Boehringer Ingelheim

Trial Statistical Analysis Plan

C10222465−03

BI Trial No.:	1218.102
Title:	A phase III, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin, administered orally once daily, in combination with insulin therapy for 24 weeks in Chinese type 2 diabetes mellitus patients with insufficient glycaemic control
Investigational Product(s):	Linagliptin (Trajenta)
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Page 1 of 47

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase (or SGPT)
ANCOVA	Analysis of Covariance
ANTE(1)	First-order Ante-dependence
AR(1)	First-order Autoregressive
ARH(1)	Heterogeneous First-order Autoregressive
AST	Aspartate Aminotransferase (or SGOT)
AUC	Area Under the Curve
BIcMQ	Boehringer Ingelheim Customised MedDRA Query
BMI	Body Mass Index
BRPM	Blinded Report Planning Meeting
CEC	Clinical Event Committee
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DMG	Dictionary Maintenance Group
DI	Disposition Index
DRA	Drug Regulatory Affairs
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMEA	European Agency for the Evaluation of Medicinal Products
EoT	End-of-Trial
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
FPI	Fasting Plasma Insulin
GFR	Glomerular Filtration Rate
HbA_{1c}	Glycosylated Haemoglobin A1c

Term	Definition / description
ICH	International Conference on Harmonisation
ITT	Intention-to-treat
IRT	Interactive Response Technology
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MQRM	Medical Quality Review Meeting
MTT	Meal Tolerance Test
NCF	Non-Completers Considered as Failure
O*C	Oracle Clinical
OC	Observed Cases
PK	Pharmacokinetics
PPG	Post-prandial Glucose
PPS	Per Protocol Set
PSTAT	Project Statistician
PT	Preferred Term
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
RS	Randomised Set

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, and randomization.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Due to an alignment of terminology and analysis of hypoglycaemic events on project level, the new definition and analyses were applied in the TSAP, including investigator defined hypoglycaemic AE and severe hypoglycaemic AE.

The definitions of treated set and full analysis set were updated to be more accurate.

Text in CTP	Adjusted text in TSAP
TS - Treated Set The treated set (TS) will consist of all patients who were randomised and treated with at least one dose of study drug.	TS - Treated Set It consists of all patients treated with at least one dose of study drug. The TS is the basis for safety analyses.
FAS - Full Analysis Set The full analysis set (FAS) will consist of all patients in the TS who had a baseline HbA_{1c} value and at least one on-treatment HbA_{1c} value.	FAS - Full Analysis Set It consists of all patients randomised in the TS who had a baseline HbA_{1c} value and at least one on-treatment HbA_{1c} value. The FAS is the basis for the intention-to-treat (ITT) analysis.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint in this study is the change from baseline in HbA_{1c} after 24 weeks of treatment (HbA_{1c} after 24 weeks of treatment minus HbA_{1c} at baseline), where "baseline" refers to the last observation prior to the start of randomised study drug, including the observation prior to the placebo run-in. HbA1c will be measured in the unit of % at all clinical visits. No transformation (e.g. logarithmic) of the change from baseline in HbA_{1c} values will be done.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable in this trial.

5.2.2 (Other) Secondary endpoint(s)

Secondary efficacy endpoints are:

- Change from baseline in FPG after 24 weeks of treatment
- Change from baseline in 2-hour PPG after 24 weeks of treatment
- Proportion of patients with HbA_{1c} on treatment <7.0% after 24 weeks of treatment
- Proportion of patients with HbA_{1c} on treatment <6.5% after 24 weeks of treatment
- Proportion of patients with HbA_{1c} lowering by at least 0.5% after 24 weeks of treatment

The secondary safety endpoints defined in CTP regarding investigator defined hypoglycaemic AE and severe hypoglycaemic AE were included in Section 7.8 Safety Analyses.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

There will be 5 treatment phases in this trial: screening period, placebo run-in period, double-blind treatment period (with either BI drug or matching placebo), post-treatment and post-study.

Table 6.1: 1 Treatment regimens / study intervals

Label	Interval	Start date	Start time
Screening	Screening period	Date of informed consent	00:00
Run-in Placebo	Placebo run-in period	Date of first administration of run-in medication	00:00
Lina 5 mg / Placebo	Double-blind treatment period	Date of first administration of study medication for double-blind treatment period	Time of first administration of study medication, 12:00 if missing
Post-treatment	Post-treatment	Date of last drug intake + X* + 1	00:00
Post-study	Post-study	Date of last contact + 1	00:00

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

The purpose of the definition in the above 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.

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

If a patient erroneously receives the wrong trial drug, the patient will be analysed ‘as randomised’. Additionally, the AEs with an onset during the time of the incorrect study treatment will also be listed separately.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Table 6.2: 1 defines the different categories of important protocol violations (IPVs) to be considered for evaluability of efficacy (E) or for patients’ right and safety (S). IPVs marked with an ‘S’ only will not lead to exclusion of a patient from the per-protocol-set (PPS). Only the IPVs marked with ‘E’ will lead to exclusion from the PPS.

Table 6.2: 1 Important protocol violations

PV Category / Code		Description	Criterion to check for PV (Comments)	Efficacy (E) or Safety (S)	PV Leading to Exclusion from PPS
A		**Entrance criteria not met**			
A1		Target indication not met			
	A1.1	No type 2 diabetes	Inclusion criterion #1 checked NO	E	Yes
	A1.2	Antidiabetic background therapy not as required	Inclusion criterion #2 checked NO or required antidiabetic background not recorded on eCRF	E	Yes
A2		**Inclusion criteria violated**			
	A2.1	HbA_{1c} out of range at start of placebo run-in period	Inclusion criteria #3 not met and/or HbA_{1c} at Visit 1 out of range for inclusion by >0.2% (i.e., <7.3% or >10.2%)	E	Yes
	A2.2	Age out of range at screening	Inclusion criteria #4 not met and/or Age < 18 years	E	Yes
	A2.3	Body mass index (BMI) out of range at screening	Inclusion criteria #5 not met and/or BMI > 45 kg/m^2	E	Yes
A3		**Exclusion criteria violated**			
	A3.1	Treatment with protocol excluded antidiabetic drugs	Exclusion criterion #2, #5 checked Or Intake of any of the excluded drugs reported on the eCRF within the time prior to informed consent specified in the exclusion criteria	E	Yes
	A3.2	Relevant concomitant diagnoses	Exclusion criterion #3 checked Or acute coronary syndrome (non-STEMI, STEMI and unstable angina pectoris), stroke or TIA recorded on concomitant diagnoses eCRF within previous 3 months	S	No
	A3.3	Impaired hepatic function	Exclusion criterion #4 checked Or ALT (SGPT) or AST (SGOT) or alkaline phosphatase > 3xULN at screening / run-in phase	S	No
	A3.4	Gastrointestinal surgery	Exclusion criterion #6 checked	E	Yes

Table 6.2: 1 (continued) Important protocol violations

PV Category / Code		Description	Criterion to check for PV (Comments)	Efficacy (E) or Safety (S)	PV Leading to Exclusion from PPS
	A3.5	Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years	Exclusion criterion #7 checked	S	No
	A3.6	Blood dyscrasias or relevant disorders	Exclusion criterion #8 checked	S	No
	A3.7	Known hypersensitivity to any of the drugs in the study regimen	Exclusion criterion #9 checked	E	Yes
	A3.8	Treatment with protocol excluded anti-obesity drugs	Exclusion criterion #10 checked Or intake of any of the excluded drugs reported on the eCRF within the time prior to informed consent specified in the exclusion criterion	E	Yes
	A3.9	Treatment with protocol excluded systemic steroids or change in thyroid hormone dose	Exclusion criterion #11 checked Or intake of any of excluded drugs reported on the eCRF within the time prior to informed consent specified in the exclusion criteria	E	Yes
	A3.10	Specific exclusion criterion for pre-menopausal women violated	Exclusion criterion #12 checked	S	No
	A3.11	Alcohol or drug abuse that may interfere with study participation	Exclusion criterion #13 checked	E	Yes
	A3.12	Participation in another trial with an investigational drug within 2 months prior to informed consent	Exclusion criterion #14 checked Final decision at the DBL meeting (medical judgement), depending on the type of drug given in the prior trial (only if investigational drug interferes with glucose metabolism).	E	Yes

Table 6.2: 1 (continued) Important protocol violations

PV Category / Code		Description	Criterion to check for PV (Comments)	Efficacy (E) or Safety (S)	PV Leading to Exclusion from PPS
B		**Informed consent**			
	B1	Informed consent not available	Date of informed consent missing Or No signature on patient's "Declaration of Informed Consent" ***Patient's data will not be used at all.***	S/E	Yes
	B2	Informed consent too late	Date of informed consent not obtained prior to any study related procedure or re-consent with new version of informed consent too late. Minimum requirement for initial informed consent <= date of Visit 1/date of any study procedure	S	No
C		**Trial medication and randomisation**			
C1		Incorrect trial medication taken			
	C1.1	No study medication taken	Patient randomised but no study medication taken. ***Exclude also from FAS and TS.***	E	Yes
	C1.2	Incorrect trial medication taken	Wrong medication taken (different medication than the patient was randomised to taken at any visit, i.e. drug kit recorded in eCRF from different treatment group than drug kit assigned by IVRS) Can only be finally judged after DBL since unblinding information is required.	E	Yes
C2		Randomisation not followed			
	C2.1	Treated without randomisation	Patient treated according to eCRF but not randomised by IVRS. ***Exclude also from FAS and RS.***	E	Yes
C3		Non-compliance			
	C3.1	Non-compliance with drug intake	Gross non-compliance issues only – based on compliance section of CRF (at least two times on treatment compliance was outside 80-120% according to eCRF) Final decision at the DBL meeting. (medical judgement)	E	Yes

Table 6.2: 1 (continued) Important protocol violations

PV Category / Code		Description	Criterion to check for PV (Comments)	Efficacy (E) or Safety (S)	PV Leading to Exclusion from PPS
	C3.2	Non-compliance with criteria for removal from the trial	Criteria for removing a patient from the trial not adhered to. Final decision at the DBL meeting. (medical judgement)	E	Yes
	C3.3	Treatment interruption for more than 10 consecutive days	Documented treatment interruption for 11 consecutive days or more.	E	Yes
C4		Medication code broken			
	C4.1	Medication code broken without just cause	Medication code was broken for no valid reason. Final decision at the DBL meeting. (medical judgement)	E	Yes
D		**Concomitant medication**			
D1		Prohibited medication use			
	D1.1	Rescue medication taken without just cause	Review of eCRF for use of rescue medication within the 24 weeks and fasting plasma glucose prior to rescue therapy < 90% of protocol requirement for rescue medication (if threshold is 240, FPG<216 mg/dL or <12 mmol/L prior to rescue medication) and no documented hyperglycaemia.	E	Yes
	D1.2	Antidiabetic drug taken that is not a protocol defined rescue medication and criterion to administer rescue medication not fulfilled	Antidiabetic drug other than protocol defined rescue medication taken and criterion for rescue therapy as in D1.1 not fulfilled.	E	Yes
	D1.3	Use of contraindicated drugs	Review of eCRF for contraindicated drugs. Final decision at the BRPM meeting. (medical judgement)	E	Yes

Note : Missing visits, evaluations, and tests will be considered missing data, not protocol deviations.

6.3 PATIENT SETS ANALYSED

SCR - Screened Patients Set

It consists of all patients screened for the trial, with informed consent given and who completed at least some screening procedures at Visit 1.

RS - Randomised set

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

TS - Treated Set

It consists of all patients treated with at least one dose of study drug. The TS is the basis for safety analyses.

FAS - Full Analysis Set

It consists of all patients randomised in the TS who had a baseline HbA1c value and at least one on-treatment HbA1c value. The FAS is the basis for the intention-to-treat (ITT) analysis.

FAS - Completers

It consists of all patients in the FAS with treatment duration no less than 149 days and did not prematurely discontinue the trial. The date of last intake of study drug should be on or after the start of the time window of the last on-treatment visit, and an HbA1c value should be available within the time window for this visit.

PPS - Per Protocol Set
It consists all patients in the FAS without important PVs for efficacy.

MTT-set - Meal Tolerance Test set

It consists all patients of the FAS with a valid MTT at baseline and at the end of the study. An MTT is considered valid if it has a valid FPG and a valid 2 hour PPG value.

Table 6.3: 1 Check-box for data set to be used for which class of endpoints

Class of endpoint	TS	FAS	MTT-set
Primary endpoint –primary analysis		X	
Primary endpoint –sensitivity analysis			
Other efficacy endpoints		X	
MTT endpoints			X
Safety endpoints	X		
Demographics	X		
Baseline for efficacy		X	

6.5 POOLING OF CENTRES

This section is not applicable as no analysis by centre will be performed.

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. A description of the various approached are given in the following:

Observed cases (OC)

One general approach that is possible for all endpoints is to analyse only the available data that were observed while patients were on treatment, i.e. excluding the missing data. Missing data in this analysis will not be replaced.

For all efficacy endpoints, this OC-technique will be adapted by setting any values taken after rescue medication to missing. The definition of rescue therapy please refers to section 5.3.

It should be noted that this method provides unbiased estimates only under the assumption that the data are missing at random; and so, this method is likely to lead to anti-conservative estimates of the treatment effects in case of data missing due to patients dropping-out because of the lack of efficacy of the drug under study. However, since it can be expected that the drop-out rate due to lack of efficacy and the rate of patients with rescue therapy is higher in

the placebo group, this approach will lead to a conservative estimates of the placebo-adjusted treatment effect of linagliptin.

Non-completers considered as failure (NCF)

For binary endpoints like a treat to target response of $HbA_{1c} < 7\%$ a conservative method to replace missing values is to consider them as "failure". Missing data due to early discontinuation will be replaced as "failure" (e.g. $HbA_{1c} \geq 7\%$) up to the planned final visit to be reached by all patients. Similarly, values obtained after the start of rescue therapy will be considered "failure".

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 values of underlying quantitative endpoint (e.g. based on imputation as described for HbA_{1c}).

Table 6.6: 1 Summary of imputation methods for efficacy endpoints

Imputation method	Endpoint	Handling of missing values	Handling of values after rescue therapy
OC	Continuous and binary endpoints	No imputation	Excluded (considered missing). One picked value per visit.
NCF	Binary endpoints derived from continuous endpoints (e.g. HbA_{1c}<7.0%)	Missing values after premature discontinuation of study drug are considered failure (endpoint not achieved). Missing values with subsequent present on-treatment values will be imputed based on the interpolated values for the underlying continuous endpoint.	Values after the start of rescue therapy are imputed as failure.

Safety and other variables

Missing safety data will not be replaced, but an analysis of the change from baseline to the last available value under treatment and the minimum and maximum post baseline will be determined for quantitative safety laboratory variables. In general, the last measurement taken between the first intake of randomised trial drug and drug-stop date + 7 days will be analysed as the last value on-treatment.

Missing dates and times

Missing or partial date and time information for AEs will be replaced according to general BI rules (2).

If the date of first drug administration is missing but the patient was randomised and treated, the date of the first drug administration will be set to the date of randomization. If the date of first administration is partially missing with the month and year present, the day will be set to the date of randomization if randomisation was in the same month. If randomization 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 an End of Treatment (EoT) visit is documented, it should be the date of the EoT visit.
- If the date is incomplete with only month and year and the EoT visit is missing, it should be the first day of the following month.
- If the patient is lost to follow-up it should be the date of the last visit + the longest treatment duration based on drug supply + 1 day.
- All other cases need to be assessed by the trial team on an individual basis, trying to use the points above as guidance.

Additional rules for the treatment set-up in O*C:

- Since usually no times are available for the start of the screening, placebo run-in period will be considered to start at 0:00 o'clock (midnight).
- Also the start of the post-treatment period will be considered at 0:00 o'clock (midnight) on the day after the study drug stop date.
- The post study period on the date after the follow-up visit, starting at 0:00 o'clock midnight.
- In general, the start if the post-treatment period is defined as date of last drug administration + 1 day. If the drug stop date is incomplete with only month and year present, the post-treatment period starts on the first day of the following month (i.e. at the same day as the imputed drug stop date).
- The post study period start is intended to start on the date of last contact + 1 day and the date of last contact is assumed to be after the date of last drug administration. In patients who discontinue the study, it can happen that the date of last contact is before date of last drug administration. To account for such cases the start of the post-study

period is defined as the maximum of the last contact date + 1 day, the date of the last visit + 1 day and the start of the post-treatment period + 1 day.

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. If the year is missing, the date will be considered missing.

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

Missing dates for meal tolerance test in the eCRF should be replaced based on the dates of the according lab samples. Missing times for the start and end of a meal will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

With regard to efficacy and safety endpoints, the term “baseline” generally refers to the last observed measurement prior to administration of any randomised study medication. For daily insulin dose the baseline will be derived from the eCRF and is equal to the daily insulin dose at day of first study medication intake. Also, for metformin, baseline dose refers to the dose at day of first study medication intake.

Measurements taken prior to the first intake of randomised study drug will be considered pre-treatment values. The pre-treatment values will be assigned to a visit according to the nominal visit number as recorded on the 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 analyse.

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
FPG	1
PPG,	0
Body weight	7
Waist circumference	7
Rescue medication (new antidiabetic treatment, increases of background antidiabetic treatment)	
If patient did not prematurely discontinue from trial medication	-1
If patient prematurely discontinued from trial medication (any reason)	0
Safety	
Adverse events	7
Safety laboratory measurements	7
Vital signs	7

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

On-treatment efficacy 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 3). Reasons to base the time widows 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 randomization, the time window for the first on-treatment visit could include times the patients was not yet on study drug.

The time window for the first visit after randomization 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 planned last observation carried forward (LOCF) approach, but may lead to an underestimation of the treatment effect at the first visit form parameters that react slowly on treatment.

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

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

Visit number	Visit label	Planned days after randomisation	Planned days on treatment	Time window (actual days on treatment)	
				Start	End[A]
3	Baseline	0	1	NA	1[B]
4	Week 4	28	29	2	43
5	Week 8	56	57	44	71
6	Week 12	84	85	72	106
7	Week 18	126	127	107	148
8	Week 24/EoT	168	169	149	Study drug stop date + X days

[A] In case of premature discontinuation of the study drug a Visit 8 (EoT) has to be performed. If such a Visit 8 falls into the time window of a previous visit, measurements will be assigned to this previous visit and the visit value will be determined as described below. In this case the time window for the visit that includes Visit 8 will end X days after the study drug stop date, including Day X. The definition of X is endpoint specific, cf. Table 6.7: 1.

[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 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 day of such an examination.

Repeated and unscheduled efficacy 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 at an on-treatment visit – the value will be selected which is closest to the protocol planned 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 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.

Safety measurements will be assigned to the nominal visit as recorded on the eCRF or as provided by the laboratory.

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 (CTR) as a frequency-distribution. The number of patients participating in the study by centre will also be analysed by treatment group and presented as a frequency distribution.

A frequency of patients with important PVs, also summarised by whether the IPV led to exclusion from the PPS, will be presented by treatment group for the treated set. The frequency of patients in different analysis sets and primary reason for exclusion will also be analysed for each treatment group on randomised set.

For in-text tables presenting descriptive analysis of the end-points and other variables, the set of summary statistics is: N (number of patient with non-missing values), mean, standard deviation (SD).

For the respective end-of-text tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For appendix tables, the set of summary statistics is: N / Mean / SD / Min / Q1 (lower quartile) / Median / Q3 (upper quartile) / Max.

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Gender, age (in years), age-groups, weight (kg), weight categories, BMI (kg/m^2), BMI categories, eGFR ($ml/min/1.73m^2$), eGFR categories, Metformin dose, baseline daily insulin dose, daily insulin dose per body weight (IU/kg), type of insulin, height (cm), waist circumference (cm), smoking-status and alcohol status. Categories for demographic and baseline characteristics are defined in Section 6.4.

Descriptive analysis of the following baseline efficacy variables will be presented on the FAS population:

HbA_{1c}, HbA_{1c} categories, FPG (mg/dL), FPG categories,

time since diagnosis of diabetes.

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency distribution of patients with different concomitant diseases and medications (including the anti-diabetic therapies at screening) will be presented.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. Frequency distribution of patients whether with compliance-level between 80% and 120% will be presented by visit (Week 0 to 4, Week 4 to 8, Week 8 to 12, Week 12 to 18 and Week 18 to 24).

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary efficacy analysis

The primary analysis will be performed on the FAS (OC) and patients will be assigned to the treatment they were randomised to. A REML-based MMRM approach is applied to compare the change in HbA1c from baseline after 24 weeks of treatment.

The statistical model will be

HbA_{1c} change from baseline = overall mean + baseline HbA_{1c} + treatment + type of insulin
+ week+ week by treatment interaction
+ baseline HbA_{1c} by week interaction
+ random error

This model includes effects accounting for the following sources of variation: ‘baseline HbA1c’, ‘treatment’, ‘type of insulin (basal insulin or any permitted pre-mixed insulin) ’, ‘week’, ‘week by treatment interaction’ and ‘baseline HbA1c by week interaction’. ‘Treatment’, ‘type of insulin’, ‘week’ and ‘week by treatment interaction’ are fixed, categorical effects, and ‘baseline HbA1c’ and ‘baseline HbA1c by week interaction’ are continuous, linear covariates. For each patient, the error terms from the on-treatment visits represent the within-patient variability, and are assumed to follow a multivariate normal distribution with an unstructured covariance matrix.

If the model fails to converge, the following covariance structures will be tested in order: ANTE(1)→ARH(1)→AR(1). The first model to converge will be used as the primary analysis. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Significance tests will be based on least squares means using a two-sided $\alpha = 0.05$ (two sided 95% confidence intervals).

Only the available data which were observed whilst patients were on treatment will be included in the analysis. Missing data are handled implicitly by the above statistical model, rather than by using any imputation.

Superiority will be tested using the p-value of the treatment effect and a two-sided 95% confidence interval for the treatment difference.

For Week 24 analysis, all levels for factor week up to Week 24 are to be considered in the model, i.e. Week 4, 8 12, 18 and 24.

In addition, descriptive statistics for HbA1c over time are presented for FAS (OC),

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

Change from baseline in FPG after 24 weeks of treatment

Analysis of change from baseline in FPG will follow the strategy for the primary endpoint. MMRM will be used to analyse the mean change from baseline in FPG after 24 weeks of treatment.

FPG change from baseline = overall mean + baseline HbA_{1c} + treatment + type of insulin
+ week+ week by treatment interaction
+ baseline FPG
+ baseline FPG by week interaction
+ random error

The analysis will include the fixed categorical effects of treatment, type of insulin, week and treatment by week interaction, as well as the continuous, fixed covariates of baseline FPG, baseline HbA1c and baseline FPG by week. An unstructured (co)variance structure will be used to model the within patients measurements. This analysis will be performed on FAS (OC).

Change from baseline in 2-hour PPG after 24 weeks of treatment

Change from baseline is calculated as the on-treatment value minus the baseline values. The descriptive statistics will be displayed based on MTT-set (OC).

As 2-hour PPG is only collected once on-treatment, an ANCOVA model will be fitted on the MTT-set (OC). The analysis will use the ANCOVA model used in the strategy for the sensitivity analysis of HbA1c, with additional baseline 2-hour PPG as a continuous covariate.

2-hour PPG change from baseline = overall mean + baseline HbA1c + treatment
+ type of insulin + baseline 2-hour PPG
+ random error

Proportion of patients with HbA1c on treatment < 7.0% after 24 weeks of treatment

Logistic regression for the patients achieving HbA1c < 7.0% at Week 24 will be performed on FAS (NCF); patients who do not complete 24 weeks of treatment will be considered non-responders. The model will include treatment, continuous baseline HbA1c and type of insulin. Patients with baseline HbA1c < 7.0% will be excluded from the analysis.

A frequency table with the number and percentage of patients with HbA1c < 7.0% at Week 24 in each treatment group will also be presented based on FAS (NCF).

Proportion of patients with HbA1c on treatment < 6.5% after 24 weeks of treatment

Logistic regression for the patients achieving HbA1c < 6.5% at week 24 will be performed on FAS (NCF); patients who do not complete 24 weeks of treatment will be considered non-responders. The model will include treatment, continuous baseline HbA1c and type of insulin. Patients with baseline HbA1c < 6.5% will be excluded from the analysis.

A frequency table with the number and percentage of patients with HbA1c < 6.5% at week 24 in each treatment group will also be presented based on FAS (NCF).

Proportion of patients with HbA1c lowering by at least 0.5% after 24 weeks of treatment

Logistic regression for the patients achieving lowering of HbA1c by at least 0.5% from baseline at Week 24 will be performed on FAS (NCF); patients who do not complete 24 weeks of treatment will be considered non-responders. The model will include treatment, continuous baseline HbA1c and type of insulin.

Frequencies regarding the number and percentage of patients with lowering of HbA1c by at least 0.5% from baseline at Week 24 in each treatment group will be also be presented based on FAS (NCF).

The analyses for further safety endpoints are specified in Section 7.8.1.

7.7 EXTENT OF EXPOSURE

Exposure to study drug will be calculated in days as (study drug stop date – study drug start date + 1) and will be tabulated as a frequency table with categorized treatment duration. In addition, median exposure and the number of patient years of exposure will be given per treatment (calculated as the sum of days over all patients per treatment group divided by 365.25).

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS. All safety data will be displayed and analysed using descriptive statistical methods. No formal inferential analysis is planned for safety comparison.

7.8.1 Adverse events

The analysis of AEs will be descriptive in nature. All analysis of AEs will be based on the number of patients with AEs (not the number of AEs) according to the BI standards (3). For this purpose, AE data will be combined in a 2-step procedure into AE records.

Processing of individual AE information

In a first step, for analysis multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- The same lowest level term is reported for the occurrences.
- The occurrences are time-overlapping or time-adjacent (time-adjacency of 2 occurrences was given if the second occurrence started on the same day or on the day after the end of the first occurrence).
- Treatment does not change between the onset of the occurrence OR treatment changes between the onset of the occurrences, but no deterioration is observed for the later occurrence.

Assignment of AEs to treatments

In a second step, AE episodes will be condensed into AE records provided that the episodes are reported with the same term on the respective MedDRA level and that the episodes are assigned to the same treatment.

The analysis of AEs will be based on the concept of treatment emergent AEs. To this end, all AEs occurring between start of treatment and end of REP will be considered

'treatment-emergent'. The REP is defined as a period of 7 days after the last dose of trial medication. That means that all AEs occurring between first drug intake till last drug intake + residual effect period (REP) will be assigned to the randomised treatment. All AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after the REP will be assigned to 'post-treatment' (for listing only). For details on the treatment definition, see Section 6.1.

In general, in-text AE tables will only present AEs assigned to the randomised treatments. End-of-text tables will display in addition AEs observed 'pre-treatment' (including AEs observed during screening and placebo run-in regardless of treatment group) and AEs observed during post-treatment regardless of treatment group.

Analysis of other significant AEs

According to ICH E3 (1), AEs classified as 'other significant' needs to be reported and will include those non-serious and non-significant AEs 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).

AE summaries

An overall summary of AEs will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for patients with other significant adverse events according to ICH E3 (1), for patients with AESI, for patients with AEs leading to discontinuation, for patients with drug-related AEs and for patients with serious adverse event (SAE).The system organ classes will be sorted alphabetically, and preferred terms will be sorted by frequency (within SOC).

The frequency of patients with AEs will also be summarised by subgroups, including age, gender, background therapy and renal function. The details of the subgroups can be found in Table 6.4: 1.

Additional AE analyses

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:

- investigator defined hypoglycaemic AE
    - hypoglycaemic AE with PG <= 70 mg/dL (<= 3.9 mmol/L) or severe hypoglycaemic AE (= confirmed hypoglycaemic AE)

- hypoglycaemic AE with PG < 54 mg/Dl (<= 3.0 mmol/L) or severe hypoglycaemic AE
- severe hypoglycaemic AE

- investigator defined symptomatic hypoglycaemic AE or severe hypoglycaemic AE
  - symptomatic hypoglycaemic AE with PG <= 70 mg/dL (<= 3.9 mmol/L) or severe hypoglycaemic AE
  - symptomatic hypoglycaemic AE with PG < 54 mg/dL (<= 3.9 mmol/L) or severe hypoglycaemic AE
  - severe hypoglycaemic AE

Asymptomatic hypoglycaemic events which are not considered to be an adverse events by the investigator and which have plasma glucose concentration >= 3.0 mmol/L and <= 3.9 mmol/L (>= 54mg/dL and <= 70 mg/dL) will be recorded by the investigator on a separate eCRF page.

Based on the above definition, different tables will be shown for (i) patients with investigator defined hypoglycaemic AEs, (ii) patients with any hypoglycaemia (investigator defined hypoglycaemic AE or asymptomatic hypoglycaemia not reported as AE), (iii) patients with any asymptomatic hypoglycaemia (investigator defined asymptomatic hypoglycaemic AE or asymptomatic hypoglycaemia not reported as AE).Each table will include total number of hypoglycaemic events, number of episodes per patient, minimum glucose level of worst episode, and time to onset of first episode.

Furthermore, patients with investigator defined hypoglycaemic AEs and confirmed hypoglycaemic AE will be tabulated by treatment group. A subgroup analysis with respect to age and rescue therapy will be performed.

The impact of treatment on the occurrence of patients with investigator defined hypoglycaemic AEs will also be explored using a logistic model involving treatment, continuous baseline HbA_{1c}, and type of insulin. Time to the onset of the first investigator defined hypoglycaemic AE will be analysed by Kaplan-Meier estimates.

Analysis of protocol specified AEs (=events of special interest)

As defined in protocol, the following events are considered as adverse events of special interest (AESI):

- Hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis
- Skin lesions such as exfoliative rash, skin necrosis, or bullous dermatitis
- Hepatic injury as defined by the following alterations of hepatic laboratory parameters: ⩾3 fold ULN of AST and/or ALT in combination with an elevation of total bilirubin >2 fold ULN measured in the same blood draw sample, hepatitis, hepatic injury, jaundice and potential Hy's Law cases

- Renal adverse events such as acute renal failure
- Pancreatitis (refer to the ISF)
- Pancreatic cancer

The categories and events included as AESIs may change over time. The definitions, including SMQs for the AESIs will be maintained on project level. All AESIs defined in the CTP are presented in the CTR. If further AESIs have been defined, they will also be included into the CTR.

For each AESI, the frequency of patients with the respective AESI will be summarised by treatment, user-defined AE category and preferred term.

Cardiovascular and neurological events qualifying for external adjudication by the Clinical Event Committee (CEC)

An independent external CEC regularly reviews events suspect of stroke, myocardial ischemia (incl. myocardial infraction), cardiovascular death 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.

Frequency tables will be provided for the preferred terms in the specified SMQs of events and for the adjudication endpoints.

Pancreatic events qualifying for external adjudication by the Clinical Event Committee (CEC)

An independent external CEC regularly reviews events suspect of acute pancreatitis, chronic pancreatitis, Asymptomatic Pancreatic Hyperenzymemia and Pancreatitis Malignancy and evaluates whether pre-specified criteria for these adjudication events are met. Details on composition of the CEC, responsibilities and clinical events 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.

Frequency tables will be provided for the preferred terms in the specified SMQs of events and for the adjudication endpoints.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (4). All analyses will be based on TS.

Baseline for safety laboratory parameters will be the last available measurement before the start of randomised study drug. Laboratory values taken up to 7 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.

Specific considerations for hepatic parameters

To support analyses of liver related adverse drug effects, *Potential Hy's law* cases are defined by the combination of the following events within a time span of 30 days:

- Any on-treatment value of ALT or AST (or both) >= 3 times upper limit of normal (ULN) with
- Total bilirubin >= 2 x ULN and
- Alkaline phosphatase <= 2 x ULN

The start of the 30 day time span is triggered by each liver tranaminase elevation above the defined thresholds.

Patients who fulfil one or two of the criteria for ALT/AST or total bilirubin elevation above for a potential Hy's law case and has no information available for the remaining parameter(s) at the same timepoint or within the 30 day time windows will be considered for presentation of potential Hy's law lab constellation as well.

All calculations for the grading will be based on the originally measured laboratory values and the ULNs given by the laboratory, not on normalised values with BI standard reference ranges.

Specific considerations for amylase and lipase

In order to support screening for highly increase amylase and/or lipase values in regards to the ULN, specific transition tables are defined. These transition tables check for erased values, values above the twofold ULN and values above the threefold ULN either at the end of treatment or at the peak value on treatment.

All calculations for the underlying grading will be based on the originally measured laboratory values and the ULNs given by the laboratory, not on normalised values with BI standard reference ranges.

Specific renal endpoints

The glomerular filtration rate (GFR) will be derived from serum creatinine* values based on the standard MDRD formula:

eGFR (ml/min/1.73 m2) = 175 x [Screatinine (µmol/L)/88.4]$^{-1.154}$ x [age]$^{-0.203}$ x [0.742 if patient is female] x [1.212 if patient is of African origin]

*: creatinine methods calibrated to an IDMS reference method

Calculation of age in the determination of eGFR will be done by:

Age = (laboratory assessment date – date of birth + 1) / 365.25.

To support analysis of renal function, eGFR throughout the trial will be categorised according to the following MDRD staging:

Table 7.8.2: 1 MDRD staging

Stage	eGFR (mL/min/1.73m²)	Description	Label for displays
1	>=90	Normal renal function	≥90 (normal)
2	60 to <90	Mild renal impairment	60 to <90 (mild)
3	45 to <60	Moderate renal impairment A	45 to <60 (moderate A)
4	30 to <45	Moderate renal impairment B	30 to <45 (moderate B)
5	<30	Sever renal impairment or endstage renal disease	<30 (end stage)

Fasting plasma glucose will be included in the safety analyses with respect to the reference range and in the analysis of possible clinically significant abnormalities. Descriptive statistics over time and further statistical analyses will be part of the efficacy analysis.

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

Reported original negative quantitative safety laboratory values will be excluded from analyses (consistently from all tables and listings). (This does not apply to normalised values, which will be used.)

7.8.3 Vital signs

Vital signs observed throughout the whole trial will be assessed with regard to possible changes compared to findings before start of treatment. Only descriptive statistics by treatment group at each on-treatment visit are planned for this section.

7.8.4 ECG

12-lead ECG measurements will be taken at Visit 3 and at the end-of-trial (Visit 8). Any clinically significant new findings in the ECG-measurement at the EoT compared to that from the first measurement will be considered as AEs.

7.8.5 Others

7.8.5.1 Physical examination

Physical Examination will be taken during placebo run-in period (Visit 2), and at the EoT. Findings in the physical examination at placebo run-in period will be considered as baseline-condition. Any clinically significant new findings in the Physical Examination at the EoT will be considered as AEs.

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] 001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", current version; IDEA for CON.
[3] 001-MCG-156: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
[4] 001-MCG-157: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**13-SEP-16**		None	This is the initial TSAP with necessary information for trial conduct.
Final	**26-SEP-17**		Sections empty in initial version	Added as it is the final TSAP.
			6.2	➢ "Uncontrolled hyperglycaemic" category deleted ➢ "Background antidiabetic therapy not taken as specified in the protocol" deleted
			6.3	➢ TS and FAS rephrased ➢ MTT-set added
			7.1	➢ Variables showed in demographic and baseline adjusted
			7.8.1	➢ Analysis of hypoglycaemic events updated based on project update ➢ "Safety topic of interest" section deleted
Revised	**14-FEB-2019**			
			7.8.2	➢ eGFR categories updated