tract infection
WHO	World health organisation

3 INTRODUCTION

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

The 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 9.4 or later version will be used for all analyses.

4 CHANGE IN THE PLANNED ANALYSIS OF THE STUDY

This TSAP assumes familiarity with changes made via Protocol Amendments, and therefore these changes are not listed here.

The derivation for total daily insulin dose will be based on 14 days prior to the visit rather than 7 days as specified in the CTP.

The back-up covariance structures, to be tested in the event that an MMRM analysis fails to converge using an unstructured covariance structure, have been updated to better fit the trial design and account for unequally spaced visits. Rather than testing compound symmetry and variance components, the following covariance structures will be tested instead: Ante-dependence ANTE(1), heterogeneous Toeplitz (TOEPH) and first-order autoregressive (AR(1)). Toeplitz (TOEP) will continue to be tested as planned.

In CTP amendment 2 (c03024901-03, 4th Jan 2017) the testing strategy was updated and a new graphical illustration added to Section 7.2. Unfortunately, the original illustration was not deleted so both are present. Only the updated illustration is valid.

Changes/adaptations included in the revised version of the TSAP:

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- Multiple imputation analysis for body weight and blood pressure will include baseline body weight and/or blood pressure respectively as additional effect.
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5 ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint in this study is the change from baseline in HbA_{1c} (%) at 26 weeks.

For the definition of baseline HbA_{1c} refer to section 6.7.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

For baseline definitions for each endpoint, refer to Section 6.7.

The key secondary endpoints in this study are:

- Rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose <54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic events confirmed by adjudication per patient-year from Week 5 to Week 26.
    - All severe hypoglycaemic AEs that are confirmed by adjudication and all investigator reported AEs that have confirmed plasma glucose <54mg/dL (<3.0 mmol/L) with symptoms reported will be counted.
- Rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose <54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic events confirmed by adjudication per patient-year from Week 1 to Week 26
    - All severe hypoglycaemic AEs that are confirmed by adjudication and all investigator reported AEs that have confirmed plasma glucose <54mg/dL (<3.0 mmol/L) with symptoms reported will be counted.
- Change from baseline in body weight (kg) at 26 weeks
- Change from baseline in the percentage of time spent in target glucose range of >70 to ≤180 mg/dL (>3.9 to ≤10.0 mmol/L) as determined by continuous glucose monitoring (CGM) in Weeks 23 to 26
- Change from baseline in interstitial glucose variability based on IQR as determined by continuous glucose monitoring (CGM) in Weeks 23 to 26
- Change from baseline in total daily insulin dose, U/kg, at 26 weeks
- Change from baseline in systolic blood pressure (SBP), mmHg, at 26 weeks
- Change from baseline in diastolic blood pressure (DBP), mmHg, at 26 weeks

5.2.2 Secondary endpoints

Since there are no secondary endpoints specified in the protocol, this section is not applicable.

6 GENERAL ANALYSIS DEFINITION

6.1 TREATMENTS

There will be six treatment phases in this trial: screening, T1DM therapy optimisation, placebo run-in, study treatment phase (with either empagliflozin or matching placebo), post-treatment and post-study, as follows.

- The screening period starts from the date of informed consent and ends on the day before the start date of the T1DM therapy optimisation period.
- The T1DM therapy optimisation period begins with the start date of the insulin therapy optimisation visit (Visit 2) up to the day before the date of first administration of placebo run-in medication (inclusive).
- The placebo run-in period begins from the date of first administration of placebo run-in medication up to the day before the date of first administration of randomised study medication (inclusive).
- The on-treatment period begins from the date of first administration of study medication up to last intake of study drug + X days (inclusive) [see definition of X in table 6.7: 1].
- The post-treatment period begins from the last intake of study drug + X days + 1 day up to the last contact date (inclusive). The last contact date is defined as the maximum of (trial completion date, and [last study drug intake + X days + 1 day].
- The post-study period begins from the last contact date +1 day and ends at trial database lock date.

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

A cut-off date will be used for the analyses at week 26, and will be defined as follows:

- For patients who are still on-treatment at the week 26 visit date:
    - The actual week 26 visit date, if the week 26 visit is within the time window defined in table 6.7: 2.
    - The planned study day 182, if there is no week 26 visit date or if the actual week 26 visit falls outside of the time window for the week 26 visit.
- For patients who prematurely discontinued the treatment prior to week 26:
    - The minimum between (drug stop date + X days) and the actual week 26 visit date, if the week 26 visit is within the time window.
    - The minimum between (drug stop date + X days) and day 182, if there is no week 26 visit date or if the actual week 26 visit falls outside of the time window for the week 26 visit.

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 randomised.

If a patient erroneously receives the wrong trial drug, the patient will be analysed as randomised. In addition, AEs with an onset during the time of the incorrect study treatment will be tabulated and listed separately.

6.2 IMPORTANT PROTOCOL VIOLATIONS (IPVS)

There are two aspects that qualify a violation of the protocol to be important.

First, there are PVs that potentially affect the rights or safety of study patients. In this case, the sponsor needs to react immediately to such PVs to prevent recurrence. In most cases, these PVs do not have an impact on whether a patient can be included in an analysis, but they need to be described in the report.

Second, a PV can potentially influence the primary outcome measure for the respective patients in a way that is neither negligible nor in accordance with the study objectives. Therefore, such PVs potentially affect the main study results and conclusions. This second category of important PVs forms the basis for the decision (during the DBL meeting) of whether a patient does or does not belong to an analysis set. All other PVs are of minor importance and it is not necessary to describe or list these PVs in the integrated clinical trial report (CTR).

As the primary endpoint is analysed after 26 weeks, IPVs related to efficacy that occur between week 26 and 52 will not lead to exclusion from analysis sets.

The following table defines the different categories of IPVs. The final column describes which IPVs will be used to exclude patients from the Per Protocol analysis Set (PPS).

Table 6.2: 1 Important protocol violations

Category/Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
A1		**Target indication not met**		
	A1.02	Antidiabetic background therapy not as required	Inclusion criteria 4 not met (No insulin recorded on eCRF Or Total daily insulin dose < 0.3 U/kg or >1.5 U/kg at visit 1[#] Or MDI patients: fewer than 1 basal and 3 bolus injections per day at visit 1[#] CSII patients: fewer than 5 months experience of using the pump prior to Visit 1[#]).	PPS

Table 6.2: 1 Important protocol violations (continued)

Category/Code		Description	Example/Comment	Excluded from
	A1.03	No Type 1 Diabetes	Inclusion criteria 2 not met, with no date of diabetes mellitus type 1 first diagnosed known.	PPS
	A1.05	Time since diagnosis out of range	Inclusion criteria 2 not met, with a date of diagnosis < 1 year prior to Visit 1.	PPS
A2		**Inclusion criteria not met**		
	A2.01	HbA_{1c} out of range	HbA_{1c} <7.3% or > 10.2% at Visit 5 Or HbA_{1c} increase > 0.5% from Visit 1 to Visit 5.	PPS
	A2.02	Age out of range	Inclusion criteria 7 not met Or Age < 18 years at Visit 1.	All
	A2.03	BMI out of range	Inclusion criteria 8 not met Or BMI <18 kg/m^2 at Visit 1.	None
	A2.04	eGFR out of range	Inclusion criteria 9 not met Or eGFR < 29.5 mL/min/1.73m2 according to CKD-EPI formula based on creatinine value at Visit 1. Central laboratory values will be used to determine whether INC9 is not met.	PPS
	A2.06	Fasting C-peptide out of range	Inclusion criteria 3 not met Or Fasting C-peptide ≥ 0.7 ng/mL at Visit 2.	PPS
A3		**Exclusion criteria not met**		
	A3.02	Additional background therapy	Exclusion criteria 3 checked Or Any antihyperglycaemic drug (e.g. metformin, AGI, GLP-1 analogues, SGLT-2 inhibitors, pramlintide, inhaled insulin, pre-mixed insulins etc.) except subcutaneous basal and bolus insulin recorded on eCRF within 3 months prior to Visit 1[#].	PPS

Table 6.2: 1 Important protocol violations (continued)

Category/Code		Description	Example/Comment	Excluded from
	A3.03	Relevant concomitant diagnoses	Exclusion criteria 4, 5, 7, 9 or 16 checked Or Any of the following: • Severe hypoglycaemia involving coma and/or seizure that required hospitalisation or hypoglycaemia related treatment by an emergency physician or paramedic within 3 months prior to Visit 1 and until randomization[#]. • Occurrence of DKA within 3 months prior to Visit 1 and until randomization[#]. • Acute coronary syndrome (non-STEMI, STEMI and unstable angina pectoris), stroke or transient ischaemic attack (TIA) within 3 months prior to Visit 1[#]. • Diagnosis of brittle diabetes. • Medical history of cancer within the last 5 years prior to Visit 1 (except resected basal cell carcinoma)[#].	None
	A3.05	Blood dyscrasias or any disorder causing haemolysis or unstable red blood cell count	Exclusion criteria 17 checked Or Relevant diagnosis (e.g. malaria, babesiosis, haemolytic anaemia) at Visit 1[#].	PPS
	A3.06	Indication of liver disease	Exclusion criteria 10 checked Or ALT, AST or alkaline phosphate > 3*ULN at Visit 1 or Visit 5.	None
	A3.10	Treatment with protocol excluded systemic steroids or recent change in thyroid hormone dose	Exclusion criteria 13 or 14 checked Or Treatment with systemic steroids or planned initiation of such therapy at Visit 1 and until randomization (excluding inhaled or topical use of corticosteroids) [#]. Or Change in dose of thyroid hormone within 6 weeks prior to Visit 1 or planned change or initiation of such therapy at Visit 1 and until randomization[#].	PPS

Table 6.2: 1 Important protocol violations (continued)

Category/Code		Description	Example/Comment	Excluded from
	A3.11	Intake of other investigational drug in another trial within 30 days prior to intake of study medication in this trial	Exclusion criteria 20 checked Or Intake of another investigational drug in another trial within 30 days prior to Visit 1[#]. Final decision at DBL meeting based on medical judgment.	PPS
	A3.12	Specific exclusion criterion for pre-menopausal women violated	Exclusion criteria 18 checked Or Positive pregnancy test or nursing at Visit 1 and until randomization[#].	None
	A3.13	Relevant alcohol or drug abuse and other conditions affecting study compliance	Exclusion criteria 19 checked Or Alcohol or drug abuse within 3 months prior to Visit 1*[#].	None
	A3.14*	Any other clinical condition unsafe for participation that would jeopardise patient safety while participating in this clinical trial	Exclusion criteria 22 checked	None
	A3.21	History of T2DM, maturity onset diabetes of the young (MODY), pancreatic surgery or chronic pancreatitis	Exclusion criteria 1 checked Or Relevant condition listed as baseline condition in eCRF[#].	PPS
	A3.22	Diagnosis of severe gastroparesis	Exclusion criteria 8 checked Or Relevant diagnosis recorded as a baseline condition in the eCRF[#].	PPS
	A3.23	Eating disorders	Exclusion criteria 11 checked Or Diagnosis of eating disorder such as bulimia or anorexia nervosa listed as a baseline condition in the eCRF[#].	PPS

Table 6.2: 1 Important protocol violations (continued)

Category/Code		Description	Example/Comment	Excluded from
B		**Informed consent**		
	B1	Informed consent not available	Inclusion criteria 1 not met Or Informed consent date missing[#].	All
	B2	Informed consent too late	Informed consent date was after Visit 1 date or after any study related procedure.	None
C		**Trial medication and randomisation**		
C1		**Incorrect trial medication**		
	C1.02*	Incorrect trial medication taken	Wrong medication taken (different medication than the patient was randomised to i.e. drug kit recorded in eCRF is from a different treatment group than the drug kit assigned by IxRS) for more than 20% of the overall treatment duration or for more than 20% of the last visit interval before the primary endpoint assessment. Can only be judged after DBL as requires unblinding information.	PPS
C2		**Randomisation not followed**		
	C2.01	Treated without randomisation	Patient treated according to eCRF, but not randomised according to IVRS.	RS, mITT, FAS, PPS
C3		**Non-compliance**		
	C3.01	Non-compliance with study drug intake	Overall compliance <80% or >120% from visit 6 onwards or since last visit prior to primary endpoint <80% or missing. For the calculation of compliance, refer to section 7.3.	PPS
C4		**Medication code broken**		
	C4.01*	Medication code broken without just cause	Medication code broken whilst on-treatment without valid reason. Final decision at the DBL meeting based on medical judgment.	PPS

Table 6.2: 1 Important protocol violations (continued)

Category/Code		Description	Example/Comment	Excluded from
D		**Concomitant medication**		
D2		**Prohibited medication use**		
	D2.01*	Use of prohibited medication during treatment period	Review of eCRF for contraindicated drugs. Final decision at the DBL meeting based on medical judgment.	PPS
I		Other safety related violations		
I2		**Pregnancy monitoring**		
	I2.01	Pregnancy test not done for woman of child bearing potential for at least one visit before treatment discontinuation	Positive pregnancy test at any post-randomisation visit Or Pregnancy during the trial*.	None
	I2.03*	Nursing	Nursing during the trial	None

[#] Criteria to be checked manually and inclusion/exclusion criteria changed if violated.

***** Manual IPV (e.g. IPV that is too complex to program or cannot be detected through the data stored in the trial database).

6.3 PATIENT SETS ANALYSED

- Screened set (SCR):

This patient set includes all patients screened for the trial, with informed consent given and who completed at least one screening procedure at Visit 1.

- Randomised set (RS):

This patient set includes all patients from the screened set who were randomised to study drug, regardless of whether any study drug was taken.

- Treated set (TS):

This patient set includes all patients who are treated with at least one dose of randomised study drug. The TS is the basis for safety analyses.

- Full analysis set (FAS):

This patient set includes all randomised patients who are treated with at least one dose of study drug, have a baseline HbA1c and at least one on-treatment HbA1c measurement. The FAS is the basis for the primary efficacy analysis.

- Modified Intention-to-Treat Set (mITT):

This patient set includes all randomised patients who are treated with at least one dose of study drug, have a baseline HbA1c and at least one post baseline HbA1c measurement. The mITT is the basis for the primary effectiveness analysis.

- Per protocol set (PPS):

This patient set includes all patients in the FAS who do not have any IPV which can be expected to have a distorting influence on the assessment of the primary endpoint. IPVs are detailed in table 6.2: 1.

Table 6.3: 1 Patient Sets Analysed

	Patient set					
Class of endpoint	SCR	TS	RS	mITT	FAS	PPS
Disposition	OR					
Demographics			OR[1]		OR	
Baseline variables					OR	
Background total daily insulin dose/concomitant medications					OR	
Concomitant diagnoses/relevant medical history					OR	
Exposure/ compliance					OR	
Primary endpoint			Sensitivity analysis (MI/PMM)[2]	Primary effectiveness analysis (OC-AD)	Primary efficacy analysis (OC)	Sensitivity analysis (OC)
Key secondary endpoints: hypos			Sensitivity analysis (OC-AD)		Primary analysis (OC)	
Key secondary endpoint: body weight, TDID			Sensitivity analysis (MI)[2]		Primary (OC) & Sensitivity analysis (OC-AD)	
Key secondary endpoint: CGM			Sensitivity analysis (MI)[2]		Primary (OC-P) & Sensitivity analysis (OC-AD)	
Key secondary endpoint: SBP, DBP			Sensitivity analysis (MI)[2]		Primary (OC-H) & Sensitivity analysis (OC-AD)	
Further efficacy endpoints					OC, OC-AD, NCF	
Safety endpoints		OR				

SCR=screened set, RS=randomised set, mITT=modified intention-to treat set, FAS=full analysis set, PPS=per protocol set. Patient sets are defined in section 6.3.

OR=original results, OC=observed cases, OC-AD=observed cases-all data, OC-P=observed cases excluding paracetamol, OC-H= observed cases excluding anti-hypertensives, MI=multiple imputation, PMM=pattern mixture model, NCF=Non-completers considered failures. Handling of missing data is described in section 6.6.

1 Presented in 16.1.9.2 for EudraCT

2 MI and PMM are applied to all randomised patients with a baseline measurement.

6.5 POOLING OF CENTERS

For descriptive statistics by centre, data from small centres within the same country will be pooled. The data from centres with fewer than 6 patients will be combined into the category 'Fewer than 6 patients' for each individual country that has centres with fewer than 6 patients. Analysis to explore centre effects includes the calculation of descriptive statistics of the primary endpoint.

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.

6.6.1 Imputation methods

6.6.1.1 Original results (OR) analysis

Original result analysis implies the analysis of data exactly as observed. OR analysis will be performed on endpoints where it is not meaningful to apply any imputation rule on them for replacing missing values.

6.6.1.2 Observed cases (OC) analysis

For all efficacy endpoints, it is planned to analyse only the available data that were observed while patients were on-treatment, i.e., excluding the missing data and any values collected after treatment discontinuation. In other words, OC-analysis will be performed and missing data in the analysis will not be replaced.

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

For blood pressure endpoints (SBP and DBP), the OC-technique will be adapted to set values measured after a change in antihypertensive therapy to missing. This technique will be called Observed Cases without values following a change in antihypertensive therapy (OC-H). The following 3 situations are considered to be the start of a change in anti-hypertensive therapy:

- Initiation of additional antihypertensive medication
- Change in dose of antihypertensive medication
- Discontinuation of antihypertensive medication

Antihypertensive medications will be identified based on WHO DD special search categories as specified in section 9.2.

For CGM endpoints, the OC-technique will be adapted to exclude data measured from the date of first intake of paracetamol until the date of last intake of paracetamol + 1 day (inclusive) from the derivation of the endpoints. This technique will be called Observed Cases without values following intake of paracetamol (OC-P). Missing values for entire CGM periods will not be replaced.

Concomitant therapies containing paracetamol will be identified using a WHO DD BI customized query (BIcQ) based on Preferred Name (PN) "Paracetamol". This includes all monotherapy and fixed dose combinations (FDC).

Values for total daily insulin dose at each visit will be calculated as the mean total daily dose over the 14 days immediately prior to the visit (excluding the visit day). If there are <4 days of valid insulin data during the 14 day period, the mean will not be calculated and the visit value will be set to missing. The same rule will apply for total daily bolus, total daily basal and number of injections per day endpoints as well. Subsequent handling of missing data will be performed via a likelihood-based method and will use the mixed-effect model repeated measures (MMRM).

6.6.1.3 Observed cases - all data (OC-AD) analysis

Additionally, it is planned to perform effectiveness analyses including all available data that were observed, i.e. both on- and off-treatment values. Missing data in the analysis will not be replaced. Subsequent handling of missing data will be performed via a likelihood-based method and will use the mixed-effect model repeated measures (MMRM).

For blood pressure endpoints, data after a change in anti-hypertensive therapy will not be excluded.

For CGM endpoints, if both on- and off treatment data are available, OC-AD will consider all measurements in the derivation of the endpoints, regardless of whether on- or off-treatment. For more details of the derivation of CGM endpoints, see section 5.4.4. Additionally, data after the intake of paracetamol will not be excluded from the derivation of the endpoints.

A similar approach will be applied to insulin endpoints if both on- and off-treatment data is available in the 14 days prior to a visit.

For pulse rate, the OC-AD imputation will be used to present descriptive statistics analyses. For blood pressure endpoints, the OC-AD imputation will serve for descriptive statistics and sensitivity analyses.

6.6.1.4 Observed cases - Off Treatment (OC-OffT) analysis

For CGM and insulin endpoints, if >=4 days (for insulin endpoints) or 24 hourly bins (for CGM) of off-treatment data is available during a derivation period, a purely off-treatment value will be derived for potential separate analyses, considering only off-treatment data. For more details of assigning CGM measurements to on- or off-treatment, see Section 5.4.4. Note this is only applicable after study drug discontinuation; prior to data will be identical to OC.

6.6.1.5 Last observation carried forward (LOCF)

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

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

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 (as described in section 6.7).

Let:

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

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

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

E_i = endpoint values for visits D_i for i= -1, 0 and 1

Then the missing endpoint value can be interpolated as:

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

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

If there are no on-treatment measurements, the value from pre-treatment or baseline will not be carried forward to populate the missing on-treatment values according to the FAS definition.

6.6.1.6 Multiple imputation (MI)

A multiple imputation approach will be used as a sensitivity analysis for the primary endpoint. Further details can be found in section 7.4.3.1.

6.6.1.7 Non-completers considered failure (NCF)

For binary endpoints, like the occurrence of a response, a conservative method to replace missing values is to consider them as "failures". Off-treatment values will be set to missing. Missing data due to early discontinuation of treatment per the completer definition will be replaced as "failure" (e.g. non-responder) up to the planned timepoint for the analysis.

For binary endpoints that are derived from quantitative endpoints (e.g. HbA1c), NCF will not apply to missing values at Week 26 within the course of measurements on-treatment. Instead these values will be interpolated based on the last value observed before the missing Week 26 value and the first value observed after the missing Week 26 value (independent of the selection of a value as the picked visit value described in section 6.7), and the binary endpoint derived from the resulting interpolated value.

6.6.2 Safety and other variables

Missing safety data will not be replaced.

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.

6.6.3 Missing dates and times

Missing or incomplete AE dates are imputed according to BI standards (see “Handling of missing and incomplete AE dates”) (6).

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 08:00 o'clock in the morning, missing administration times at on-treatment visits will be imputed by 08:00 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 or visit 16 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 + 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.

If only the year of birth is known, the day and month of birth will be imputed as 01 January.

For partial start and stop dates for concomitant therapies (CT) 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.

For other incomplete date information (except to assess the overall compliance, see below) 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.

In case of missing visit date for a compliance record, the following hierarchy will be used to select a date to impute the missing visit date:

- The visit date registered in the IRT system
- The date of the vital sign measurement
- The date of the safety laboratory sampling
- The start date of the CGM period (only applicable to Visit 11)

All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

6.7 BASELINE, TIME WINDOW, 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. For specific endpoints, baseline definitions are as follows:

Hypoglycaemia rate

The event rate of hypoglycaemia (using the respective endpoint definition) during the 4 weeks prior to randomisation (from Day -28 up to Day -1). Collapsing will be performed as per the rules in sections 5.4.6.3 and 5.4.7. Rates will be presented per 30 days and also per patient year.

Insulin dose (total daily, total daily basal or total daily bolus)

Mean daily insulin requirement during the run-in period (Visit 5 to Visit 6, excluding day of randomisation). If < 4 days of valid insulin data is reported during the run-in period then the measurement will be considered missing. For data handling rules see section 5.4.6.2.

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
Body weight	1
Blood pressure	1
Insulin dose	0
Hypoglycaemia	1
Safety	
Adverse events	7
Hypoglycaemia [1]	1

*Refer to section 5.4.4 for the assignment of CGM measurements to the on-treatment period
[1] Refers to all hypoglycaemia analyses except the general hypoglycaemia AE analysis by SOC and PT.

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

Efficacy, safety, 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 (see table 6.7: 2).

Table 6.7: 2 Time windows for HbA_{1c} measurements at scheduled visits after randomisation

			Time window (actual days on treatment)	
Visit number	Visit label	Planned days	Start	End[A]
6	Baseline	0	NA	1[B]
8	Week 4	28	2	56
9	Week 12	84	57	105
10	Week 18	126	106	154
12	Week 26	182	155	241
14	Week 43	301	242	332
16	Week 52/EOT	364	333	Study drug stop date + X days

[A] In case of premature discontinuation of the study drug an eEOT visit has to be performed. Measurements from the eEOT visit will be assigned to the appropriate visit according to the table. In this case the time window for the visit that includes the eEOT visit 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. Patients will then be asked to continue in the study according to the visit schedule. Off-treatment measurements will be assigned to visits in the same manner. No time window for optional 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.

The mid-point between two 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 (end of treatment (EoT)) is endpoint dependent (cf. table 6.7: 1). As endpoints are planned to be measured according to different visit schedules, this midpoint algorithm will be applied and the time windows modified accordingly.

For example, the time windows for the blood pressure endpoints have been detailed in table 6.7: 3.

Table 6.7: 3 Time windows for blood pressure measurements at scheduled visits after randomisation

			Time window (actual days on treatment)	
Visit number	Visit label	Planned days	Start	End[A]
6	Baseline	0	NA	1[B]
7	Week 1	7	2	17
8	Week 4	28	18	56
9	Week 12	84	57	105
10	Week 18	126	106	154
12	Week 26	182	155	210
13	Week 34	238	211	269
14	Week 43	301	270	318
15	Week 48	336	319	350
16	Week 52/EOT	364	351	Study drug stop date + X days

[A] In case of premature discontinuation of the study drug an eEOT visit has to be performed. Measurements from the eEOT visit will be assigned to the appropriate visit according to the table. In this case the time window for the visit that includes the eEOT visit 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. Patients will then be asked to continue in the study according to the visit schedule. Off-treatment measurements will be assigned to visits in the same manner. No time window for optional 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.

For insulin endpoints, as data is available on an ongoing basis, a value will be derived using the 14 days prior to drug stop date and time windowing will be applied as outlined above based on the drug stop date. Only data from within the visit window will be used to derive the visit value.

Repeated and unscheduled efficacy and safety measurements will be assigned to the nominal visits and listed in the subject data listings according to the time windows described above. Only one observation per time window will be selected for analysis. For OC analyses, only on-treatment values will be considered. For OC-AD analyses, both on- and off-treatment values will be considered. If there are multiple values within a time-window, the value closest to the protocol planned visit day will be selected. 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 earliest 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. 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. For the Week 26 primary analysis, this is applicable if study drug is stopped during the time window of the Week 26 visit.

Data prior to randomisation will be based on nominal visits and time windowing will not be applied. For these time points, data from the scheduled visit will always be selected. Unscheduled visits will only be considered if no data from the scheduled visit is available. If no data from a scheduled visit is available and multiple unscheduled values are available for a visit, the first value will be selected.

For standard descriptive tables of laboratory parameters by visit (created by the BI standard macro XLAB2), in case of multiple measurements within a post-baseline time window for a visit, the worst value of these multiple measurements will be used for calculations.

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. Also for interpolation any valid values can be used, regardless of whether they were selected as visit values. For more details on LOCF refer to section 6.6.

7 PLANNED ANALYSES

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.

The overall disposition information will be presented as well as the disposition status at week 26.

The number of patients participating (screened, randomised, screened but not randomised, etc.) in the study by region, country and, for treated patients, centre, will also be analysed by treatment group and presented as a frequency distribution. The reason for not randomising screened patients will also be summarised. See table 9.1: 1 for assignment of countries within region.

In addition, the number of patients who discontinued trial medication due to fatal and non-fatal adverse events will be displayed in Appendix 16.1.9.2, as well as the number of screened patients by country and the number of screened patients by age groups. These analyses will be done for public data disclosure on European Union Drug Regulating Authorities Clinical Trials (EudraCT).

A summary of the number of patients in each randomisation stratum per treatment will also be shown. This summary will be based upon the data received from the IxRS provider.

For efficacy analyses, patients will be analysed according to the stratum to which they belong (regardless of any mis-assignment based on identification of the wrong stratum). For patients who were mistakenly randomised on both MDI and CSII at baseline, the stratification factor from IxRS will be used.

These two IPV analyses will be presented at week 26 and an additional overall IPV table will be created to summarize all the IPVs up to week 52.

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

For the in-text, end-of-text and appendix tables presenting descriptive analysis of the endpoints and other variables (analysed on logarithmic scale), the respective summary statistics (e.g., gMean, gCV, etc.) will be used.

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" (7)

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 (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

Treatment comparison

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

7.1 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

7.1.1 Baseline evaluation

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

Sex, race, ethnicity, region, age (years), age-groups, BMI (kg/m^2) categories, height (cm), smoking history and alcohol status, time since diagnosis of diabetes (years) (continuous and in categories), eGFR by CKD-EPI creatinine equation (continuous and in categories) and eGFR by CKD-EPI creatinine-cystatin C (continuous and in categories).

See section 7.8.2.4 for details on the derivation of eGFR endpoints.

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

HbA_{1c} (%) (continuous and in categories), FPG (mg/dL) (continuous and in categories), weight (kg) (continuous and in categories), waist circumference (cm), blood pressure (mmHg) (continuous and in categories), UACR (mg/gcrea) (continuous and in categories), fasted serum BHB (mmol/L) (continuous and in categories), capillary daily patient self-measured BHB (mmol/L) (continuous and in categories) and capillary morning patient self-measured BHB (mmol/L) (continuous and in categories).

Baseline hypoglycaemia rates will be presented in a separate table, displaying both the rate (per 30 days) and the frequency (from day -28 to day -1, inclusive) of 'severe hypoglycaemia events confirmed by adjudication' and 'symptomatic hypoglycaemia AEs with confirmed plasma glucose <54mg/dL and/or severe hypoglycaemia events confirmed by adjudication'. For the rates, the statistics will include the number of patients overall (N), the number of patients with at least 1 event (Nh), mean, SD, SE, min, 5th percentile (P5), P10, P25, median, P75, P90, P95, and max.

A separate table will display baseline CGM variables, including time spent in target glucose range of >70 to ≤180 mg/dL (%), time spent in hypoglycaemia (%), time spent in hyperglycaemia (%), IQR, MAGE, %CV, hourly mean area under the median curve over 24 hours.

Categories for baseline characteristics are defined in section 6.4.

Demographic and baseline characteristics tables will be presented on the FAS.

The demographic analysis will be repeated on the randomised population in Appendix 16.1.9.2 for disclosure on EudraCT.

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 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.

The summary on concomitant therapies during randomised treatment will be presented up to week 26 as well as up to week 52.

Separate summaries of use of antihypertensives, ASA or lipid lowering drugs at baseline by preferred name will be presented. The displayed categories and defining ATC levels and ATC codes are shown in table 9.2: 1.

Background pre-existing insulin therapy, including a categorisation of patients using MDI versus CSII will be presented. This summary will include background total daily insulin dose at baseline in insulin 'unit' and ‘units/kg’ as units of insulin per kg body weight at baseline. The table will also display the total daily basal insulin dose and the total daily bolus insulin dose at baseline. The number of insulin injections at baseline will be presented for MDI patients.

Concomitant diseases will be summarised by MedDRA System Organ Class (SOC) and preferred term (PT). Relevant diabetic medical history will also be presented by treatment group.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report.

Frequency distribution of patients with an overall compliance between 80% and 120% (inclusive) will be reported, as well as patients outside this range.

The overall compliance will be calculated as a weighted average of reported compliance. The sum of all reported compliance over the planned visits (disregarding of run-in) will be divided by the total duration (until last visit where medication is returned).

Refer to section 6.6.3 for how handling a single missing visit date for a compliance record, in the overall compliance calculation.

If compliance is missing at more than one on-treatment visit (>1), the overall compliance will be set to missing.

If a patient has a temporary treatment interruption, this should be reflected in the calculation of compliance.

If a patient prematurely discontinues from treatment, compliance will be calculated until last study drug intake. Missing compliance values for off-treatment visits will not be considered in the calculation for overall compliance.

The compliance analysis will be reported up to week 26 as well as up to week 52.

The FAS patient set will be considered.

7.4 PRIMARY ENDPOINT

7.4.1 Primary analysis

The primary endpoint in this trial is the change from baseline in HbA_{1c} (%) at 26 weeks. Efficacy and effectiveness will be tested in a hierarchical manner.

The primary efficacy analysis will be performed on the FAS (OC). Patients will be assigned to the treatment they were randomised to. Only on-treatment HbA_{1c} values will be included in the primary analysis. Only data up to the Week 26 timepoint will be included. All randomised treatment groups will be included in the same analysis.

Mean changes from baseline in HbA_{1c} after 26 weeks will be analysed using a restricted maximum likelihood-based repeated measures approach (MMRM analysis). Analyses will include the fixed categorical effects of treatment, pre-existing insulin therapy, week and treatment by week interaction, as well as the continuous, fixed covariates of baseline HbA_{1c}, baseline eGFR and baseline HbA_{1c} by week interaction. Patient will be included as random effect. An unstructured (co)variance structure will be used to model the within patient measurements.

If this analysis fails to converge, the following covariance structures will be tested: first-order ante-dependence (ANTE(1)), heterogeneous Toeplitz (TOEPH), Toeplitz (TOEP) and first-order autoregressive (AR(1)). The (co)variance structure converging to the best fit, as determined by Akaike's information criterion, will be used as the primary analysis.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.025$ (two-sided 97.5% confidence intervals). The residuals are assumed to have a multivariate normal distribution with zero means and covariance matrix as specified above. The primary treatment comparisons will be the contrasts between active treatments and placebo at Week 26.

The statistical model will be:

HbA_{1c} change from baseline = overall mean + continuous baseline HbA_{1c} + pre-existing insulin therapy + continuous baseline eGFR + treatment + week + baseline HbA_{1c} by week interaction + treatment by week interaction + random error

If the null hypothesis is successfully rejected for the efficacy analysis, then an effectiveness analysis will be performed on the mITT (OC-AD), including both on- and off-treatment data. The model will be the same as the model for the efficacy analysis described above.

7.4.2 Model diagnostics

In order to check the validity of assumptions used in the primary efficacy and effectiveness analysis models, model diagnostics will be performed as follows:

- Residuals from the primary model will be checked for normality using a Q-Q plot.
- Variance homogeneity across treatment groups, potential outliers and leverage points will be inspected using descriptive statistics and graphical methods.

These analyses will be reported in Section 16.1.9.2 of the trial report.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

7.5.1.1 Rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose <54 mg/dL and/or severe hypoglycaemic events confirmed by adjudication

Confirmatory analysis

The analysis of the rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose <54 mg/dL and/or severe hypoglycaemic events confirmed by adjudication will utilise a negative binomial model, with terms for treatment, continuous baseline rate, continuous baseline HbA_{1c}, continuous baseline eGFR and pre-existing insulin therapy as fixed effects and log(time at risk) as an offset. The results will be presented as a rate per patient-year. This analysis will be performed on the FAS (OC).

The baseline rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL and/or severe hypoglycaemic events confirmed by adjudication will be calculated based on the event rate during the 4 weeks prior to randomisation, see section 6.7.

The analysis of the rate from Week 5 to Week 26 will include all on-treatment events from the start of Week 5 (Day 29) until the Week 26 cut-off date (as defined in section 6.1). This period will also define the time at risk.

The analysis of the rate from Week 1 to Week 26 will include all on-treatment events from the date of first study drug intake until the Week 26 cut-off date (as defined in section 6.1). This period will also define the time at risk.

7.5.1.2 Change from baseline in body weight (kg) after 26 weeks

Confirmatory analysis

The analysis of change from baseline in body weight after 26 weeks will follow the strategy for the primary endpoint, MMRM. The model will include the fixed categorical effects of treatment, pre-existing insulin therapy, week and treatment by week interaction, as well as the continuous, fixed covariates of baseline HbA_{1c}, baseline eGFR, baseline body weight and baseline body weight by week interaction. This analysis will be performed on the FAS (OC), including all available on-treatment data up to the Week 26 timepoint.

A descriptive statistics table will present body weight (kg) and body weight change from baseline over time on the FAS (OC, OC-AD).

The treatment response over the treatment period will be illustrated on the FAS (OC) for each visit by plotting the adjusted means (SE) for change from baseline in body weight (kg) at each visit based on the MMRM model. A similar graphic will be created plotting the descriptive mean body weight (kg) at each visit using the FAS (OC).

7.5.1.3 Change from baseline in CGM endpoints after 26 weeks

Confirmatory analysis

The change from baseline in the percentage of time spent in target glucose range as determined by CGM after 26 weeks will be analysed using an ANCOVA model. The statistical model will be:

% time in target range change from baseline = overall mean + continuous baseline HbA_{1c} + pre-existing insulin therapy + continuous baseline eGFR + treatment + continuous baseline % time in range + random error

Treatment and pre-existing insulin therapy are fixed classification effects and baseline HbA_{1c}, baseline eGFR and baseline % time in target range are linear covariates. The random error is assumed to be normally distributed with mean 0 and unknown variance σ^2.

This analysis will be performed on the FAS (OC-P). All evaluable on-treatment data will be used.

The Week 26 value used for the analysis of change from baseline will be derived from the evaluable data from Week 23 to Week 26. Patients who do not have evaluable data at both Baseline and Week 26 will be excluded from the analysis. See section 5.4.4 for details.

A descriptive statistics table will present time in target range (%) and time in target range change from baseline at week 26 on the FAS (OC, OC-P).

The change from baseline in IQR (mg/dL) as determined by CGM after 26 weeks will be analysed using a similar ANCOVA model, replacing % time in target range with IQR.

7.5.1.4 Change from baseline in total daily insulin dose (U/kg) after 26 weeks

Confirmatory analysis

The analysis of change from baseline in total daily insulin dose after 26 weeks will follow the strategy for the primary endpoint, MMRM. The model will include the fixed categorical effects of treatment, pre-existing insulin therapy, week and treatment by week interaction, as well as the continuous, fixed covariates of baseline HbA_{1c}, baseline eGFR, baseline total daily insulin dose and baseline total daily insulin dose by week interaction. This analysis will be performed on the FAS (OC), including all available on-treatment data up to the Week 26 timepoint.

The baseline total daily insulin dose will be calculated based on the mean daily insulin requirement during the run-in period (Visit 5 to Visit 6). The total daily insulin dose will be calculated for each visit, based on the mean daily insulin requirement over the 14 days prior to the visit (excluding the day of the visit). If <4 days of valid insulin data is available, the visit value will be set to missing. The source data for the total daily insulin dose is the e-diary and this does not undergo a cleaning process. For data handling rules, see section 5.4.6.2.

A descriptive statistics table will present total daily insulin dose (U/kg), total daily insulin dose absolute change from baseline and total daily insulin dose relative change from baseline over time on the FAS (OC, OC-AD).

The treatment response over the treatment period will be illustrated on the FAS (OC) for each visit by plotting the adjusted means (SE) for change from baseline in total daily insulin dose (U/kg) at each visit based on the MMRM model. A similar graphic will be created plotting the descriptive mean total daily insulin dose (U/kg) at each visit using the FAS (OC).

7.5.1.5 Change from baseline in blood pressure after 26 weeks

Confirmatory analysis

The analysis of change from baseline in blood pressure after 26 weeks will follow the strategy for the primary endpoint, MMRM. The model will include the fixed categorical

effects of treatment, pre-existing insulin therapy, week and treatment by week interaction, as well as the continuous, fixed covariates of baseline HbA_{1c}, baseline eGFR, baseline blood pressure and baseline blood pressure by week interaction. This analysis will be performed on the FAS (OC), including all available on-treatment data up to the Week 26 timepoint.

A descriptive statistics table will present blood pressure (mmHg) and blood pressure change from baseline over time on the FAS (OC, OC-AD).

The treatment response over the treatment period will be illustrated on the FAS (OC) for each visit by plotting the adjusted means (SE) for change from baseline in blood pressure (mmHg) at each visit based on the MMRM model. A similar graphic will be created plotting the descriptive mean blood pressure (mmHg) at each visit using the FAS (OC).

All analyses will be performed separately for SBP and DBP.

7.5.2 (Other) Secondary endpoint(s)

This section is not applicable as no secondary endpoints have been specified in the protocol.

7.7 EXTENT OF EXPOSURE

A descriptive statistics table with mean, SD, median and range of the number of days a patient was on treatment will be provided for the treated set. The tables will also provide the sum of the total time (in years) that all patients pooled together were on each treatment.

A separate listing will be created of any patients that switched treatment at any time indicating exposure to each treatment.

A frequency table of number and percent of patients belonging to each categorical range of exposure weeks will be provided:

> 0 to 4 weeks, > 4 to 8 weeks, > 8 to 16 weeks, > 16 to 24 weeks, > 24 to 32 weeks, > 32 to 40 weeks, > 40 to 46 weeks, > 46 to 54 weeks, > 54 weeks. Note that "> 4 to 8 weeks" stands for 29 to 56 days.

In addition, the following exposure cumulative categories will be provided:

For the analysis at week 26, the following exposure cumulative categories will also be provided: ≥1 day, ≥1 week, ≥4 weeks, ≥8 weeks, ≥16 weeks, ≥24 weeks, ≥28 weeks. Note that "≥1 week" category refers to 7 days.

For the analysis at week 52, the following exposure cumulative categories will also be provided: ≥1 day, ≥4 weeks, ≥8 weeks, ≥16 weeks, ≥24 weeks, ≥32 weeks, ≥40 weeks, ≥46 weeks, ≥54 weeks.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set, except one hypoglycaemia analysis that will also be performed on the FAS for a sensitivity purpose (refer to section 7.8.1.5).

The safety analysis will be primarily performed up to 26 weeks of treatment, and then repeated up to 52 weeks of treatment.

7.8.1 Adverse events

AEs will be coded using the latest version of the MedDRA coding dictionary at database lock.

Any clinically significant new finding in the physical examination, vital signs (pulse symptoms) and in the 12-lead ECG starting after visit 6 (randomisation visit) will be considered as an AE and will be reported as such.

Unless otherwise specified (refer to section 7.8.1.4 for analysis on number of hypoglycaemia events, and respectively to Section 7.8.1.5 for analysis on number of DKA events) the analyses of adverse events will be descriptive in nature and analyses of AEs will be based on the number of patients with AEs (not the number of AEs).

For analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data 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).
- In addition certain analyses (other than the general analyses by SOC and PT produced by the XAE macro) will have their own collapsing rules. This concerns the following endpoints:
    - Genital infection events will not be collapsed if they are representative of different types (i.e. fungal balanitis or vulvovaginitis versus other than fungal balinitis or vulvovaginitis);
    - Sepsis events will not be collapsed if they are representative of different sources of infection (i.e. urinary tract (urosepsis) versus other than urinary tract);
    - Severe hypoglycaemia endpoint confirmed by adjudication will not be collapsed;
    - Hypoglycaemia adverse events will not be collapsed (except in case of occurrences with identical onset date, time and glucose value);
    - Lower limb amputation endpoint will not be collapsed
- 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.

For further details on summarization of AE data, please refer to (8).

7.8.1.1 Assignment of AEs to treatment

In general, the analysis of adverse events will be based on the concept of treatment emergent adverse events.

This means that all adverse events occurring between first drug intake until 7 days after last drug intake will be assigned to the randomised treatment. All adverse events occurring before first drug intake will be assigned to 'screening' and all adverse events occurring after last drug intake + 7 days will be assigned to 'post-treatment'. For details on the treatment definition, see section 6.1.

For all adverse event analyses at week 26 except the specific analyses on hypoglycaemia (i.e. not the general hypoglycaemia AE analysis by SOC and PT), all adverse events with an onset date up to the minimum of (treatment stop + 7 days) and the week 26 cut-off date will be included. Events occurring after this date will be censored for the week 26 analysis. Refer to Section 6.1 for details on the week 26 cut-off date definition.

For the specific analyses on hypoglycaemia, the events with an onset date up to the minimum of (treatment stop + 1 day) and the week 26 cut-off date will be included.

7.8.1.2 Analysis of other significant AEs

Other significant AEs will be reported and summarised according to ICH E3 criterion. Thus, AEs classified as 'other significant' will include those non-serious and non-significant adverse events with:

- ‘action taken = discontinuation’ or ‘action taken = reduced’, or
- 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 or Blinded Report Planning Meeting.

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 according to ICH E3 (9), 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).

Appendix 16.1.9.2 will include the following analyses:

- an analysis on patients with adverse events by outcome,
- an analysis on the frequency of patients with non-serious adverse events occurring with incidence in preferred term greater than 5 % by treatment for disclosure on clinicaltrials.gov website.

The following analyses will also be reported in Appendix 16.1.9.2 for disclosure on EudraCT:

- AEs per treatment arm

This analysis includes the number of patients with serious AEs, the number of patients with non-serious AEs >5%, the total number of deaths (all causes), as well as the total number of deaths resulting from drug-related adverse events.

- Number of patients with non-serious AEs > 5% within any treatment arm, for each preferred term (grouped by standard SOC terms)
- Number of patients with serious AEs on preferred term level (grouped by standard SOC terms)

7.8.2 Laboratory data

For continuous safety laboratory parameters standardised and normalised values will be derived as well as the differences to baseline. The process of standardisation and normalisation as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data (10). All analyses considering multiple of times upper limit of normal (ULN) will be based on original and not normalized data.

The analyses of laboratory data will be descriptive in nature and will be based on BI standards.

Results of laboratory analyses will be presented based on both SI units and US conventional units.

Baseline for safety laboratory parameters will be the last available measurement before the start of randomised study drug. In general, laboratory measurements taken up to 3 days after the last administration of randomised study drug will be considered as on-treatment. The exception will be for the liver enzyme elevation analysis (see below).

For all laboratory analyses at week 26, all laboratory parameters measured up to the minimum of (treatment stop + 3 days) and the week 26 cut-off date will be included. Laboratory measures observed after this date will be censored for the week 26 analysis. Refer to section 6.1 for details on the week 26 cut-off date definition.

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.

7.8.2.1 General laboratory evaluation

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 based on normalised values, as well as on the basis of standardized values for parameters with an incomplete reference range (e.g. ALT).

Descriptive statistics will in addition be calculated for the change from baseline in haematocrit over time, including during the follow-up period. In particular, statistics will be provided for last-value on-treatment, follow-up, change from baseline from last on-treatment value and follow-up, and change from last on-treatment assessment to follow-up.

Frequency tables will summarise the number of patients with potentially clinically significant abnormalities as defined for the new XLAB macro (version 2.03) and the criteria for clinically significant abnormalities based on normalised laboratory values will be listed.

7.8.3 Vital signs

Other than the analysis of SBP and DBP as key secondary endpoints, only descriptive statistics are planned for the summary of pulse rate (bpm) and change from baseline in pulse rate over time based on the treated set (OC, OC-AD).

Pulse rate observation measured up to the minimum of (treatment stop + 1 day) and the week 26 cut-off date will be included in the week 26 analysis. Pulse rate observation observed after this date will be censored for the week 26 analysis. Refer to Section 6.1 for details on the week 26 cut-off date definition.

7.8.4 ECG

12-lead ECG measurements will be taken at baseline (visit 6), at visit 12 and at EOT (visit 16). 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 ECG will be considered as AEs and analysed as planned in Section 7.8.1.

7.8.5 Others

Not applicable

8 REFERENCES

1	CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2	Service FJ; Glucose Variability; Diabetes 62:1398-1404, 2013 [R14-4138]
3	Baghurst PA.; Calculating the mean amplitude of glycemic excursion from continuous glucose monitoring data: an automated algorithm; Diabetes Technology & Therapeutics 2011; 13(3):296-302 [R14-4136]
4	Fritzsche G, Kohnert KD, Heinke P, Vogt L, and Salzsieder E; The use of a computer program to calculate the mean amplitude of glycemic excursions; Diabetes Technology & Therapeutics 2011; 13(3) L319-325 [R14-4137]
5	001-MCS 36-472: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
6	001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", version 2.0; IDEA FOR CON.
7	001-MCG-159, "Reporting of clinical trials and project summaries", current version; IDEA FOR CON.
8	001-MCG-156: «Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA FOR CON.
9	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.
10	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	Author	Sections changed	Brief description of change
Final	12-JUN-17		None	This is the final TSAP without any modification
Revised	08-NOV-17		7.5.1.2 7.5.1.5	• Multiple imputation analysis for body weight and blood pressure adapted • • Minor changes in the wording and correction of typos