Trial Statistical Analysis Plan

c02873013-03

BI Trial No.:	1218.149
Title:	A 24 week randomised, double-blind, placebo-controlled, parallel group, efficacy and safety trial of once daily linagliptin, 5 milligrams orally, as add on to basal insulin in elderly Type 2 Diabetes Mellitus patients with insufficient glycaemic control. Including Global Protocol Amendment 1 [c02204602-03]
Investigational Product(s):	Tradjenta®, Trajenta®, Trayenta®, Trazenta®, linagliptin
Responsible trial statistician(s):	[redacted] Tel: [redacted] Fax: [redacted]
Date of statistical analysis plan:	9 November 2016 REVISED
Version:	Final

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LIST OF TABLES

2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
[redacted]	[redacted]
ADS	Analysis data sets
AE	Adverse event
AGI	Alpha-glucosidase inhibitors
ALT	Alanine transaminase
[redacted]	[redacted]
[redacted]	[redacted]
AST	Aspartate transaminase
BIcMQ	Boehringer Ingelheim customized MedDRA Query
BMI	Body Mass Index
BRPM	Blinded report planning meeting
CI	Confidence Interval
CT	Concomitant therapies
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
(e)CRF	(Electronic) Case Report Form
DBL	Database Lock
[redacted]	
ECG	Electro-cardiogram
EMA	European Medicines Agency
EoT	End of treatment
FAS	Full analysis set
FPG	Fasting Plasma Glucose
GPSP	Good Post-Marketing Study Practice
GVP	Good Vigilance Practice
HbA_{1c}	Glycosylated Haemoglobin
HBGM	Home blood glucose monitoring
HLT	Higher Level Term

Term	Definition / description
ICH	International Conference on Harmonisation
[redacted]	[redacted]
ITT	Intention-to-Treat
IRT	Interactive Response Technology
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed model repeated measures
O*C	Oracle Clinical
OC	Observed Cases
[redacted]	[redacted]
[redacted]	[redacted]
PHQ	Patient Health Questionnaire
PK	Pharmacokinetics
PPS	Per protocol set
PSTAT	Project Statistician
PT	Preferred term
PV	Protocol violation
Q-Q	Quantile-Quantile
ROC	Rescue observed cases
SD	Standard deviation
SLUMS	Saint Louis University Mental Status exam
SMQ	Standardised MedDRA query
SOC	System organ class
TCM	Trial Clinical Monitor
TOC	Table of contents
TMW	Trial Medical Writer
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

3. INTRODUCTION

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

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

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The following modifications regarding the analysis of trial data are implemented:

Analysis specified in CTP	**Adjusted Analysis specified in TSAP**
Primary endpoint: Baseline insulin is fixed categorical effect.	Primary endpoint: Baseline basal insulin is linear continuous covariate.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Due to an alignment of terminology on project level, it was necessary to re-phrase some endpoints in the TSAP.

Analysis: Text in CTP	**Analysis: Adjusted text in TSAP**
Secondary endpoint: Proportion of patients experiencing at least one confirmed hypoglycaemic event during 24 weeks of treatment.	Proportions of patients experiencing at least one hypoglycaemia accompanied by a glucose value during 24 weeks of treatment.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint in this study is the change from baseline in HbA_{1c} (%) after 24 weeks of randomised treatment.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

There are no key secondary endpoints in this trial.

5.2.2 Secondary endpoints

Secondary endpoints are the following:

- Proportion of patients experiencing at least one hypoglycaemia accompanied by a glucose value during 24 weeks of treatment. Hypoglycaemia accompanied by a glucose value is defined as

    - any investigator reported asymptomatic hypoglycaemic event or AE with a reported blood glucose measurement less than 54 mg/dL (<3.0mmol/L)
        [AE.SYMI=0 and ((AE.GLUCOSE <54 and AE.LABU=232) or (AE.GLUCOSE <3.0 and AE.LABU=301))

        or

        (HYPOASYM.GLUCOSE <54 and HYPOASYM.LABU=232) or (HYPOASYM.GLUCOSE <3.0 and HYPOASYM.LABU=301)]

    or

    - any investigator reported symptomatic hypoglycaemic AE confirmed by a reported blood glucose measurement less than or equal to 70 mg/dL (≤ 3.9 mmol/L)
        [AE.SYMI=1 and ((AE.GLUCOSE ≤70 and AE.LABU=232) or (AE.GLUCOSE ≤3.9 and AE.LABU=301))]

    or

    - a severe hypoglycaemic AE, i.e.,., an event that requires the assistance of another person to actively administer carbohydrates or glucagon because the patient is unable to take the substance on his or her own.
        [AE.ASSIST=1]

        Note: If another person hands the carbohydrate or glucagon to the patient without having to actively administer the substance because the patient is able to take the substance on his or her own, the hypoglycaemic AE does not qualify as severe.

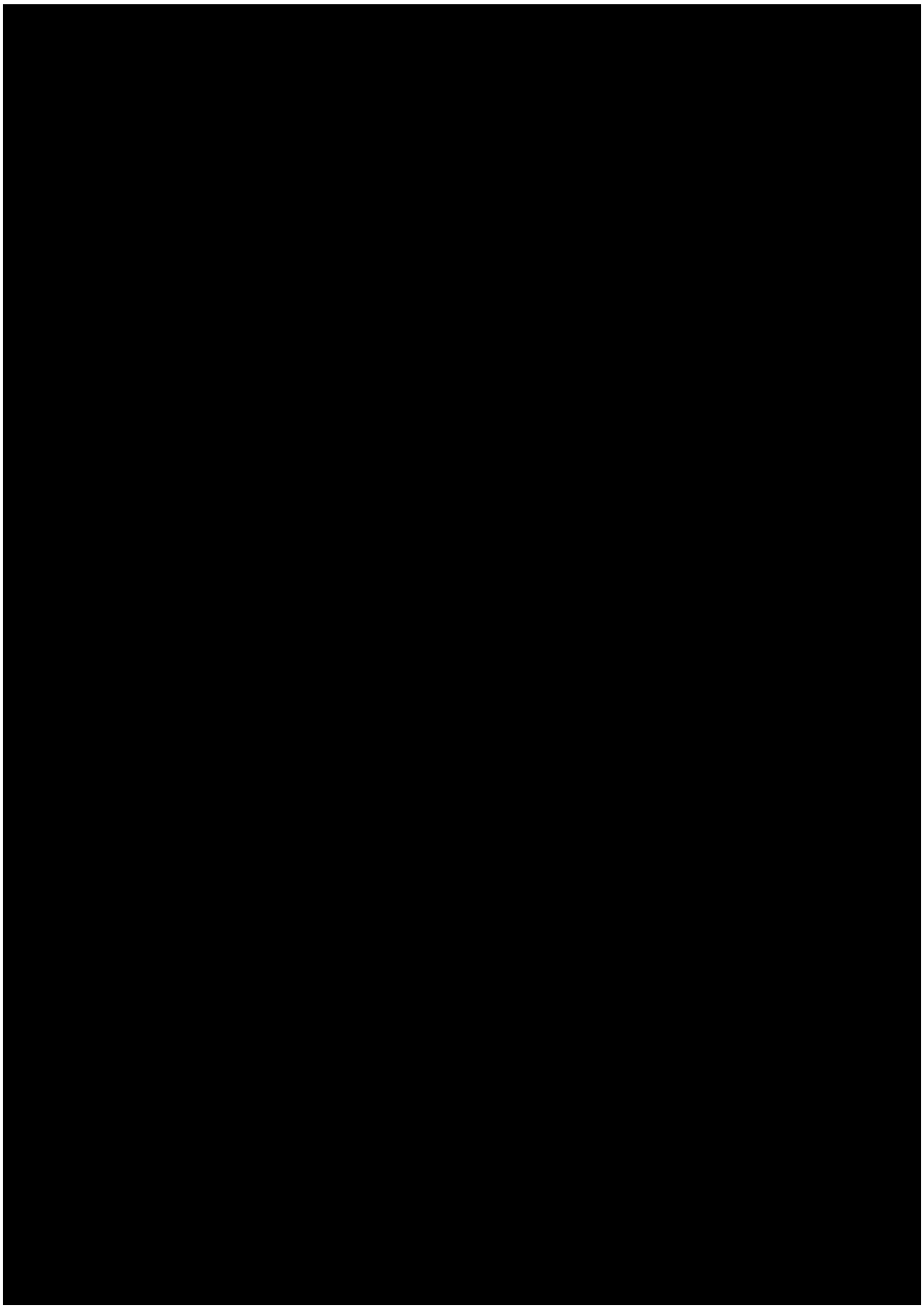
Note:

(i) Hypoglycaemias are counted only once, i.e., a severe episode that has also symptoms indicated on the CRF is counted only once.

(ii) If *AE.SYMI is missing* and *((AE.GLUCOSE <54 and AE.LABU=232) or (AE.GLUCOSE <3.0 and AE.LABU=301)* and *AE.ASSIST<>1*, then the patient is considered for this analysis.

If *AE.SYMI is missing* and [*((AE.GLUCOSE >=54 and AE.LABU=232) or (AE.GLUCOSE >=3.0 and AE.LABU=301)* or *AE.ASSIST<>1*], then the patient is not considered for this analysis.

- Proportion of patients with HbA_{1c} on treatment <8.0% 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} lowering by at least 0.5% after 24 weeks of treatment.
- Change from baseline in FPG (mg/dL) after 24 weeks of treatment.



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

In this section, the treatment set-up (treatment regimens/study intervals and randomised treatment) is defined.

6.1.1 Treatment regimens / study intervals

There will be five treatment phases in this trial: screening, placebo run-in, treatment, post-treatment and post-trial.

The purpose of the table below is to describe all the different trial/treatment intervals, in which a patient can lie during the course of the trial. Note that the term “treatment regimen” can also cover time periods with no active treatment.

Table 6.1.1: 1 Treatment regimens / study intervals (Analno 1)

Short label	Interval	Sort order	Start date / Start time (HH:MM)	End date / End time (HH:MM)
Screening	Screening	1	Date of informed consent / 00:00	Date of first administration of run-in medication / 00:00
Run-in	Run-in	2	Date of first administration of run-in medication / 00:00	Date and time of first administration of study medication
Placebo / Lina 5mg	On-treatment	3 / 4	Date of first administration of study medication / Time of first administration of trial medication – if missing: 12:00 noon	Last day of trial medication intake + 1day, 00:00
Post treat	Post-treatment	5	last day of trial medication intake +1day, 00:00	Date of V99 +1day, 00:00
Post-trial	Post-trial	6	Date of V99 +1day, 00:00	

For purposes of the analysis, the residual period for assigning measurements to the on-treatment period is dependent on the endpoint and therefore the analysis is based on visit windows as opposed to treatment regimens. Visit windows are further defined in Section 6.7.

6.1.2 Randomised treatment

Patients who receive an incorrect treatment at any visit (one which they were not randomised to) will be analysed for both efficacy and safety under the treatment which they were randomised to, for the entire trial period.

A special listing of Adverse Events only for patients that took a wrong treatment between visits within the course of the trial will be created.

6.2 IMPORTANT PROTOCOL VIOLATIONS

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

First, there are protocol violations (PVs) that potentially affect the rights or safety of patients in the trial. 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 reported.

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 protocol violations (IPVs) forms the basis for the decision (during the database lock [DBL] meeting) of whether a patient should be excluded from an analysis set. The decision regarding whether such patients are to be excluded or not from an analysis set will made the treatment blind is broken.

As the primary endpoint is analysed at 24 weeks, PVs related to efficacy and satisfying the criteria for IPVs that occur in Japan between day 176 and the end of the trial (Week 52) will not lead to exclusion from analysis sets.

All other PVs, i.e. those discussed and assessed during MQRMS, are of minor importance and it is not necessary to describe or list these PVs in the integrated clinical trial report (CTR).

The following table defines the different categories of IPVs. The final column describes which PVs 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**	**T+**
A		**Entrance criteria not met**			
A1		**Target indication not met**			
	A1.1	No type 2 diabetes		PPS	E
	A1.2	Antidiabetic background therapy not as required	Inclusion criteria 2b, 2c or 2d not met as specified in the protocol or Basal insulin [insulin neutral protamine Hagedorn (NPH) and isophane insulin; Humalog Basal®, insulin degludec; insulin detemir; and insulin glargine] not recorded on electronic case report form (eCRF) or Basal Insulin dose changed >20% within 4 weeks prior to randomisation (8 weeks for Germany) or metformin/AGI dose changed within 12 weeks prior to randomisation if applicable.	PPS	E
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} <7.5% if version 1 of informed consent signed, <7.0% if version 2 of informed consent signed or >10.0% at Visit 1 (>9.0% for Germany).	PPS	E
	A2.2	Age out of range at screening	Inclusion criteria 2a not met and/or age <70 years if version 1 of informed consent signed or <60 years if version 2 of informed consent signed at Visit 1.	PPS	E
	A2.3	Body mass index out of range at screening	Inclusion criteria 4 not met and/or Body mass index (BMI) >45kg/m^2 at Visit 1.	PPS	E
A3, A4, A5		**Exclusion criteria violated**			
	A3.1	Relevant concomitant diagnoses	Exclusion criteria 4 checked and/or Acute coronary syndrome, stroke or TIA recorded on concomitant diagnoses eCRF within 3 months prior to Visit 1.	None	S

Table 6.2: 1 Important protocol violations (cont.)

Category/ Code		Description	Example/Comment	Excluded from	T+
	A3.2	Impaired hepatic function	Exclusion criteria 5 checked and/or Alanine Transaminase (ALT) or Aspartate Transaminase (AST) or alkaline phosphatase > 3x upper limit of normal (ULN) during screening and/or run-in [Gilbert-Meulengracht syndrome is permitted].	None	S
	A3.3	Known hypersensitivity to any of the drugs in the study regimen	Exclusion criteria 12 checked.	PPS	E S
	A3.4	Treatment with protocol excluded antidiabetic drugs	Exclusion criteria 9 or 10 or 11 checked and/or Treatment with GLP-1 analogues within 3 months prior to informed consent (Visit 1) and/or Treatment with sulphonylureas, thiazolidinediones, SGLT2 inhibitors, or DPP-4 inhibitors within 3 months prior to randomisation (Visit 3) and/or Treatment with rapid acting or short acting insulin and/or pre-mixed insulin containing rapid acting or short acting insulin within 3 months prior to randomisation (Visit 3).	PPS	E
	A3.5	Treatment with protocol excluded anti-obesity drugs	Exclusion criteria 13 checked and/or Intake of any of the excluded drugs reported on the eCRF within the time prior to informed consent specified in the exclusion criteria.	PPS	E
	A3.6	Diagnosis of Type 1 Diabetes Mellitus	Exclusion criteria 3 checked and/or Type 1 Diabetes Mellitus on concomitant diagnoses eCRF.	PPS	E
	A4.1	Treatment with any drugs that have significant effect on glucose metabolism, protocol excluded systemic steroids or change in thyroid hormone dose	Exclusion criteria 14 checked and/or Intake of any of the excluded drugs reported on the eCRF within the time prior to informed consent specified in the exclusion criteria.	PPS	E

Table 6.2: 1 Important protocol violations (cont.)

Category/ Code		Description	Example/Comment	Excluded from	T+
	A4.2	Alcohol or drug abuse that may interfere with study participation	Exclusion criteria 15 checked.	PPS	E
	A4.3	Participation in another trial with an investigational drug within 2 months prior to informed consent	Exclusion criteria 16 checked Final decision at the DBL meeting (medical judgment), depending on the type of drug given in the prior trial (only if investigational drug interferes with glucose metabolism).	PPS	E
	A4.4	Patient has undergone bariatric surgery within 2 years prior to informed consent	Exclusion criteria 6 checked and/or Evidence of surgery reported on eCRF.	None	E
	A4.5	Medical history of cancer (except basal cell carcinoma) within 5 years prior to informed consent	Exclusion criteria 7 checked.	None	S
	A4.6	Unstable Red Blood Cells	Exclusion criteria 8 checked and/or Diagnosis of blood dyscrasias or any disorder causing hemolysis or unstable red blood cells (e.g., malaria, babesiosis, haemolytic anaemia) listed on concomitant diagnoses page of eCRF.	None	E
	A4.7	Psychological, familial, sociological, or geographical factors potentially hampering compliance with the protocol, visits, or trial procedures or any other clinical condition that would jeopardize patient safety while participating in this clinical trial in the opinion of the investigator	Exclusion criteria 17 checked.	None	S
	A4.8	Inability to commit to regular overnight fasting of at least 10 hours duration and attendance to trial site visits between 07:00 and 11:00am	Exclusion criteria 18 checked.	PPS	S

Table 6.2: 1 Important protocol violations (cont.)

Category/ Code		Description	Example/Comment	Excluded from	T+
	A5.1	Impaired cognitive ability	Exclusion criteria 1 violated and/or Saint Louis University Mental Status (SLUMS) score of 21-26 (high school education) or 20-24 (no high school education) and no confirmation from investigator to rule out cognitive impairment. and/or SLUMS score of 20 or less (high school education) or 19 or less (no high school education) indicating dementia. **Note:** The first version of the eCRF contained the following statement: Saint Louis University Mental Status (SLUMS) Examination scores of 25 or less for those patients with high school education or 23 or less for those patients who did not complete a high school education indicate that the patient probably have impaired cognitive ability. [CONDT.PROTAM = 1.0 or 2.0]	None	S
	A5.2	Depressed mood	Exclusion criteria 2 checked and/or Patient Health Questionnaire (PHQ) score ≥10 at Visit 1.	None	S
	A5.3	Acute pancreatitis or Chronic pancreatitis	Germany only. Exclusion criteria 19 checked and/or Diagnosis of acute pancreatitis within 3 months of screening and/or Medical history of chronic pancreatitis.	None	S
B		**Informed consent**			
	B1	Informed consent not available/not done	Inclusion criteria 1 not met and/or Date of informed consent for the study missing and/or No signature on patient's "Declaration of Informed Consent" ***Patient's data will not be used at all.***	All	R

Table 6.2: 1 Important protocol violations (cont.)

Category/ Code		Description	Example/Comment	Excluded from	T+
B		**Informed consent**			
	B2	Informed consent too late	Date of informed consent for the study 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.	None	S
	B3	Informed consent for sub-study not available	No separate informed consent for DNA banking (unspecified DNA sample). Note: Pre-specified DNA and RNA samples are covered by the trial informed consent and therefore no additional informed consent is required. In Australia and the UK pre-specified DNA sample is forbidden according to local amendment. Patient's unspecified DNA sample will not be retained or analysed. For Australia and UK, the pre-specified DNA will not be retained or analysed.	None	S
C		**Trial medication and randomisation**			
C1		**Incorrect trial medication taken**			
	C1.1	No trial medication taken	Patient randomised but no trial medication taken.	TS, FAS and PPS	E
	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 the interactive response technology (IRT) and/or Gross misuse of trial medication (e.g. unacceptable dose of trial medication). Can only be finally judged after DBL since unblinding information is required.	PPS	E
C2		**Randomisation not followed**			
	C2.1	Treated without randomisation	Patient treated according to eCRF, but not randomised according to IRT.	RS, FAS and PPS	E

Table 6.2: 1 Important protocol violations (cont.)

Category/ Code		Description	Example/Comment	Excluded from	T+
C3		**Non-compliance**			
	C3.1	Non-compliance with drug intake	Gross non-compliance issues only – based on compliance section of eCRF (at least two times on treatment compliance was outside 80-120% according to eCRF) Final decision at the DBL meeting (medical judgment).	PPS	E
C3		**Non-compliance**			
	C3.2	Non-compliance with criteria for removal from trial	Criteria for removing a patient from the trial not adhered to. Final decision at the DBL meeting (medical judgment).	None	E
	C3.3	Treatment interruption for more than 10 consecutive days	Documented treatment interruption for 11 consecutive days or more.	PPS	E
	C3.4	Non-compliance with HBGM data collection	Compliance with completing HBGM < 50% and/or No tests performed for 5 consecutive days.	None	E
C4		**Medication code broken**			
	C4.1	Medication code broken without just cause	Medication code broken for no valid reason. Final decision at the DBL meeting (medical judgment).	PPS	E
D		**Concomitant medication**			
D2		**Prohibited medication use**			
	D2.1	Rescue medication taken without just cause	Use of rescue medication (as defined in Section 4.2.1 in CTP) with FPG prior to rescue therapy ≤240 mg/dL for Visit 3 to Visit 4 or ≤200 mg/dL for Visit 5 to Visit 98 and/or Review of eCRF for use of rescue medication without 6 week dose adjustment period (i.e. prior to Visit 4).	PPS	E
	D2.2	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 D2.1 not fulfilled.	PPS	E

***** IPVs will be checked programmatically, including double programming checks for inclusion/exclusion criteria, where possible. IPVs where inclusion/exclusion criteria possibly need to be confirmed manually with respect to time A3.1, A3.4, A3.5, A4.1, A4.4, A4.5, A5.1, A5.3 and D2.3. For A1.2 dose changes may need to be checked manually. IPVs which can only be identified manually are A4.2, A4.3, A4.7, A4.8 and C3.2.

+ IPV-type: 'E' refers to efficacy IPV, 'S' refers to safety IPV and 'R' refers to general (regulatory) IPV.

6.3 PATIENT SETS ANALYSED

- Randomised set (RS):
  This patient set includes all randomised patients, whether treated or not.

- Treated set (TS):
  This patient set includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

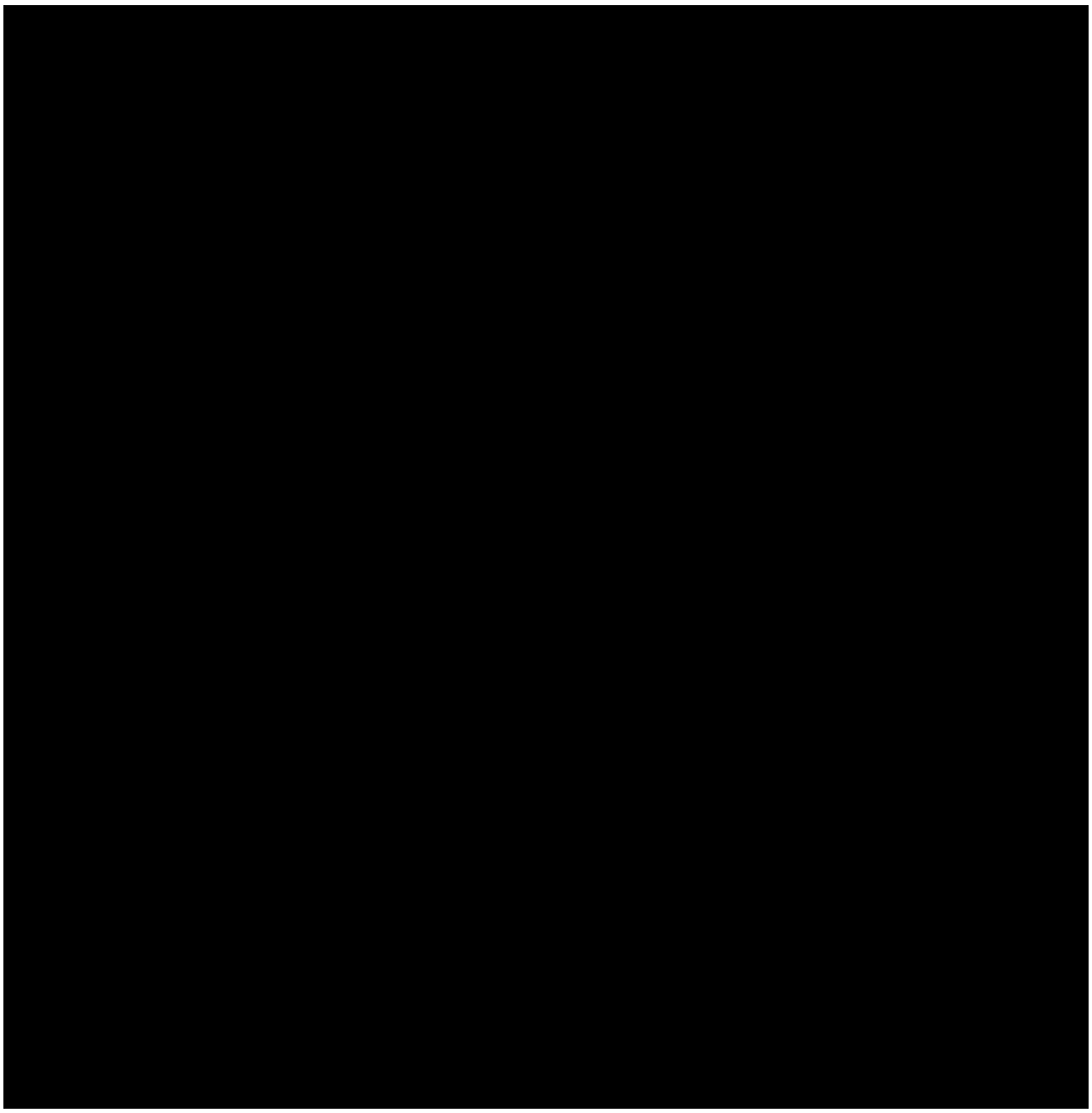
- Full analysis set (FAS):
  This patient set includes all patients randomised in the TS who have a baseline and at least one on-treatment HbA_{1c} value.

- FAS-completers-24 (FASC24):
  This patient set includes all patients in the FAS who complete a minimum treatment duration of 149 days, did not prematurely discontinue the trial and have an available HbA_{1c} measurement within the time window for the Week 24 visit (Visit 98 for non-Japanese and Visit 7 for Japanese patients up to day 176). This analysis set is not required for the analysis at Week 52. See Table 6.7: 1.

- Per protocol set (PPS):
  This patient set includes all patients in the FAS who do not have any IPVs relating to efficacy, cf. Table 6.2: 1.

Table 6.3: 1 Patient sets analysed

	Patient set			
Class of endpoint	TS	FAS	PPS	FASC24
Primary endpoint		Primary analysis	Sensitivity analysis	Sensitivity analysis
Secondary and further endpoints		X		
Safety endpoints	X			
Demographics	X			
Baseline efficacy variables		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

Patients may drop out of the trial before they reach the planned observation time. In particular, patients with a lack of efficacy can be expected to drop out with a higher probability than patients showing a good response. Therefore various methods will be used to assess the

impact of missing data on the efficacy endpoints of the trial. The following paragraphs give a general description of the various approaches.

Original Results (OR) analysis

For some of the efficacy endpoints, analysis will be done directly on the observed data, without any derivation performed on them. OR analysis is relevant in cases rescue therapy was taken.

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 using OC, this OC-technique will be adapted by setting any values taken after rescue medication to missing. In addition values after the addition of a new anti-diabetic therapy or an increase in metformin and/or AGI dose as specified in Section 5.3 will be set to missing.

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 non-conservative estimates of the treatment effects in case of data missing due to patients dropping – out because of lack of efficacy of the study medication under treatment.

Observed cases – Rescue observed cases (OC-ROC)

In this case, values taken after rescue medication are neither set to missing nor are imputed otherwise but taken as measured.

Last observation carried forward (LOCF)

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

The last observation on-treatment must not necessarily be a value selected as a visit value as described in Section 6.7. If multiple measurements were performed within a time window for a visit, 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 date of last drug administration or the first value observed in the time window.

Baseline values will not be carried forward in general, but can be used for interpolation. Only for patients with rescue medication before the first on-treatment HbA_{1c} measurement, baseline HbA_{1c} values will be used to replace values after the start of rescue medication.

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 (cf. Section 6.7) to be used in the descriptive analysis by visit. Replacement of missing values will only be performed for visits up to the planned visit to be reached by all randomised patients in the trial.

Interpolation will be done according to the formula described below:

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

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

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

E_i = endpoint value for visits D_i for $i = -1, 0, 1$.

Then the missing endpoint value can be interpolated as:

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

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 7.4.2.

Non-completers considered failure (NCF)

For binary endpoints like a treat to target response of HbA_{1c} <7.0% a conservative method to replace missing values is to consider them as “failures”. Missing data due to early discontinuation will be replaced as “failure” (e.g. HbA_{1c} ≥7.0%) 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 value of the 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
OR	Continuous, binary, time to event and count	No imputation	All data included as measured. Multiple measurements per visit possible.
OC	Continuous	No imputation	Excluded – considered missing. One picked value per visit (cf. Section 6.7).
OC-ROC	Continuous, binary, time to event and count	No imputation	Included as measured. One picked value per visit (cf. Section 6.7).
LOCF	HbA_{1c} (at each visit and change from baseline)	Missing values at the end of the trial are replaced by the last on-treatment value. Missing values with subsequent present on-treatment values are imputed by interpolation. Baseline values are not carried forward, except where rescue medication is taken prior to first on-treatment measurement. Baseline values can be used in interpolation.	Values after the start of rescue therapy are replaced by the last available measurement. If no on-treatment HbA_{1c} measurement prior to rescue therapy is available baseline values are carried forward.
MI	HbA_{1c}	Missing values are imputed by a two-step approach. Firstly, a monotone missing pattern is generated in the data (MCMC method). Secondly, missing values are imputed by a sequential regression based method.	Considered missing and thus imputed.

Table 6.6: 1 Summary of imputation methods for efficacy endpoints (cont.)

Imputation method	Endpoint	Handling of missing values	Handling of values after rescue therapy
NCF	Binary endpoints derived from continuous endpoints (e.g. HbA_{1c}<7.0%)	Missing values after premature discontinuation of trial medication 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.

[redacted]

[redacted]

Safety and other variables

Missing safety data will not be replaced, but an analysis of the changes from baseline to the last available value under treatment and the minimum and maximum post baseline will be determined for quantitative safety laboratory variables. For safety analysis, as last on-treatment value the last measurement between the first intake of randomised trial drug and drug-stop date + 7 days will be analysed as the last value on-treatment for non-Japanese patients. If a Japanese patient stops drug intake prior or at day 175 a residual period of 7 days will be added for Week 24 safety analysis. If a Japanese patient does not stop drug intake prior day 176, no residual period is added for safety analysis.

Missing dates and times

Missing or partial date and time information for adverse events (AEs) will be replaced according to general Boehringer Ingelheim (BI) rules (cf. 1).

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 randomisation.
If the date of first administration is partially missing with the month and year present, the day will be set to the date of randomisation if randomisation was in the same month. If randomisation was in the month prior to the first drug administration the missing day will be imputed as the first day of the month.

A missing time of first drug administration will be imputed as 12:00 o'clock noon, missing administration times at on-treatment visits will be imputed by 8:00 o'clock in the morning.

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

- If an End of Treatment (EoT) visit is documented, it should be the date of the EoT visit (Visit 98).

- 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.
- After application of any of the first 3 rules, the post-treatment phase starts at the same day as the imputed drug stop date (instead of treatment stop + 1 day).

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

For other incomplete date information always the midpoint of the possible interval will be used. If only the year is present the day and month will be imputed as 01 July, if year and month is present the day will be imputed as 15. If the year is missing, the date will be considered missing. 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.
If date and time information as well as a flag is missing for start of concomitant therapy, then the concomitant therapy is considered on-going at screening.
If date and time information as well as a flag is missing for end of concomitant therapy, then the concomitant therapy is considered on-going at end of study.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Definition of baseline

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. Baseline daily basal insulin dose is derived from eCRF and is equal to the daily basal insulin dose at day of first study medication intake. If patients are treated by a combination of a fast-acting and basal insulin, only the proportion of basal insulin is used for deriving the baseline daily basal insulin dose. If that proportion cannot be derived, baseline daily basal insulin is set to missing.

If patients are treated with an intermediate type if insulin, than this dose is completely considered for daily basal dose.

Also, for metformin and AGI, baseline doses refer to the dose at day of first study medication intake.

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

The date and clock time of the first study medication administration will be used to separate pre-treatment from on-treatment values.

The definition of screening for the analysis of concomitant therapies (CTs) is the time period from informed consent up to the first dose of trial medication.

Definition of on-treatment for analyses

Measurements taken after the first intake of randomised study medication will be considered on-treatment values if they have been obtained up to 7 days after study medication stop (inclusive) – this also holds for hypoglycaemia (efficacy endpoints) and hypoglycaemic adverse events (safety endpoints). The only exceptions are FPG [redacted] for which will be up to 1 day after drug stop (inclusive) due to reacting quicker. All on-treatment measurements will be assigned to the randomised trial medication for analyses.

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

Visit windows for efficacy variables

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 trial medication (this is at Visit 3).

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 (7 days after last intake for all variables except FPG [redacted] which are 1 day).

Table 6.7: 1 Time windows for on-treatment $HbA1_c$ and FPG measurements scheduled for each on-treatment visit – Week 24

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]
[redacted]					
98[C]	Week 24	168	169	149	Trial medication stop date + x[D] days
		For Japanese Patients Only			
7	Week 24	168	169	149	176

[A] In case of premature discontinuation of the trial medication a Visit 98 (end of treatment) has to be performed. If such a Visit 98 falls into the time window of a previous visit, measurements will be assigned to this previous visit. In this case the time window for the visit that includes Visit 98 will end x days after the trial medication stop date, including day x. The definition of x is endpoint specific, cf. Table 5.3: 1

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

[C] Only for non-Japanese patients.

[D] cf. Table 5.3: 1.

For examinations that are not planned at every on-treatment visit, the time windows will be defined according to the same algorithm, based on the midpoint between the planned visit 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 (visit value / picked value) will be selected for analysis at an on-treatment visit – the value will be selected which is closest to the protocol planned visit day; except for last study drug intake. In case of last study drug intake, the value which is closest to the date of last study drug intake is chosen. 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.

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.

For daily basal insulin the value at the visit will be determined as the last prescribed dose prior to the picked HbA1c value of the visit.

Visit windows will not be applied to hypoglycaemia or use of rescue therapy and events will not be assigned to visits. All on-treatment events will be considered in the analysis.

Visit windows for safety variables

Safety measurements will be assigned to the nominal visit as recorded on the eCRF or as provided by the laboratory. In general, visit windows will not be applied. However, for the Week 24 analysis, if a Japanese patient stops drug intake prior or at day 175 a residual period of 7 days will be added for safety analysis. If a Japanese patient does not stop drug intake prior day 176, no residual period is added for safety analysis at Week 24.

7. PLANNED ANALYSIS

For End-Of-Text tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum

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.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

For baseline eGFR calculations (MDRD) the following rules are to be applied regarding multiple race categories and Japanese patients:

- eGFR for patients with multiple race category Black & White will be calculated as eGFR for patients with race category Black
- eGFR for patients with multiple race category American Indian/Alaska Native & White will be calculated as eGFR for patients with race category White
- eGFR for patients with race Asian outside the region Asian will calculated as eGFR for Japanese patients.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. Concomitant medication table will additionally be produced at Week 52 for Japanese patients only.

7.3 TREATMENT COMPLIANCE

Compliance with trial medication intake will be calculated by the investigator as a percentage of the number of pills taken relative to the number of pills that were planned to be taken since the last visit. On the eCRF only the information whether this calculated compliance was within the range of 80% to 120% since the previous visit is recorded. Treatment interruptions of greater than 7 consecutive days will be recorded in the eCRF.

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

7.4 PRIMARY ENDPOINT

7.4.1 Primary efficacy analysis

The primary analysis will be performed on the FAS (OC); patients will be assigned to the treatment they were randomised to and analysed according to the stratum to which they belong (regardless of any incorrect assignment to treatment based on identification of wrong stratum).

Mean changes from baseline in HbA_{1c} after 24 weeks of treatments will be analysed using a restricted maximum likelihood-based repeated measures approach (mixed model repeated measures [MMRM]).
Analyses will include the fixed, categorical effects of *treatment*, *week*, and *treatment by week* interaction – accounting for the respective sources of variation. The model also includes the continuous, fixed linear covariates of *baseline HbA_{1c}, baseline daily basal insulin dose* and *baseline HbA_{1c} by week interaction* that control the *treatment* and *week* effects for possible impact from these underlying factors. 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: Toeplitz, AR (1), and compound symmetry. 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 $\alpha = 0.05$ [two-sided 95% confidence intervals (CI)]. The residuals are assumed to have a multivariate normal distribution with zero means and covariance matrix as specified above. All analyses will be implemented using SAS®. The primary treatment comparisons will be the contrast between treatments at Week 24.

The statistical model will be:

HbA_{1c} change from baseline = overall mean + treatment + week
+ treatment by week interaction
+ baseline HbA_{1c} + baseline daily basal insulin dose
+ baseline HbA_{1c} by week interaction
+ random error.

The model's random error is assumed to follow a normal distribution.

For Week 24 analysis, all levels for factor *week* up to Week 24 are to be considered in the model, [redacted]

In addition, descriptive statistics for HbA_{1c} (in %) over time are presented for FAS(OC), FAS(OC-ROC) and FAS(LOCF).

[redacted]

[redacted]

7.5 SECONDARY ENDPOINTS

7.5.1 Key Secondary Endpoint

Not Applicable.

7.5.2 Secondary endpoints

Proportion of patients with at least one hypoglycaemia accompanied by a glucose value during 24 weeks of treatment

Logistic regression for the proportion of patients experiencing at least one hypoglycaemia after 24 weeks will be performed on the FAS (OC); all on-treatment hypoglycaemias will be considered:

- up to drug stop date if a patient prematurely discontinues (Japanese patients that prematurely discontinue prior or at day 175)

- up to trial medication stop date – 1 if a non-Japanese patient does not prematurely discontinue
- up to day 175 if a Japanese patient does not prematurely discontinue prior day 176.

The model will include *treatment* as fixed effect and *baseline HbA_{1c}* and *baseline daily basal insulin dose* as linear covariates.

Frequencies regarding the number and percentage of patients experiencing at least one hypoglycaemia accompanied by a glucose value during 24 weeks in each treatment group will also be presented based on FAS(OC) .

Proportion of patients with HbA_{1c} on treatment <8.0% after 24 weeks of treatment

Logistic regression for the patients achieving HbA_{1c} <8.0% 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* as fixed effect and *baseline HbA_{1c}* and *baseline daily basal insulin dose* as linear covariates. Patients with baseline HbA_{1c} <8.0% will be excluded from the analysis.

A frequency table with the number and percentage of patients with HbA_{1c} <8.0% at Week 24 in each treatment group will be also be presented based on FAS (NCF).

Proportion of patients with HbA_{1c} on treatment <7.0% after 24 weeks of treatment

Logistic regression for the patients achieving HbA_{1c} <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* as fixed effect and *baseline HbA_{1c}* and *baseline daily basal insulin dose* as linear covariates. Patients with baseline HbA_{1c} <7.0% will be excluded from the analysis.

Frequencies regarding the number and percentage of patients with HbA_{1c} <7.0% at Week 24 in each treatment group will be also be presented based on FAS (NCF).

Proportion of patients with HbA_{1c} lowering by at least 0.5% after 24 weeks of treatment

Logistic regression for the patients achieving lowering of HbA_{1c} 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* as fixed effect and *baseline HbA_{1c}* and *baseline daily basal insulin dose* as linear covariates .

Frequencies regarding the number and percentage of patients with lowering of HbA_{1c} by at least 0.5% from baseline at Week 24 in each treatment group will be also be presented based on FAS (NCF).

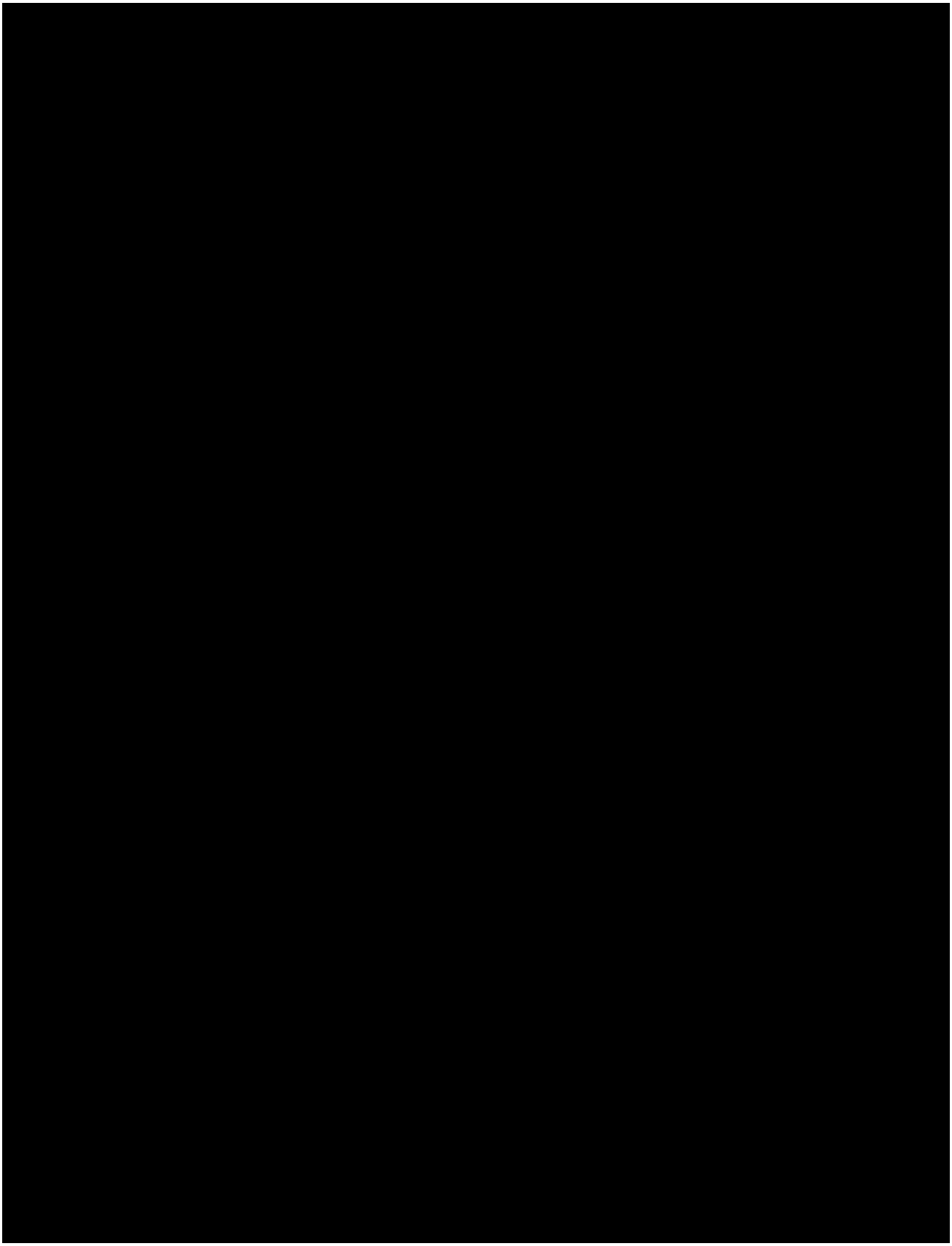
Change from baseline in FPG after 24 weeks of treatment

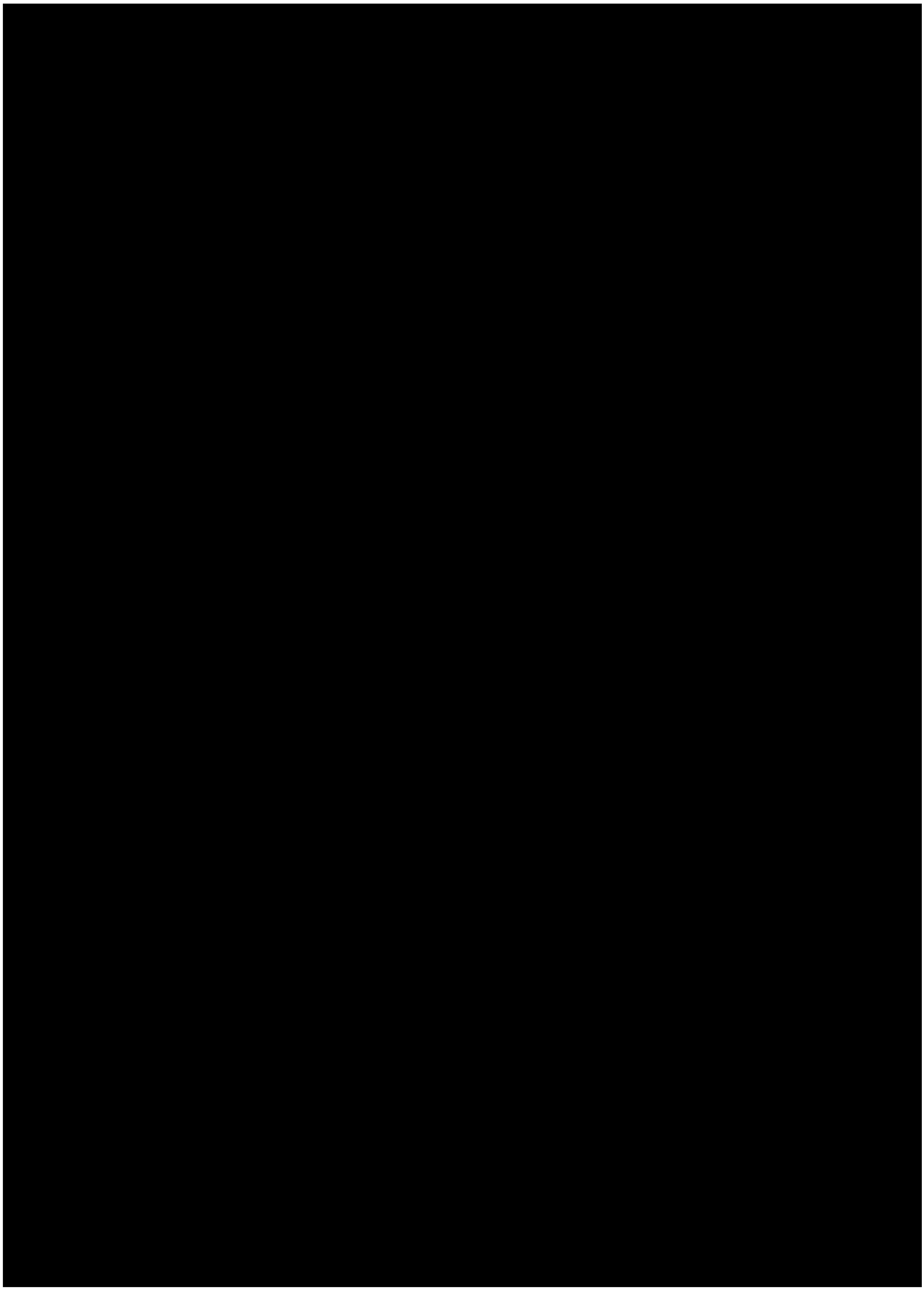
Analysis of change from baseline in FPG will follow the strategy for the primary endpoint. MMRM will be used to analyse the mean changes from baseline in FPG after 24 weeks of treatments.

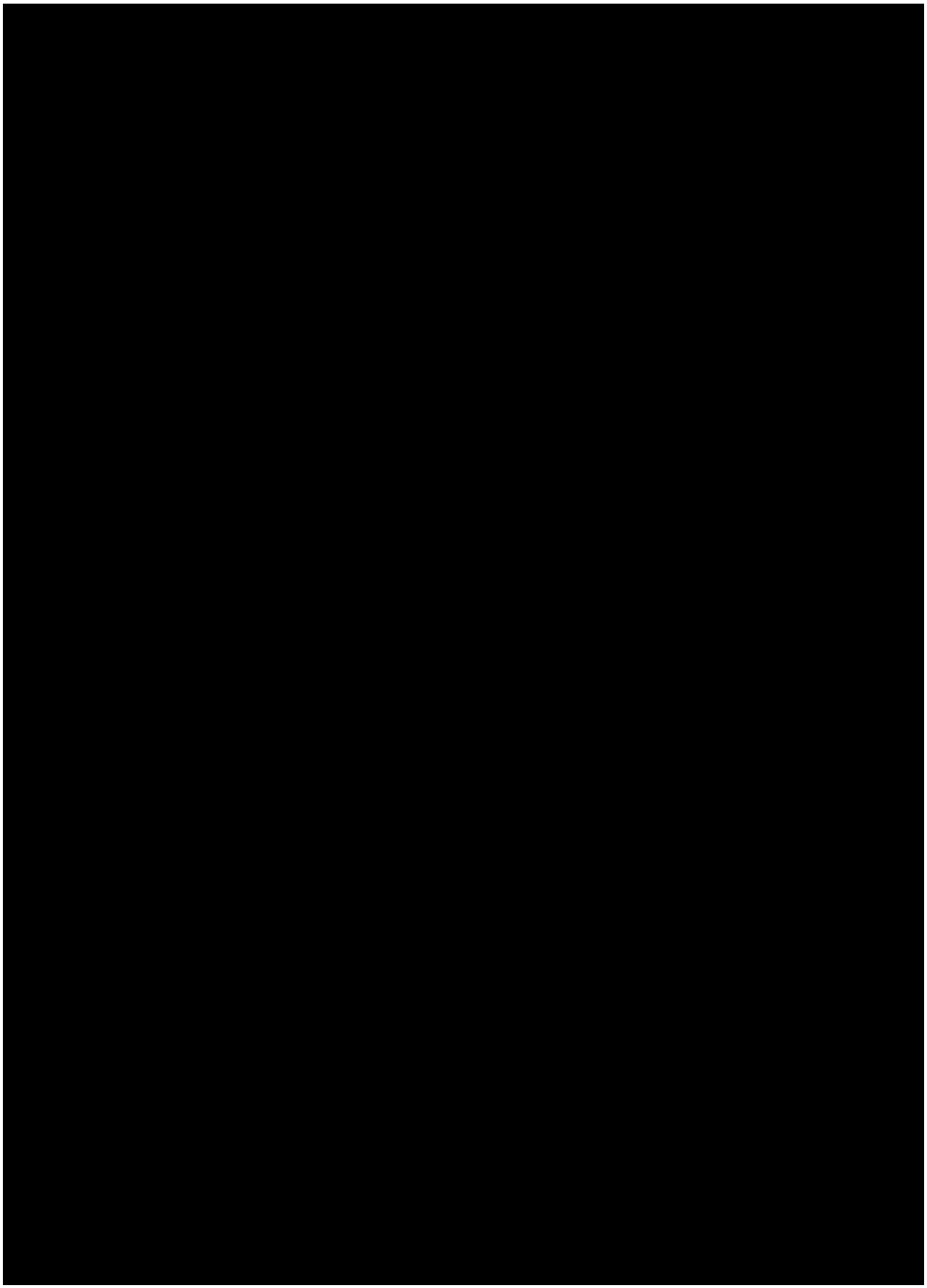
FPG change from baseline = overall mean + treatment + week
+ treatment by week interaction
+ baseline HbA_{1c} + baseline daily basal insulin dose
+ baseline FPG
+ baseline FPG by week interaction
+ random error.

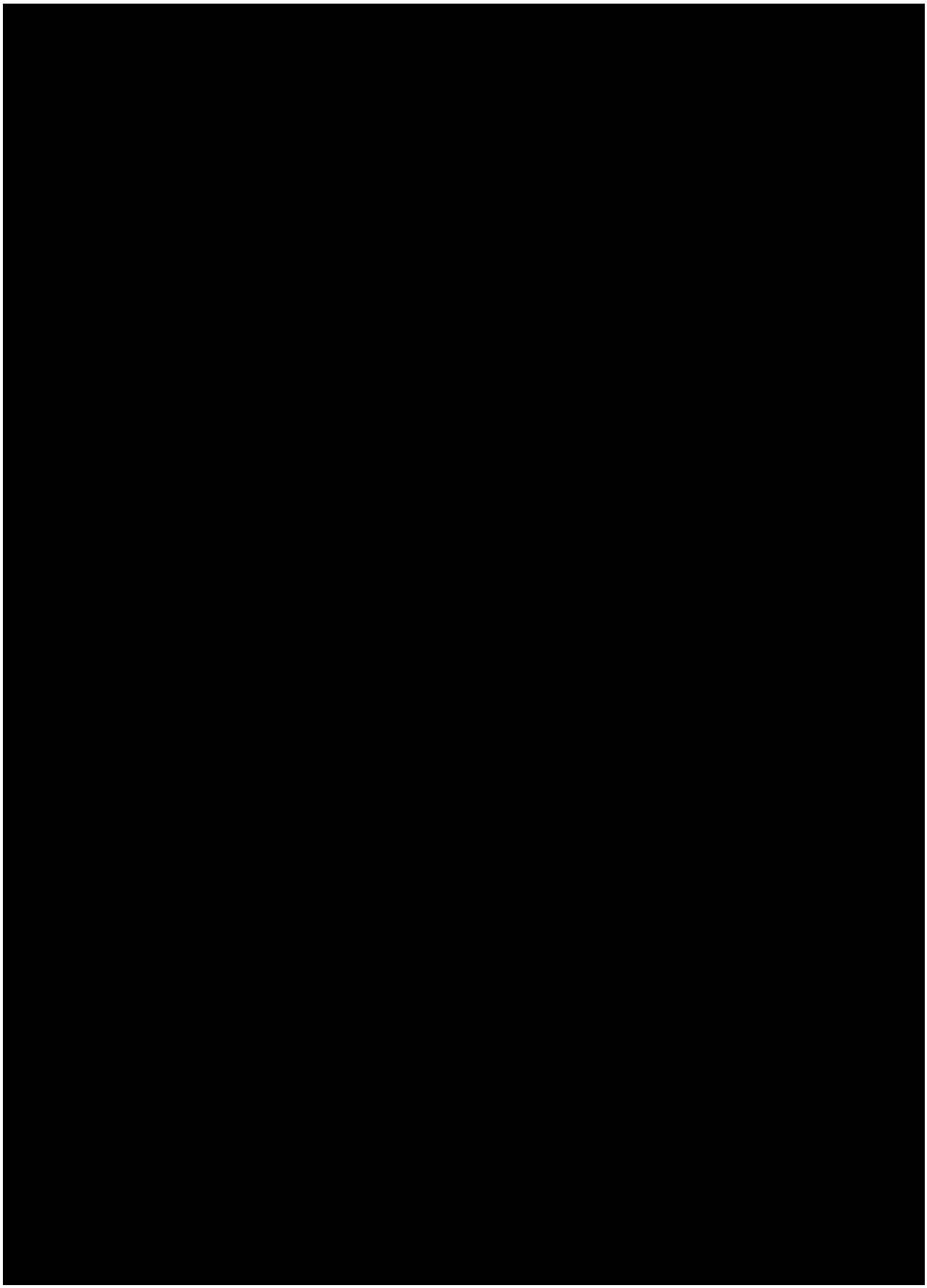
The analysis will include the fixed, categorical effects of *treatment*, *week* and *treatment by week interaction*, as well as the continuous, fixed covariates of *baseline FPG*, *baseline daily basal insulin dose*, *baseline* HbA_{1c} and *baseline FPG by week*. An unstructured (co)variance structure will be used to model the within patient measurements. This analysis will be performed on FAS (OC).

[redacted]









7.7 EXTENT OF EXPOSURE

Exposure to trial medication will be calculated in days as (trial medication stop date – trial medication start date +1) and will be tabulated as a frequency table with categorised 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). This table will additionally be produced at Week 52 for Japanese patients.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

The analysis will be based on data collected up 24 weeks at DBL. For non-Japanese patients an additional residual period of 7 days is added to the drug stop data.

For Japanese patients, all AEs up to and including day 175 are considered. An additional residual period of 7 days is added for Japanese patients that prematurely discontinue prior or at day 175.

Any data up to day 176 inclusive that is updated or entered after DBL will be summarised in the analysis including data up to 52 weeks only.

7.8.1 Adverse events

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

Furthermore, 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).
- 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 summarisation of AE data, please refer to the guideline 'Handling and summarization of AE data for clinical trial reports and integrated summaries' (2).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake until 7 days after last drug intake will be assigned to the randomised treatment; in these cases the date and time of the AE onset are used. All AEs 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 listings only). For details on the treatment definition, see Section 6.1. Japanese patients who did not prematurely discontinue prior or at day 175 do not have a post-treatment period for Week 24 analysis.

According to International Conference on Harmonisation (ICH) E3 (3) AEs classified as ‘other significant’ will include those non-serious 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 Blinded Report Planning Meeting.

An overall summary of AEs will be presented. In addition, the frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for patients with other significant adverse events according to ICH E3 (3) for patients with serious adverse events, AELDs, AEs by severity, and AEs by outcome.

The frequency of patients with adverse events will also be summarised by subgroups

- Age (in years: <70, ≥70 to <75,. ≥75)
- Gender
- Background therapy (Insulin+/-AGI, Insulin+Metformin+/-AGI, Insulin+Metformin+SU)
- Renal Function (in units mL/min/1.73m$^{2:}$ <60, ≥60 and <30, ≥30 to <60, ≥60 to <90, ≥90)
- Race.

In addition, frequencies of patients with post-treatment AEs will be displayed.

The system organ classes and preferred terms will be sorted alphabetically.

Analysis of investigator defined hypoglycaemic adverse events

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

- investigator defined hypoglycaemic AE with
  - confirmed plasma glucose level of ≤70mg/dL (≤3.9mmol/L) or severe hypoglycaemic AE
  - confirmed plasma glucose level of <54mg/dL (<3.0mmol/L) or severe hypoglycaemic AE
  - severe hypoglycaemic AE

- investigator defined symptomatic hypoglycaemic adverse event or any severe hypoglycaemic AE with
  - confirmed plasma glucose level of ≤70mg/dL (≤3.9mmol/L) or severe hypoglycaemic AE
  - confirmed plasma glucose level of <54mg/dL (<3.0mmol/L) or severe hypoglycaemic AE
  - severe hypoglycaemic AE.

A frequency table will be provided for the number of patients per treatment group that experienced any investigator defined hypoglycaemic AE as defined above.

Asymptomatic hypoglycaemia events which do not represent an AE will also be collected on a separate CRF page. No symptoms are recorded for these events, only plasma glucose levels.

An overview table with frequency of patients who experienced any hypoglycaemia – reported as investigator defined AE or as asymptomatic hypoglycaemia (not as AE) will be presented. Also frequencies for asymptomatic hypoglycaemic events (reported as AE or non-AE) will be shown. The number of patients with hypoglycaemic events (as AE or non-AE) will be tabulated by treatment group.

The impact of the occurrence of investigator defined hypoglycaemic AEs will be explored using logistic regression; the model will include *treatment*, *continuous baseline* HbA_{1c} and *baseline daily basal insulin dose*. Time to first onset of the first investigator defined hypoglycaemic AE will be analysed by Kaplan-Meier estimates if enough events occur.

[redacted]

Adverse events of special interest

Adverse Events of Special Interest (AESI) are topics under close surveillance in all clinical trials including linagliptin. At the time of finalisation of this protocol, the AESI categories and types of events include:

- Hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis (narrow SMQ Hypersensitivity)

- Skin lesions such as exfoliative rash, skin necrosis, or bullous dermatitis (narrow SMQ SCAR)

- Hepatic events such as ≥3 fold upper limit of normal (ULN) of AST and/or ALT, hepatitis, hepatic injury, jaundice and potential Hy's Law cases
    - AEs based – Table based on following (sub) SMQs
        - Drug related hepatic disorders - severe events only (SMQ)
        - Liver related investigations, signs and symptoms (SMQ)
        - Cholestasis and jaundice of hepatic origin (SMQ)

    - Lab based: DILI evaluation listing (potential Hy's Law cases) – listing of all patients that have at least one AST/ALT value greater or equal than 3 times ULN or one Total bilirubin case greater or equal 2 times ULN

- Renal adverse events such as acute renal failure (Narrow SMQ acute renal failure)

- Pancreatitis (Pancreatic event tables)

- Pancreatic cancer (will be captured in pancreatic event tables and proposed malignancy table)

The categories and events included as AESIs may change according to the active pharmacovigilance of linagliptin and are expected to be updated on a periodic basis. Definitions, including Standardised MedDRA Queries (SMQs) for the AESIs will be maintained on project level and presented in Section 16.2.7.

AESIs will be summarised by preferred term.

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

An independent external CEC regularly reviews cardiovascular and neurovascular events and evaluates whether pre-specified criteria for these adjudicated endpoints are met. Details on composition of the CEC, responsibilities and clinical event definitions are provided in a separate CEC Charter. Events qualifying for adjudication will be selected based on the SMQs (as detailed in the latest CEC charter version):

- Ischemic heart disease (excluding selected PTs as listed in the CEC charter)
- Cardiac failure (excluding selected PTs as listed in the CEC charter)
- Torsade de pointes / QT prolongation
- Central nervous system vascular disorders (excluding selected PTs as listed in the CEC charter)
- Further simple preferred terms and
- All fatal cases

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

Adjudication will be incorporated to the database and will include the following adjudication endpoints:

- Cardiovascular death, including presumed cardiovascular death and other cardiovascular death, fatal stroke, fatal myocardial infarction, sudden death, worsening of heart failure, cardiogenic shock
- Myocardial infarction (non-fatal)
- Stroke (non-fatal)
- Hospitalisation for unstable angina pectoris

- Stent thrombosis
- Heart failure requiring hospitalisation
- Coronary revascularisation procedures (Coronary Artery Bypass Grafting (CABG) or Percutaneous Coronary Intervention (PCI))
- Transient ischemic attack (TIA)

Additionally, a separate independent, blinded, external committee will regularly review pancreatic events. The adjudication process for these events is clarified in a separate CEC charter.

This independent and external CEC will regularly review events suspect of acute pancreatitis, chronic pancreatitis, asymptomatic pancreatic hyper-enzymemia and pancreatic malignancy and will evaluate whether pre-specified criteria for these adjudication events are met. Details on composition of the CEC, responsibilities and clinical event definitions are provided in the charter. Events qualifying for adjudication will be selected based on the latest CEC charter version:

- SMQs acute pancreatitis (excluding selected PTs as listed in the CEC charter)
- Trigger events of acute pancreatitis
- Trigger events of chronic pancreatitis
- Trigger events pancreatic malignancy

A list of amylase and lipase laboratory values that are ≥ 3 times the upper limit of normal (ULN) and not reported as AE, but considered for adjudication by Team Member medicine (TMM) or Team Member Drug Safety (TMDS).

The CEC will be provided with additional, specified background material on the patients with these events and will perform an assessment of the events.
Adjudication assessments will be incorporated to the database and will include the following adjudication endpoints:

- Acute pancreatitis (with organ failure)
- Acute pancreatitis (without organ failure)
- Chronic pancreatitis (with organ failure)
- Asymptomatic pancreatic hyper-enzymemia
- Pancreatic malignancy

Frequency tables by treatment group will be provided for the adjudicated endpoints (cardiovascular and pancreatic events, respectively) and for the preferred terms in the specified SMQs of events.

Tables will be provided for cardiovascular and pancreatic events respectively that were confirmed or non-assessable

  - Frequency [N (%)] of patients with adverse events qualifying for CECP adjudication by treatment, system organ class and preferred term − TS

- Adjudication results: Frequency [N(%)] of patients with CECP confirmed pancreatic adverse events by treatment – TS.

Other selected safety topics

Other selected safety topics are topics that are under close surveillance in trials with linagliptin. At the time of finalisation of this protocol, the following safety topic was included

- Malignancy.

Frequencies of patients in each treatment group will be provided by user-defined AE category and preferred term. The SMQ "Malignant or unspecified tumours" is to be applied.

7.8.2 Laboratory data

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

Laboratory values taken after the first dose of randomised treatment up to a period of 7 days after the last dose of study medication will be assigned to the treatment period for evaluation. Descriptive statistics for baseline, last value on treatment and difference from baseline will be presented. Laboratory values will be compared to their reference ranges and a frequency table will be provided for the number of patients with transitions relative to reference ranges at baseline. A frequency table of patients with possible clinically significant abnormalities will also be presented.

In order to support screening for highly increased amylase and/or lipase values with respect to upper limit of normal (ULN), a specific transition table will be provided. The table lists the number and frequency of patients with last value or maximum value on treatment

- less than or equal ULN
- greater than ULN
- greater than 2 ULN
- greater than 3 ULN

for baseline categories

- less than LLN
- greater than or equal LLN and less than or equal ULN
- greater than ULN and less than or equal 3ULN
- greater than 3ULN

All analyses will be based on the treated set (TS).

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report. The following parameters are analysed: pulse, systolic blood pressure, diastolic blood pressure.

7.8.4 ECG

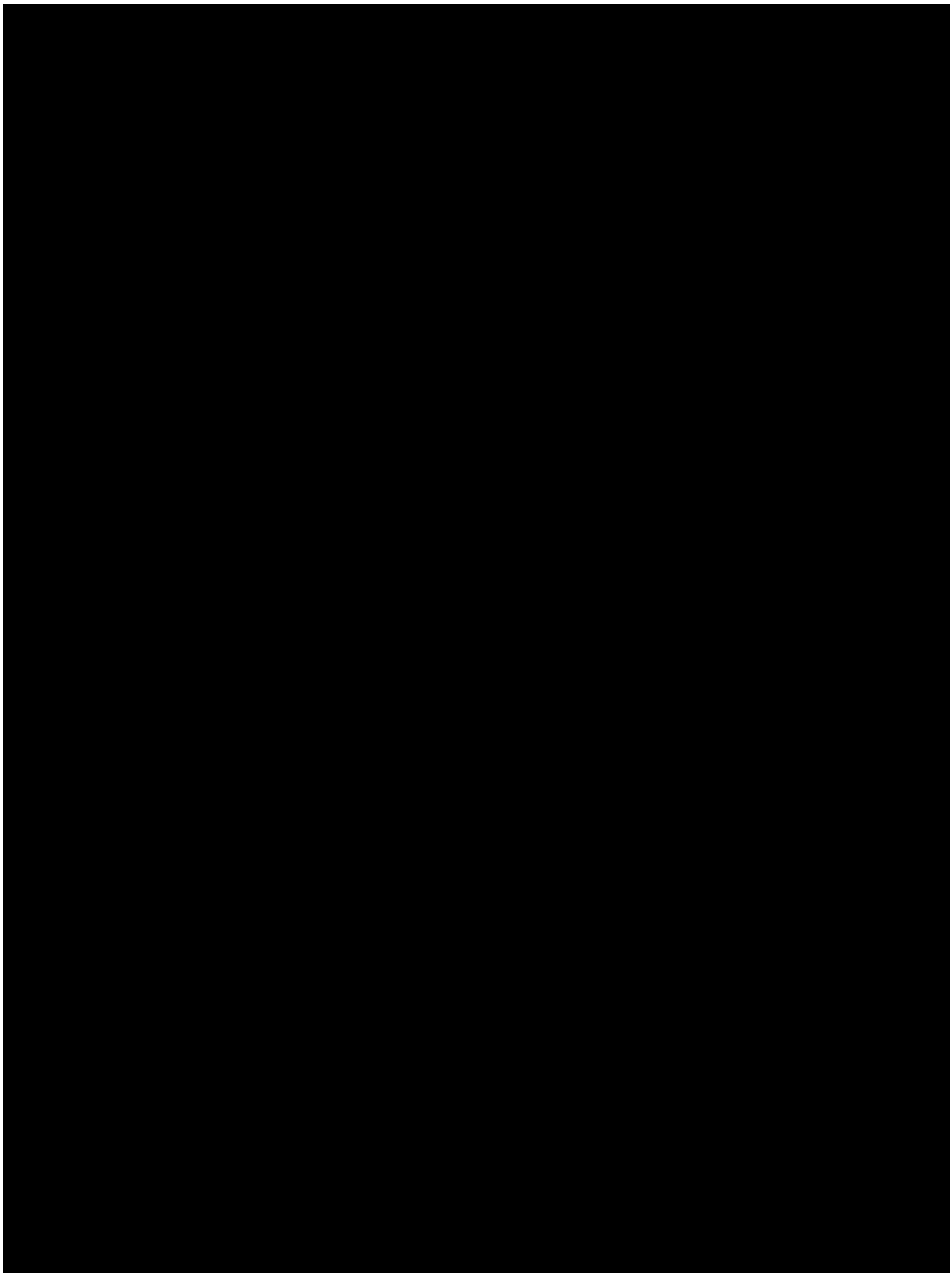
12-lead ECG measurements will be taken at baseline (Visit 3) and after 24 weeks (Visit 98 [EoT] for non-Japanese patients, Visit 7 for Japanese patients) and additionally at Week 36 and 52 (EoT) for Japanese patients. ECG-findings before randomisation will be considered as baseline conditions. Any clinically significant new findings in the ECG-measurement after the first screening ECG will be considered AEs and analysed as planned in Section 7.8.1.

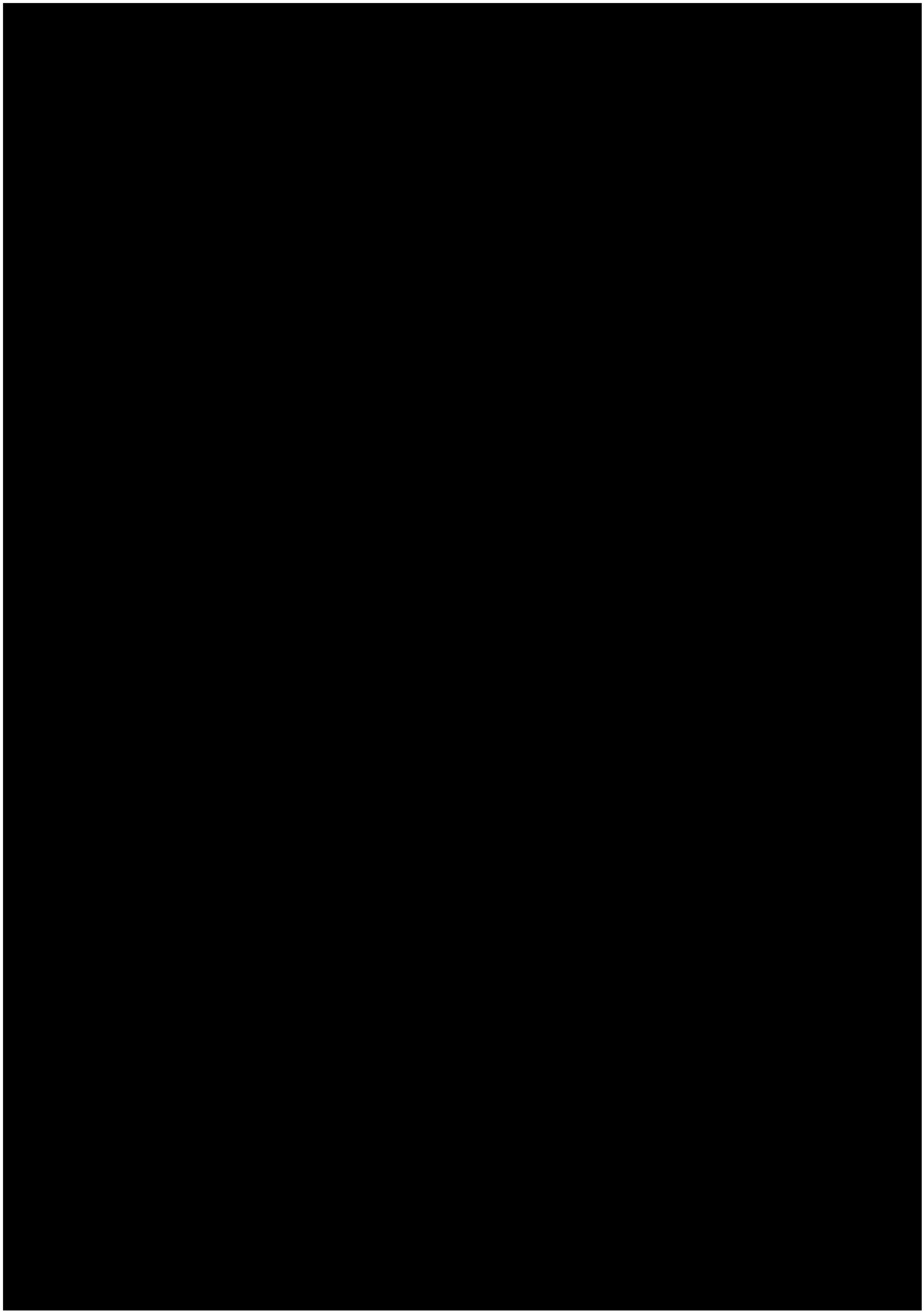
7.8.5 Others

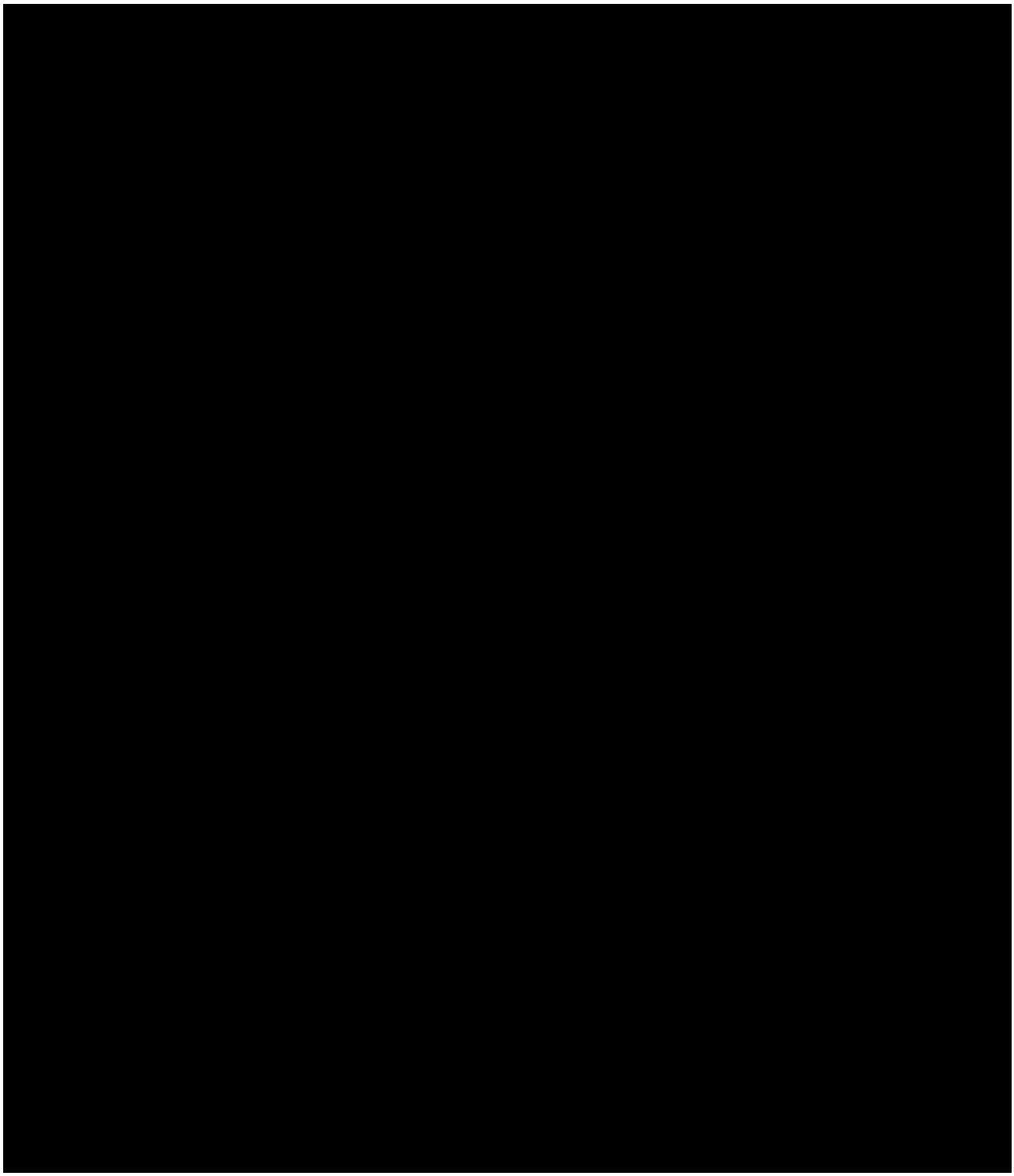
Physical Examination will be taken at screening (Visit 1), and at the end of the treatment (Visit 98). Findings in the physical examination at screening will be considered a baseline condition. Any clinically significant new findings in the Physical Examination during the course of the trial will be considered AEs and analysed as planned in Section 7.8.1.

8. REFERENCES

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







10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**12-Oct-16**	[redacted]	None	This is the final TSAP without any modification
Revised	**09-Nov-2016**	[redacted]	6.2	Table 6.2: 1 additional column defining the type of the IPV, FPG limits adjusted footnote added
			[redacted]	[redacted]
			6.8	section omitted from TSAP, will move to ADS plan
			7.8.1	age, renal function and background therapy subgroups for AE and hypoglycaemic AE analyses adjusted, [redacted]
			[redacted]	[redacted]