Trial Statistical Analysis Plan

c07659061-02

BI Trial No.:	1245.72
Title:	A Phase III, randomised, double blind, placebo-controlled, parallel group, efficacy, safety and tolerability trial of once daily, oral doses of **E**mpagliflozin as **A**djunctive to in**S**ulin th**E**rapy over 26 weeks in patients with Type 1 Diabetes Mellitus (EASE-3) Including Protocol Amendment 2 1245.72 [c02993089-03]
Investigational Product(s):	Empagliflozin
Responsible trial statistician:	[redacted] Phone [redacted] Fax: [redacted]
Date of statistical analysis plan:	11 OCT 2017 REVISED
Version:	Revised

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2 LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical classification
AUC	Area under the curve
BHB	Beta-hydroxybutyrate
BI	Boehringer Ingelheim
BIcMQ	BI-customised MedDRA query
BMI	Body mass index
CEC	Clinical event committee
CRF	Case report form
CSII	Continuous subcutaneous insulin infusion
CT	Concomitant therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBP	Diastolic blood pressure
DKA	Diabetic Ketoacidosis
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DST	Daylight saving time
ECG	Electrocardiogram
eCRF	Electronic case report form
e-diary	Electronic diary
EMA	European medicines agency
eGFR	Estimated glomerular filtration rate
EoT	End of treatment
FAS	Full analysis set
FPG	Fasting plasma glucose

Term	Definition / description
GI	Genital infection
HbA_{1c}	Glycated haemoglobin
HCRU	Health care resource utilisation
HLT	High level term
ICH	International Conference on Harmonisation
IPV	Important protocol violation
ITT	Intention to treat
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
MAGE	Mean amplitude of glucose excursions
MDG	Mean daily glucose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention to treat
MMRM	Mixed model for repeated measures
NCF	Non-completers considered failure
O*C	Oracle Clinical
OC	Observed cases
OC-AD	Observed cases – all data
OC-H	Observed cases – excluding anti-hypertensives
OC-OffT	Observed cases – off-treatment
OC-P	Observed cases – excluding paracetamol
OR	Original results
PG	Plasma glucose
PK	Pharmacokinetics
PPS	Per protocol set
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
RS	Randomised set
SBP	Systolic blood pressure

Term	Definition / description
SCR	Screened set
SD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System Organ Class
SSC	Special search category
TBL	Total bilirubin
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
UTI	Urinary tract infection
WHO	World health organisation

3 INTRODUCTION

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

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

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

4 CHANGE IN THE PLANNED ANALYSIS OF THE STUDY

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

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

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

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

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

5 ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint in this study is the change from baseline in HbA1c (%) at 26 weeks.

For the definition of baseline HbA1c refer to Section 6.7.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

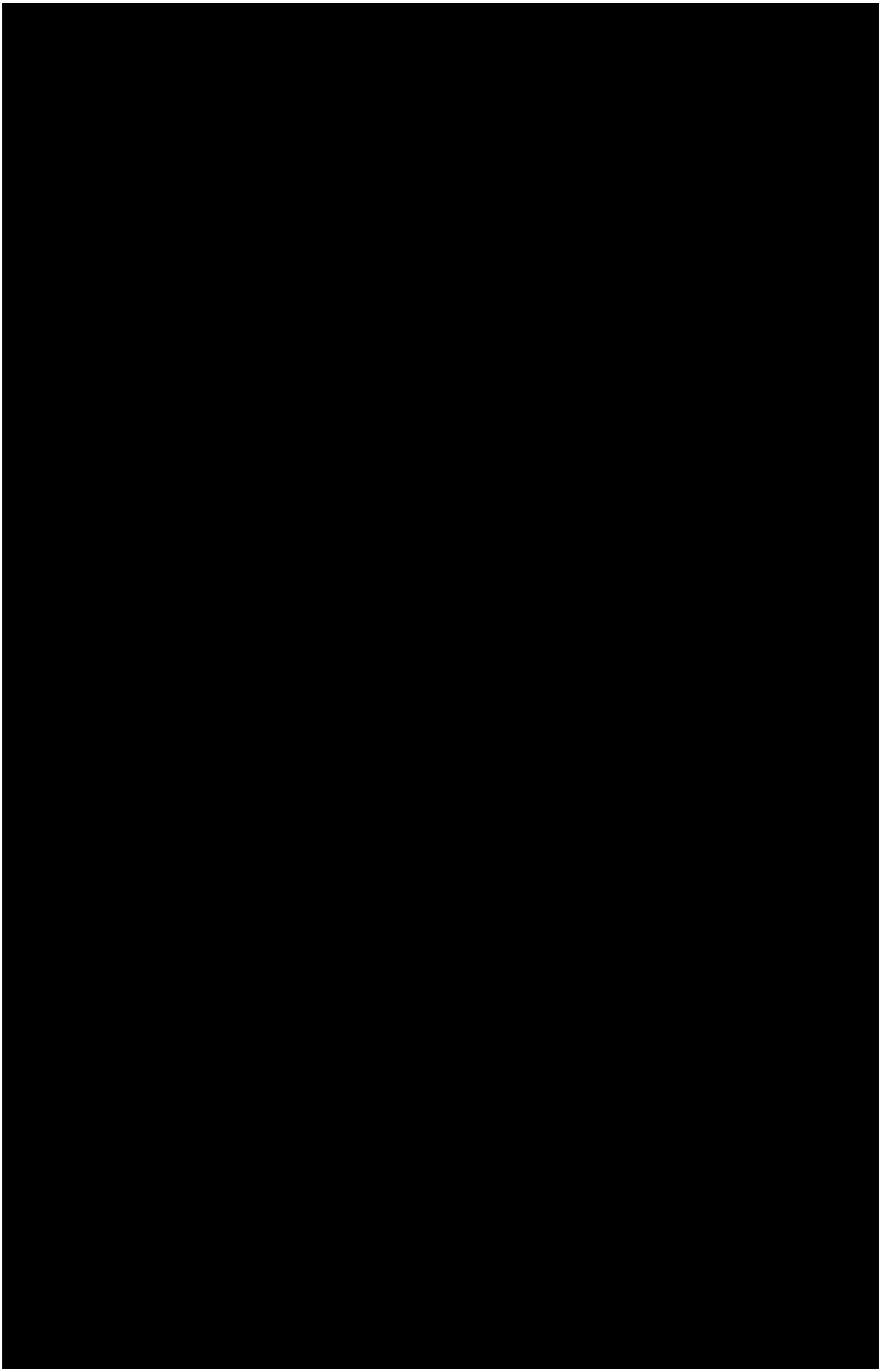
For baseline definitions for each endpoint, refer to Section 6.7.

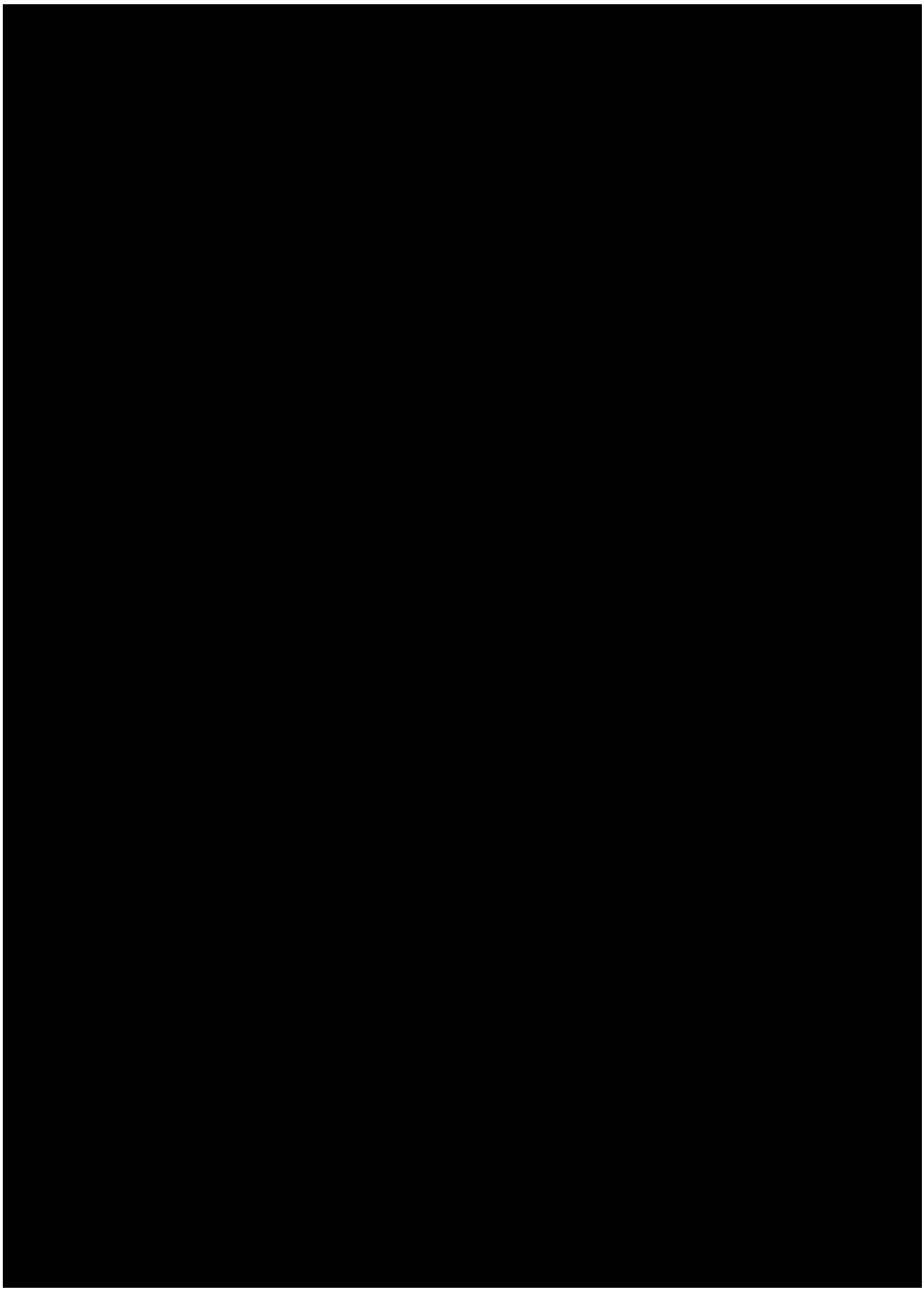
The key secondary endpoints in this study are:

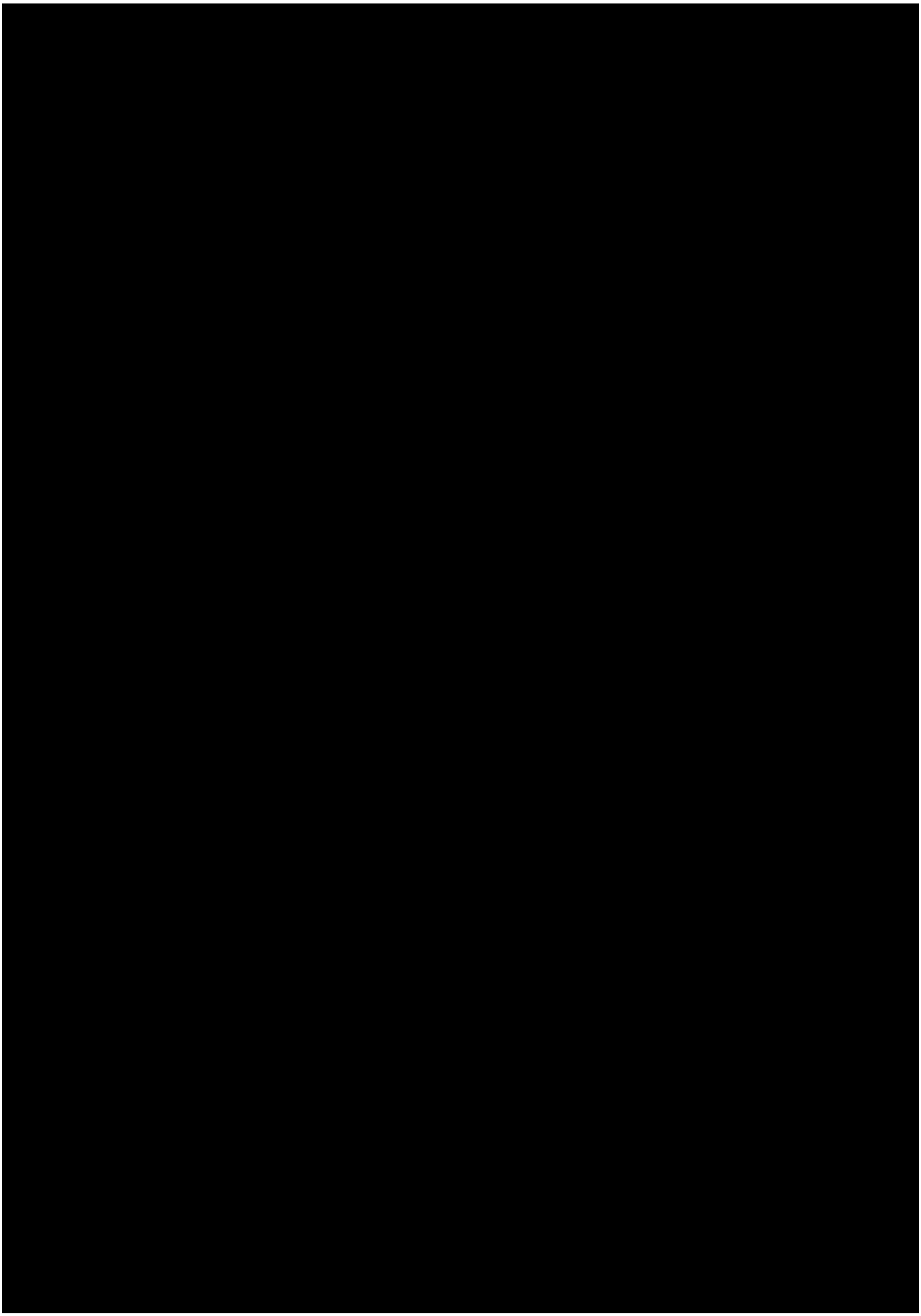
- Rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose <54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic events confirmed by adjudication per patient-year from Week 5 to Week 26.
    - All severe hypoglycaemic AEs that are confirmed by adjudication and all investigator reported AEs that have confirmed plasma glucose <54mg/dL (<3.0 mmol/L) with symptoms reported will be counted.
- Rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose <54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic events confirmed by adjudication per patient-year from Week 1 to Week 26
    - All severe hypoglycaemic AEs that are confirmed by adjudication and all investigator reported AEs that have confirmed plasma glucose <54mg/dL (<3.0 mmol/L) with symptoms reported will be counted.
- Change from baseline in body weight (kg) at 26 weeks
- Change from baseline in total daily insulin dose, U/kg, at 26 weeks
- Change from baseline in systolic blood pressure (SBP), mmHg, at 26 weeks
- Change from baseline in diastolic blood pressure (DBP), mmHg, at 26 weeks

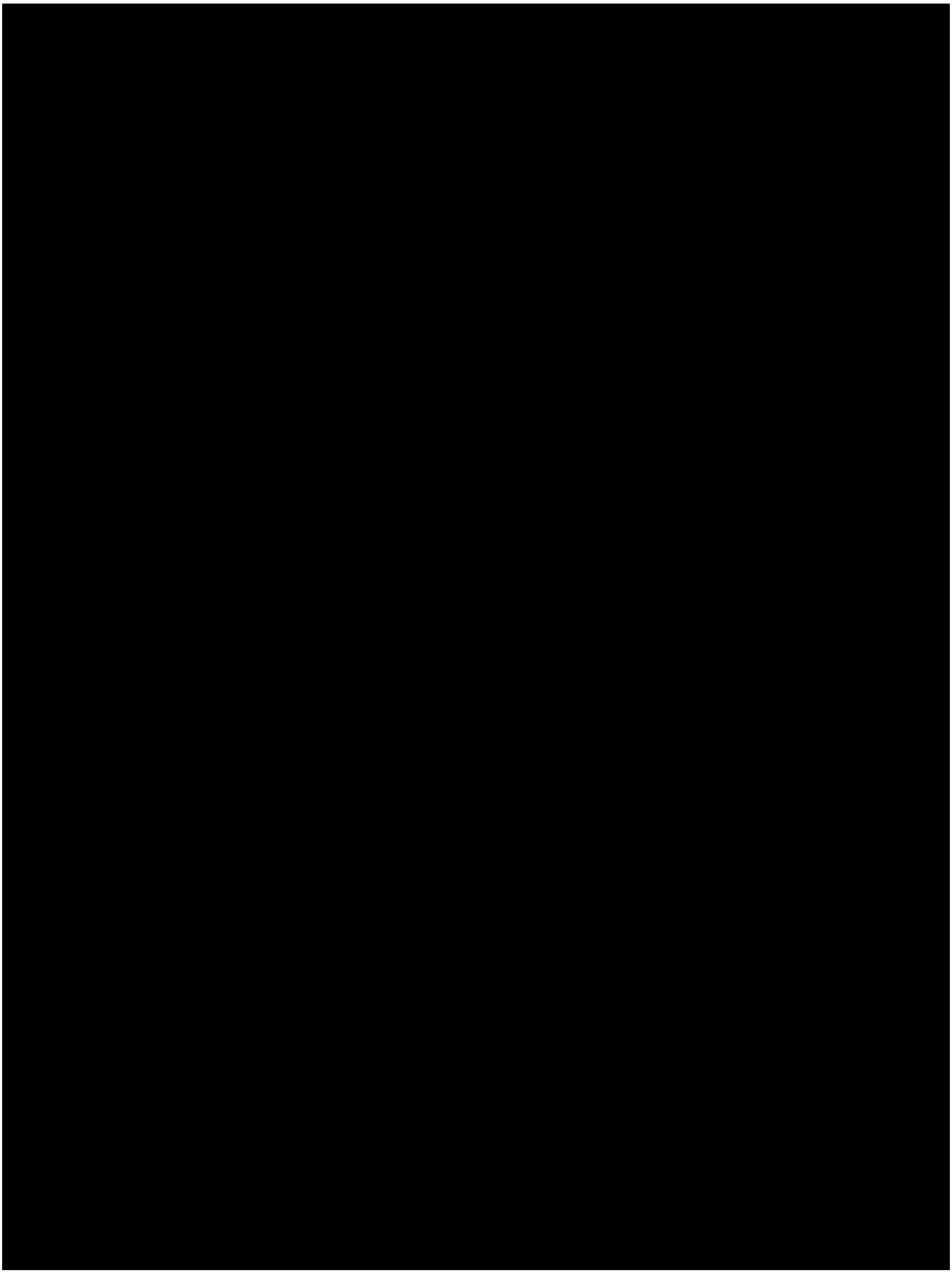
5.2.2 Secondary endpoint

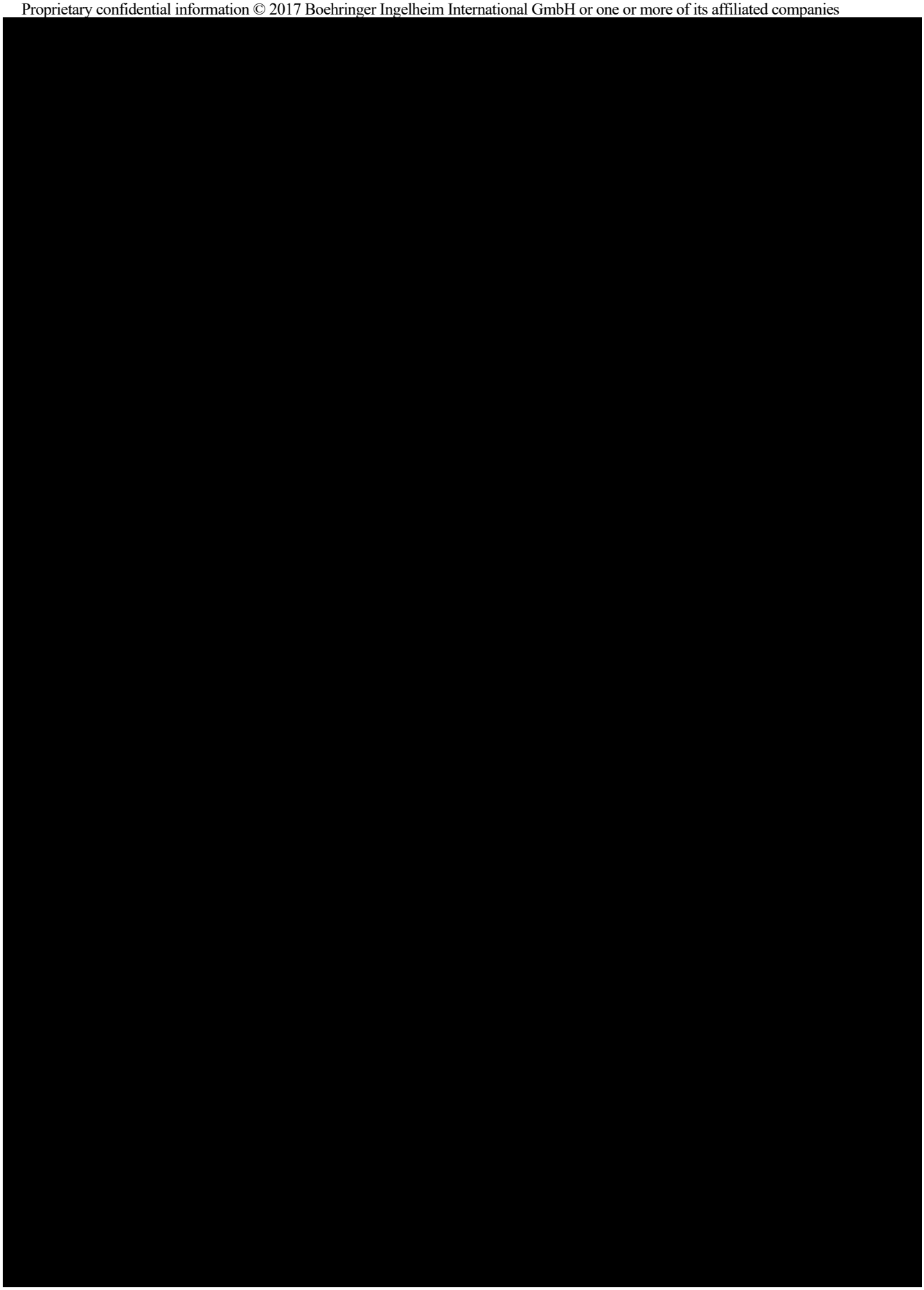
Since there are no secondary endpoints specified in the protocol, this section is not applicable.

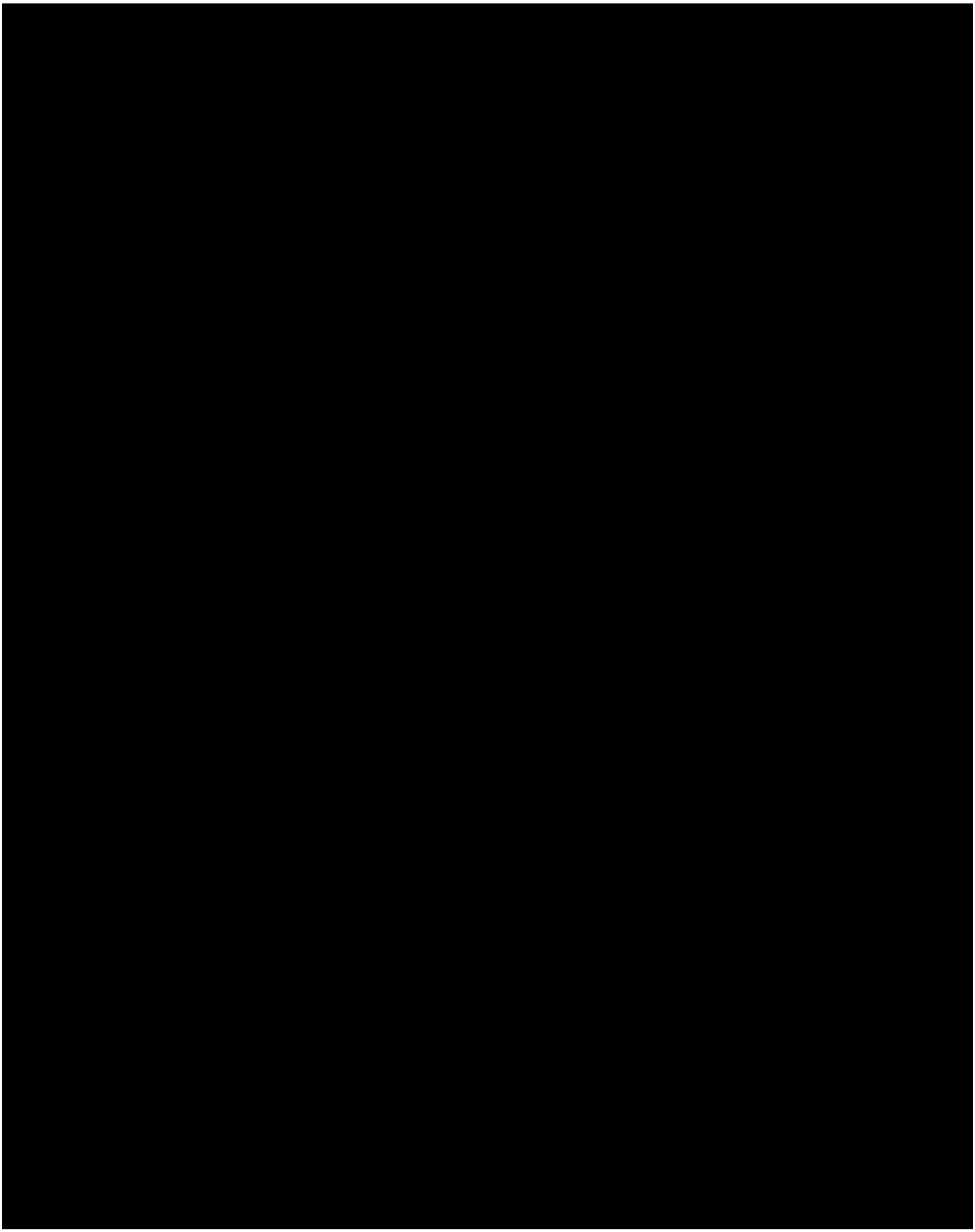


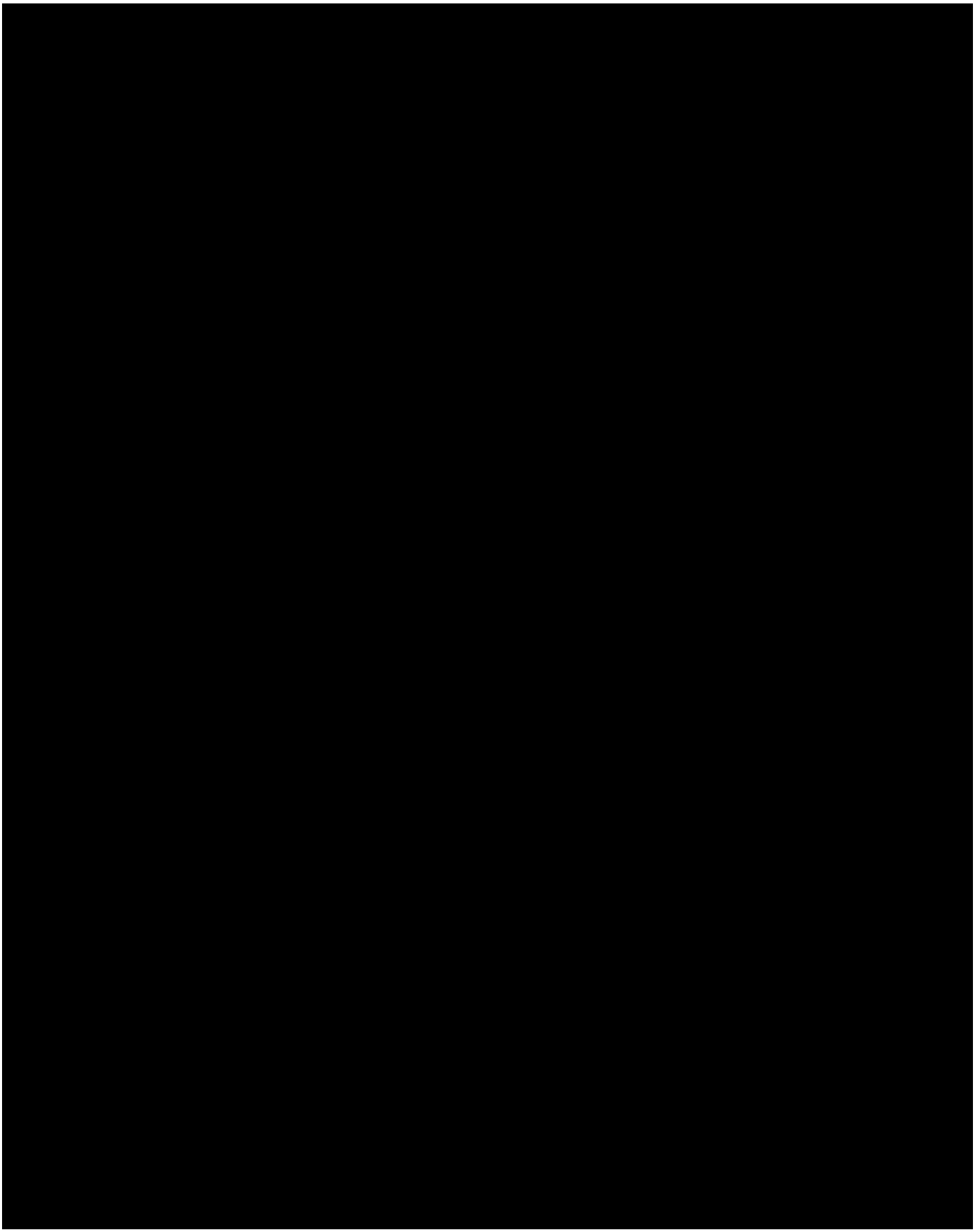


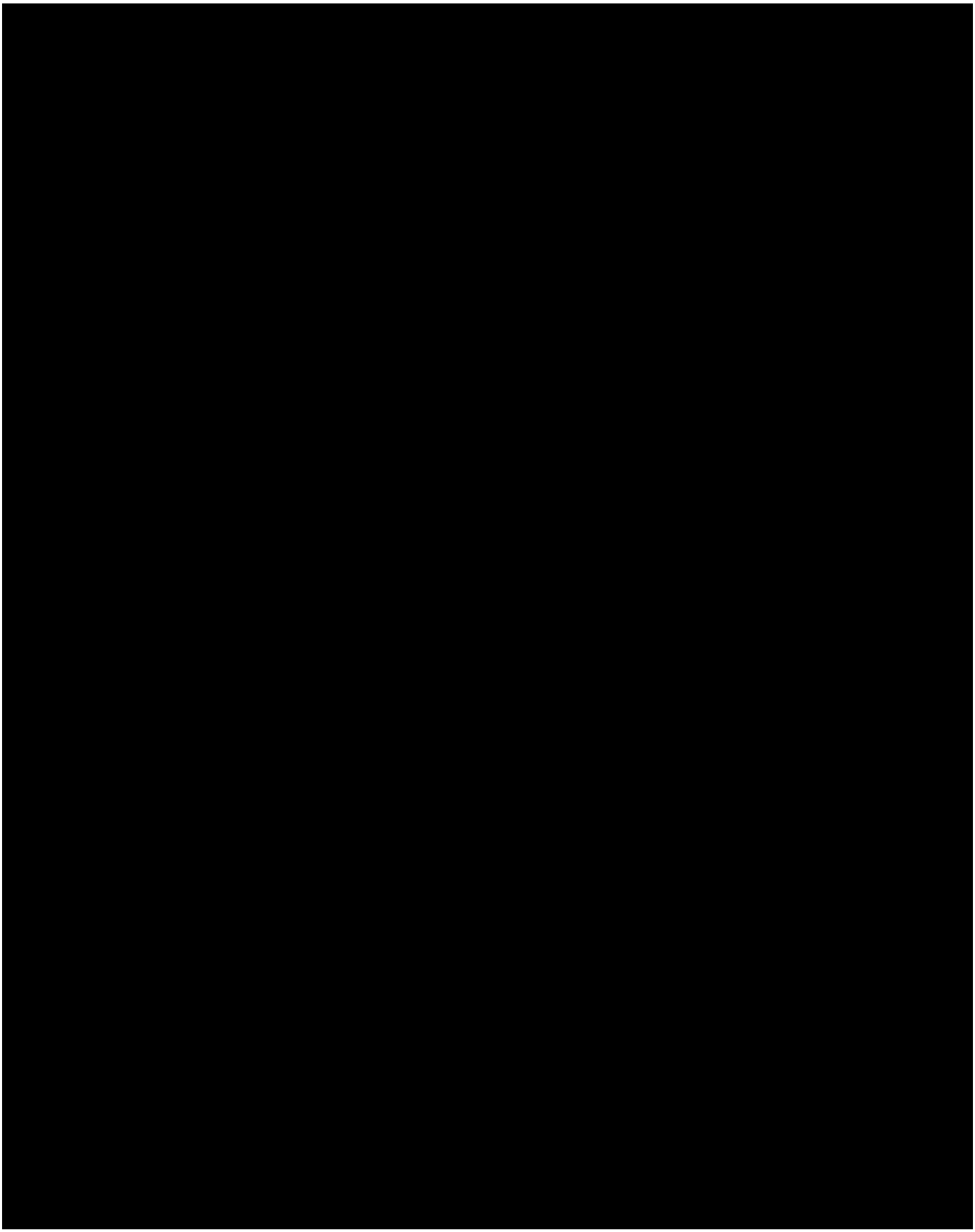












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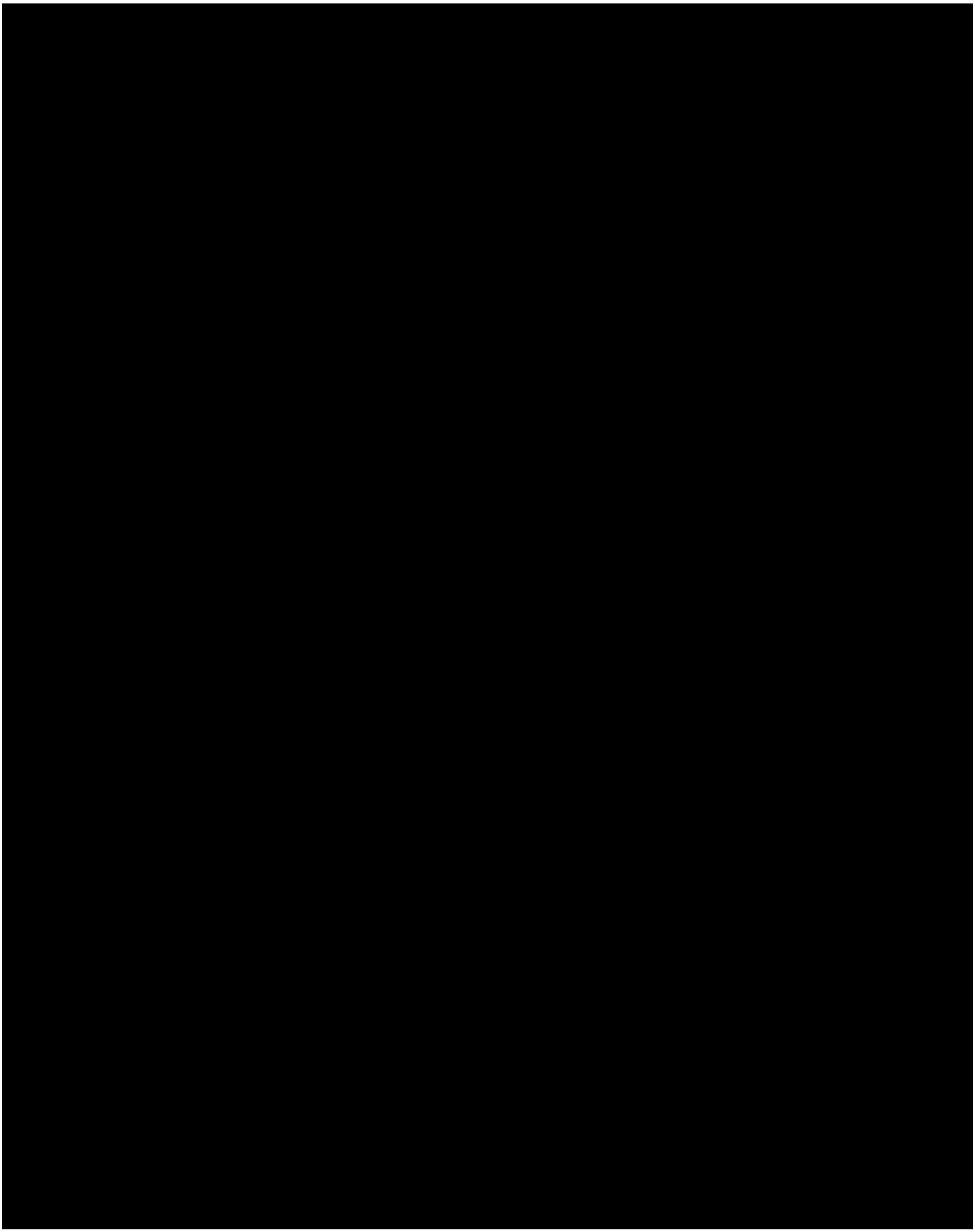

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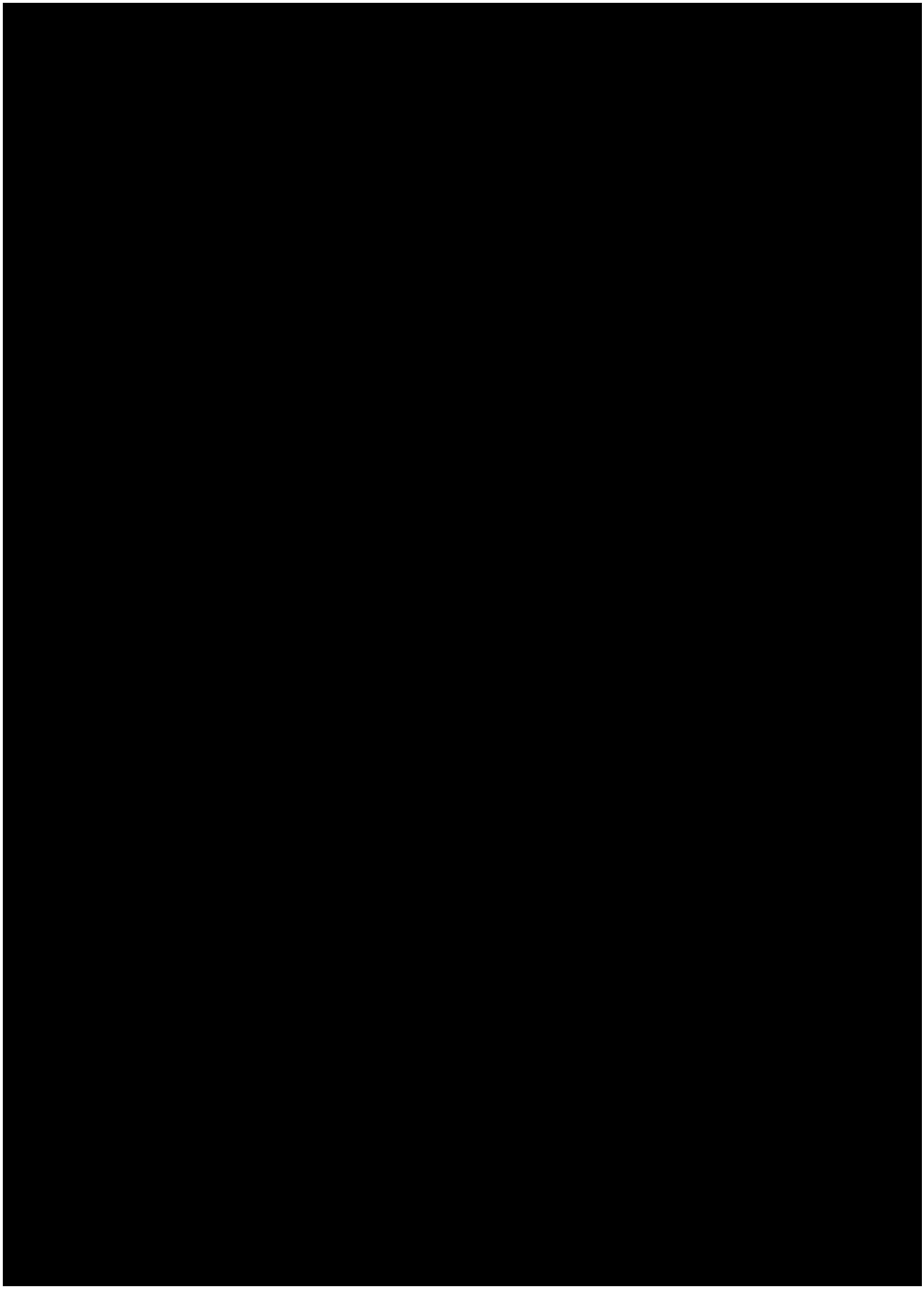
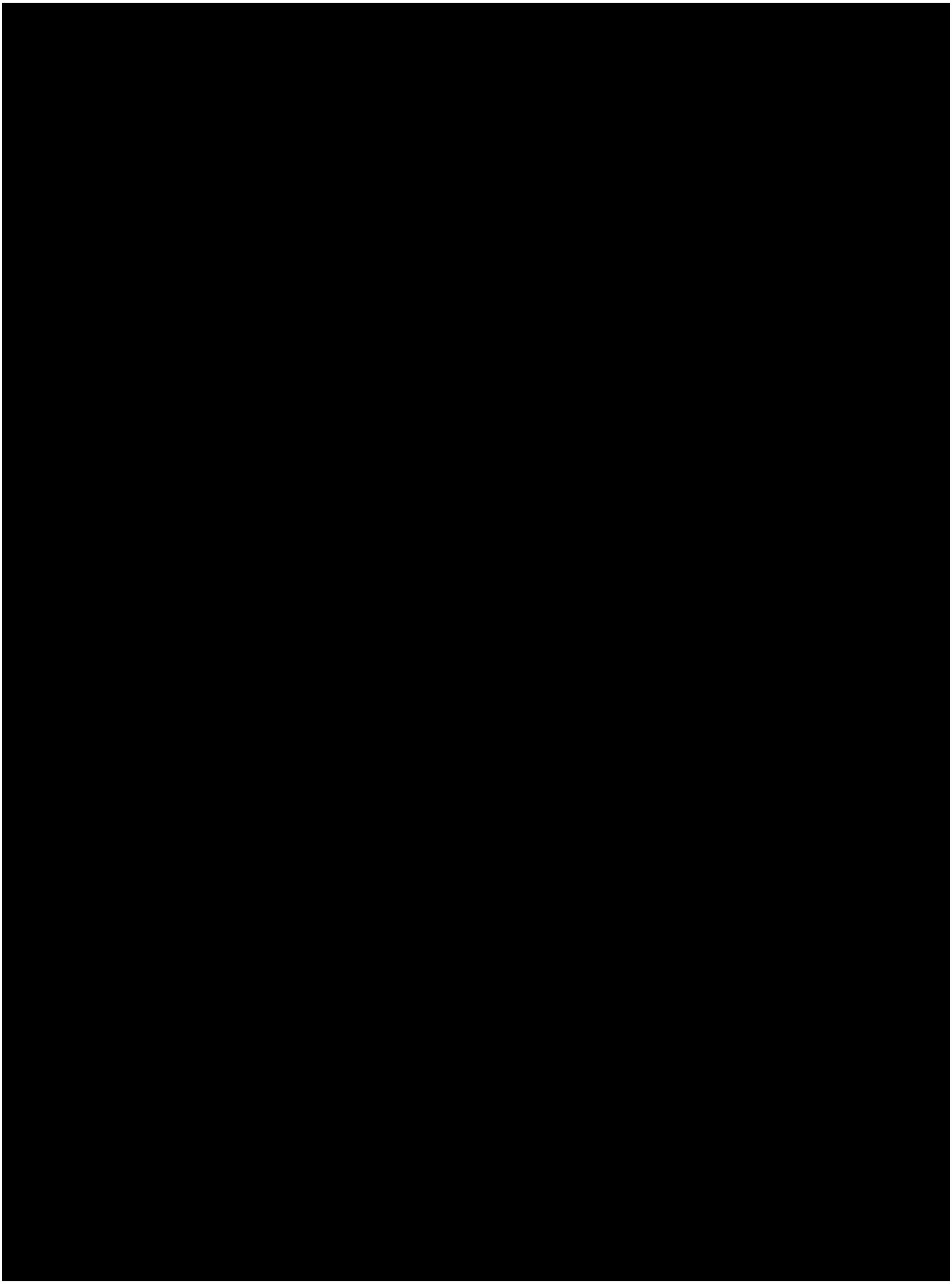
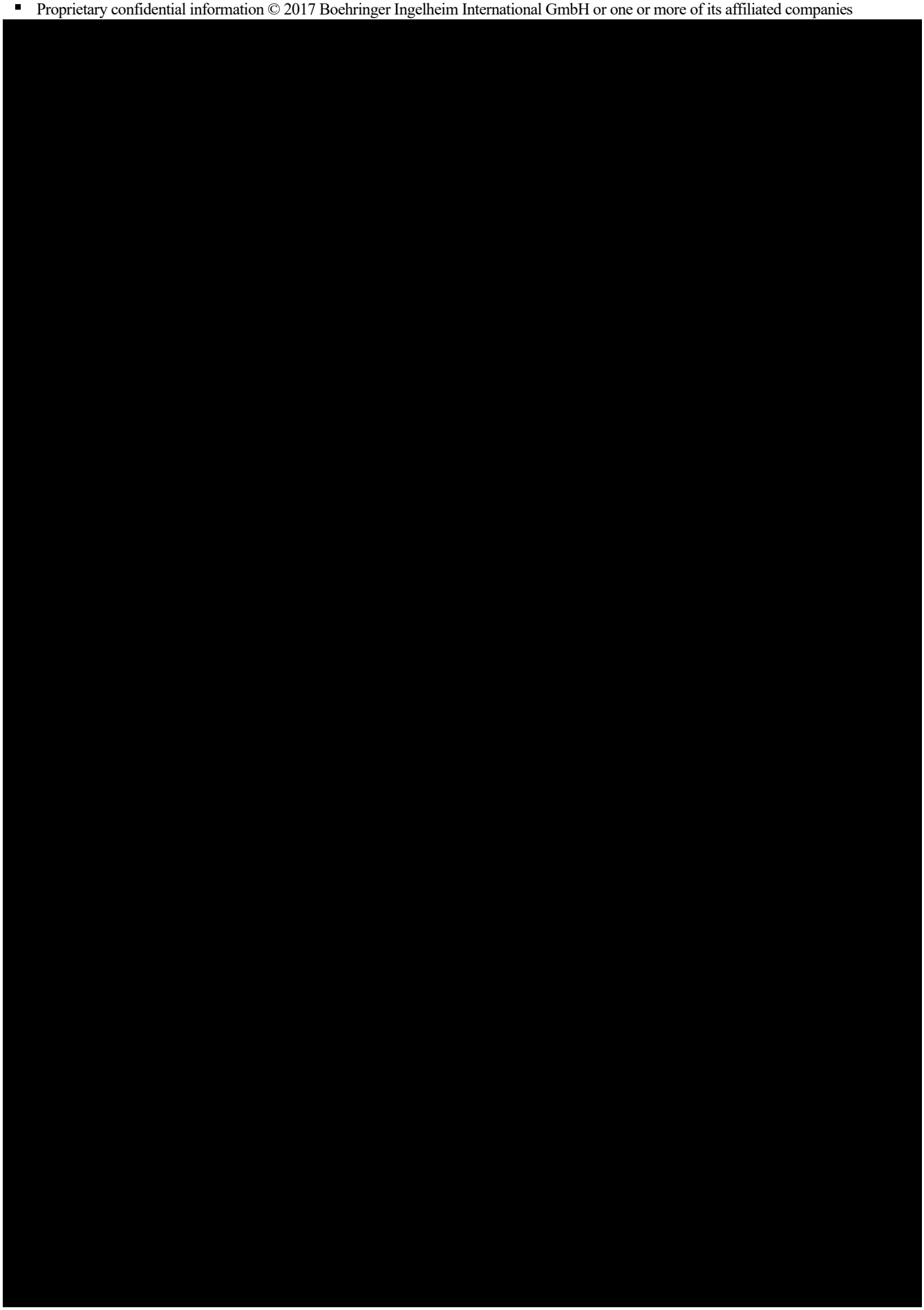
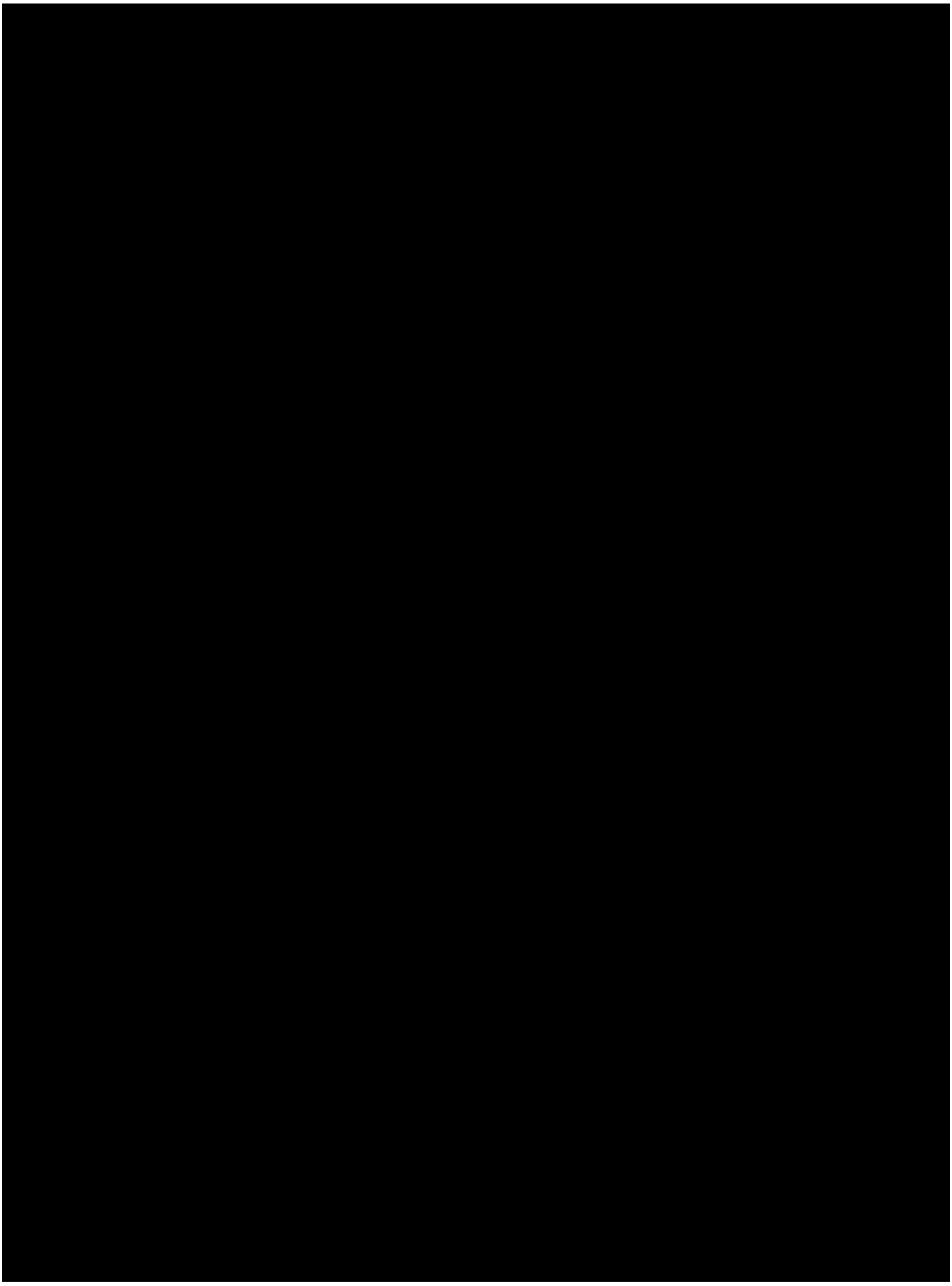








5.4.9 Safety data

In addition to the standard adverse event attributes, laboratory endpoints, and vital signs the following safety endpoints will be analysed:

- Change from baseline in lipid profile parameters. Lipid profile consists of total cholesterol, HDL cholesterol, LDL cholesterol, LDL/HDL cholesterol ratio, non-HDL cholesterol, triglycerides, free fatty acids, Apo A-1, and Apo B.

6 GENERAL ANALYSIS DEFINITION

6.1 TREATMENTS

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

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

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

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

Safety analyses will assign patients to the treatment group as randomised.

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

6.2 IMPORTANT PROTOCOL VIOLATIONS (IPVS)

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

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

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

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

Table 6.2: 1 Important protocol violations

Category/Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
A1		**Target indication not met**		
	A1.02	Antidiabetic background therapy not as required	Inclusion criteria 4 not met (No insulin recorded on eCRF Or Total daily insulin dose < 0.3 U/kg or >1.5 U/kg at visit 1[#] Or MDI patients: fewer than 1 basal and 3 bolus injections per day at visit 1[#] CSII patients: fewer than 5 months experience of using the pump prior to Visit 1[#]).	PPS
	A1.03	No Type 1 Diabetes	Inclusion criteria 2 not met, with no date of diabetes mellitus type 1 first diagnosed known.	PPS
	A1.05	Time since diagnosis out of range	Inclusion criteria 2 not met, with a date of diagnosis < 1 year prior to Visit 1.	PPS
A2		**Inclusion criteria not met**		
	A2.01	HbA_{1c} out of range	HbA_{1c} <7.3% or > 10.2% at Visit 5 Or HbA_{1c} increase > 0.5% from Visit 1 to Visit 5.	PPS
	A2.02	Age out of range	Inclusion criteria 7 not met Or Age < 18 years at Visit 1.	All

Table 6.2: 1 Important protocol violations (continued)

Category/Code		Description	Example/Comment	Excluded from
	A2.03	BMI out of range	Inclusion criteria 8 not met Or BMI <18 kg/m^2 at Visit 1.	None
	A2.04	eGFR out of range	Inclusion criteria 9 not met Or eGFR < 29.5 $mL/min/1.73m^2$ according to CKD-EPI formula based on creatinine value at Visit 1. Central laboratory values will be used to determine whether INC<9> is not met.	PPS
	A2.06	Fasting C-peptide out of range	Inclusion criteria 3 not met Or Fasting C-peptide ≥ 0.7 ng/mL at Visit 2.	PPS
A3		**Exclusion criteria not met**		
	A3.02	Additional background therapy	Exclusion criteria 3 checked Or Any antihyperglycaemic drug (e.g. metformin, AGI, GLP-1 analogues, SGLT-2 inhibitors, pramlintide, inhaled insulin, pre-mixed insulins etc.) except subcutaneous basal and bolus insulin recorded on eCRF within 3 months prior to Visit 1[#].	PPS
	A3.03	Relevant concomitant diagnoses	Exclusion criteria 4, 5, 7, 9 or 15 checked Or Any of the following: • Severe hypoglycaemia involving coma and/or seizure that required hospitalisation or hypoglycaemia related treatment by an emergency physician or paramedic within 3 months prior to Visit 1 and until randomisation#. • Occurrence of DKA within 3 months prior to Visit 1 and until randomisation#. • Acute coronary syndrome (non-STEMI, STEMI and unstable angina pectoris), stroke or transient ischaemic attack (TIA) within 3 months prior to Visit 1#. • Diagnosis of brittle diabetes. • Medical history of cancer within the last 5 years prior to Visit 1 (except resected basal cell carcinoma) #.	None

Table 6.2: 1 Important protocol violations (continued)

Category/Code		Description	Example/Comment	Excluded from
	A3.05	Blood dyscrasias or any disorder causing haemolysis or unstable red blood cell count	Exclusion criteria 16 checked Or Relevant diagnosis (e.g. malaria, babesiosis, haemolytic anaemia) at Visit 1[#].	PPS
	A3.06	Indication of liver disease	Exclusion criteria 10 checked Or ALT, AST or alkaline phosphate > 3*ULN at Visit 1 or Visit 5.	None
	A3.10	Treatment with protocol excluded systemic steroids or recent change in thyroid hormone dose	Exclusion criteria 13 or 14 checked Or Treatment with systemic steroids or planned initiation of such therapy at Visit 1 and until randomisation[#] (excluding inhaled or topical use of corticosteroids). Or Change in dose of thyroid hormone within 6 weeks prior to Visit 1 or planned change or initiation of such therapy at Visit 1 and until randomisation[#]. Final decision at DBL meeting based on medical judgment.	PPS
	A3.11	Intake of other investigational drug in another trial within 30 days prior to intake of study medication in this trial	Exclusion criteria 19 checked Or Intake of another investigational drug in another trial within 30 days prior to Visit 1[#]. Final decision at DBL meeting based on medical judgment.	PPS
	A3.12	Specific exclusion criterion for pre-menopausal women violated	Exclusion criteria 17 checked Or Positive pregnancy test or nursing at Visit 1 and until randomisation[#].	None
	A3.13	Relevant alcohol or drug abuse and other conditions affecting study compliance	Exclusion criteria 18 checked Or Alcohol or drug abuse within 3 months prior to Visit 1[#].	None

Table 6.2: 1 Important protocol violations (continued)

Category/Code		Description	Example/Comment	Excluded from
	A3.14*	Any other clinical condition unsafe for participation that would jeopardise patient safety while participating in this clinical trial	Exclusion criteria 21 checked	None
	A3.21	History of T2DM, maturity onset diabetes of the young (MODY), pancreatic surgery or chronic pancreatitis	Exclusion criteria 1 checked Or Relevant condition listed as baseline condition in eCRF[#].	PPS
	A3.22	Diagnosis of severe gastroparesis	Exclusion criteria 8 checked Or Relevant diagnosis recorded as a baseline condition in the eCRF[#].	PPS
	A3.23	Eating disorders	Exclusion criteria 11 checked Or Diagnosis of eating disorder such as bulimia or anorexia nervosa listed as a baseline condition in the eCRF[#].	PPS
B		**Informed consent**		
	B1	Informed consent not available	Inclusion criteria 1 not met Or Informed consent date missing[#].	All
	B2	Informed consent too late	Informed consent date was after Visit 1 date or after any study related procedure.	None
	B3	Informed consent not available for substudy	No informed consent for the CGM substudy was obtained.	All CGM analyses
	B4	Informed consent too late for substudy	The informed consent for the CGM substudy was obtained too late.	None
C		**Trial medication and randomisation**		
C1		**Incorrect trial medication**		

Table 6.2: 1 Important protocol violations (continued)

Category/Code		Description	Example/Comment	Excluded from
	C1.02*	Incorrect trial medication taken	Wrong medication taken (different medication than the patient was randomised to i.e. drug kit recorded in eCRF is from a different treatment group than the drug kit assigned by IxRS) for more than 20% of the overall treatment duration or for more than 20% of the last visit interval before the primary endpoint assessment. Can only be judged after DBL as requires unblinding information.	PPS
C2		**Randomisation not followed**		
	C2.01	Treated without randomisation	Patient treated according to eCRF, but not randomised according to IVRS.	RS, FAS, PPS
C3		**Non-compliance**		
	C3.01	Non-compliance with study drug intake	Overall compliance <80% or >120% from visit 6 onwards or since last visit prior to primary endpoint <80% or missing. For the calculation of compliance, refer to Section 7.3.	PPS
C4		**Medication code broken**		
	C4.01*	Medication code broken without just cause	Medication code broken whilst on-treatment without valid reason. Final decision at the DBL meeting based on medical judgment.	PPS
D		**Concomitant medication**		
D2		**Prohibited medication use**		
	D2.01*	Use of prohibited medication during treatment period	Review of eCRF for contraindicated drugs. Final decision at the DBL meeting based on medical judgment.	PPS
I		**Other safety related violations**		
I2		**Pregnancy monitoring**		
	I2.01	Pregnancy test not done for woman of child bearing potential for at least one visit before treatment discontinuation	Positive pregnancy test at any post-randomisation visit Or Pregnancy during the trial[#].	None
	I2.03*	Nursing	Nursing during the trial.	None

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

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

6.3 PATIENT SETS ANALYSED

- Screened set (SCR):

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

- Randomised set (RS):

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

- Treated set (TS):

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

- Full analysis set (FAS):

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

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

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

- Per protocol set (PPS):

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

Table 6.3: 1 Patient Sets Analysed

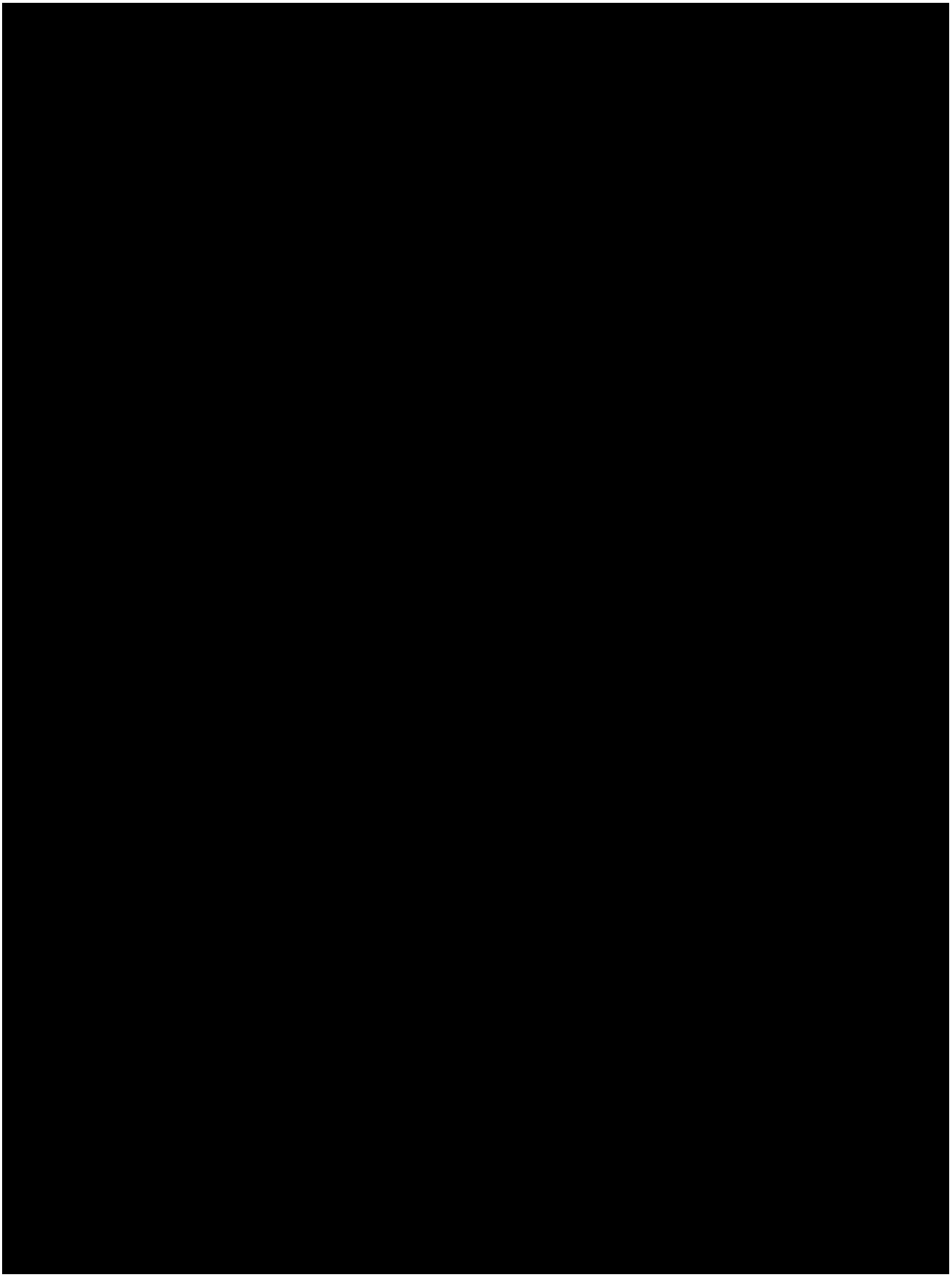
	Patient set					
Class of endpoint	SCR	TS	RS	mITT	FAS	PPS
Disposition	OR					
Demographics			OR[1]		OR	
Baseline variables					OR	
Background total daily insulin dose/concomitant medications					OR	
Concomitant diagnoses/relevant medical history					OR	
Exposure/ compliance					OR	
Primary endpoint	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

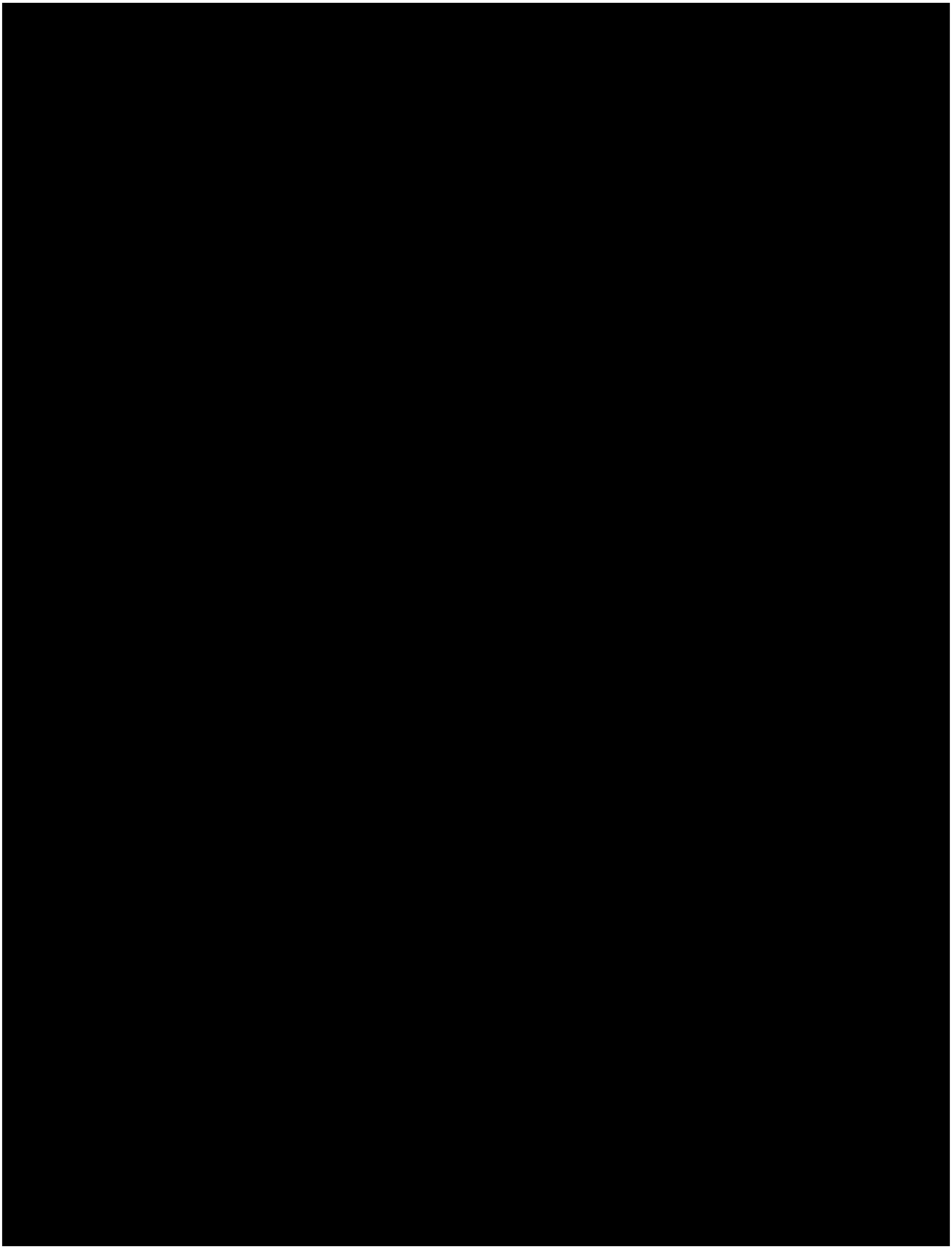
SCR=screened set, RS=randomised set, mITT=modified intention-to treat set, FAS=full analysis set, PPS=per protocol set. Patient sets are defined in Section 6.3.

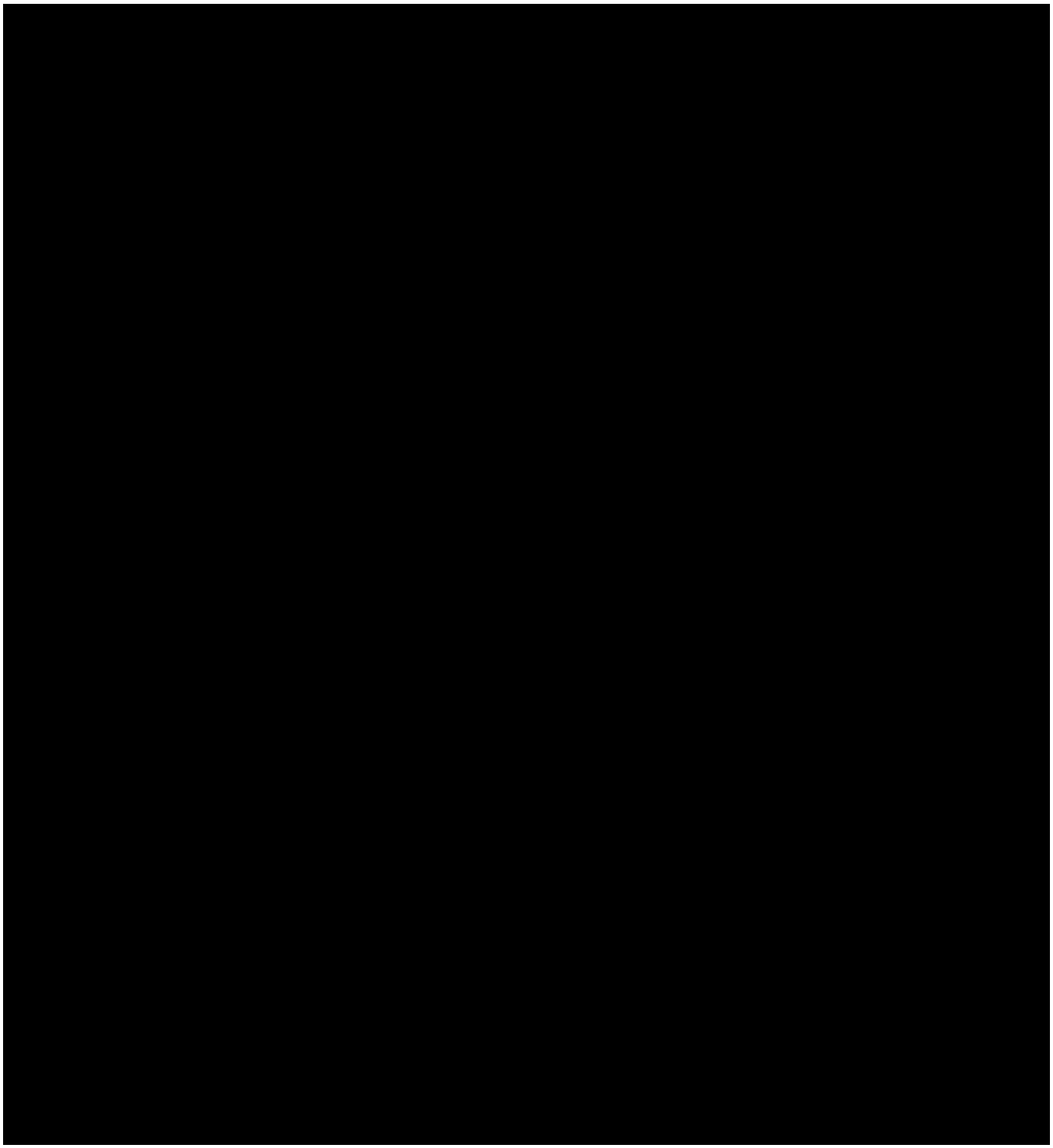
OR=original results, OC=observed cases, OC-AD=observed cases-all data, OC-P=observed cases excluding paracetamol, OC-H= observed cases excluding anti-hypertensives, MI=multiple imputation, PMM=pattern mixture model, NCF=Non-completers considered failures. Handling of missing data is described in Section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

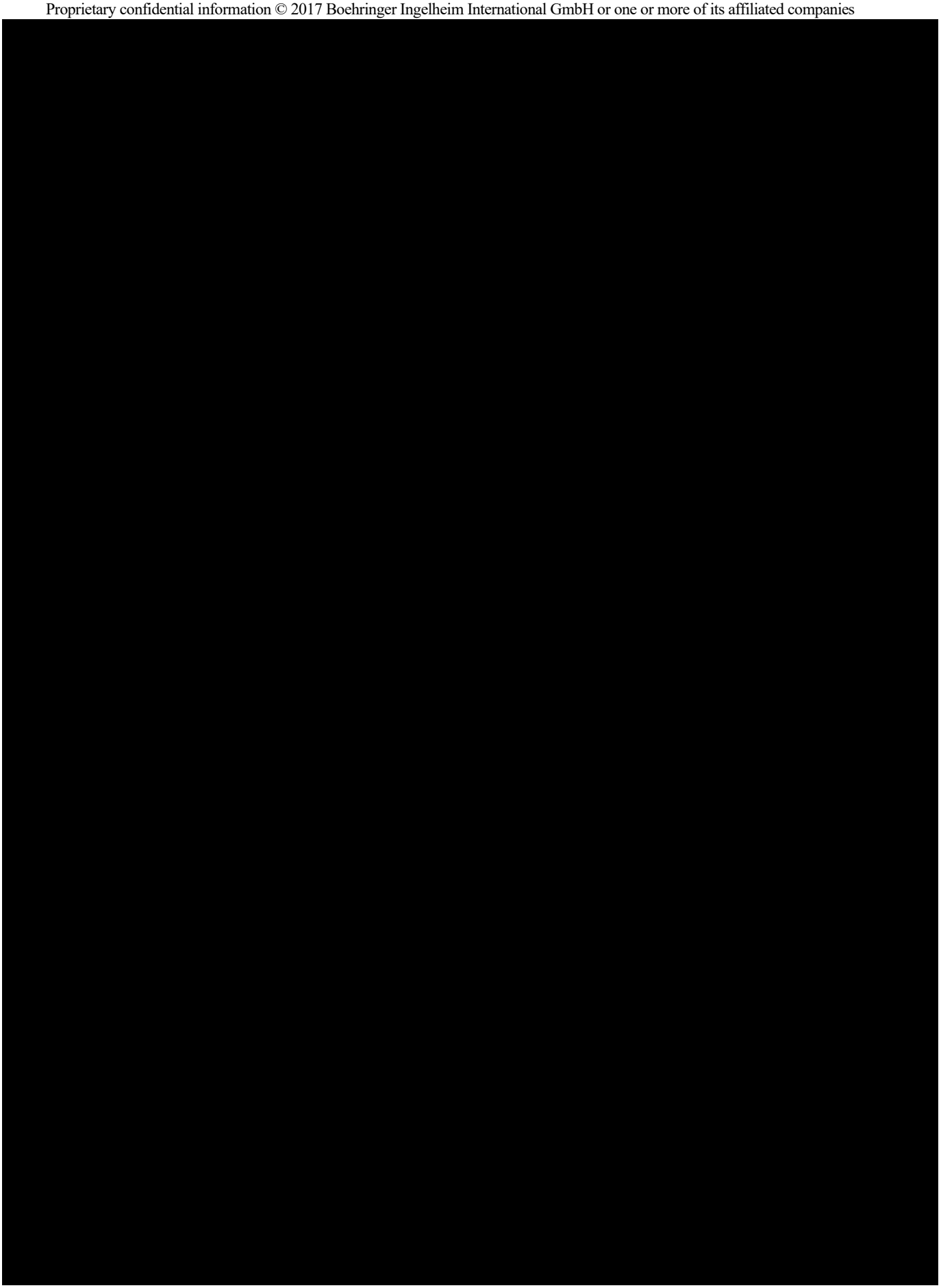
1 Presented in 16.1.9.2 for EudraCT

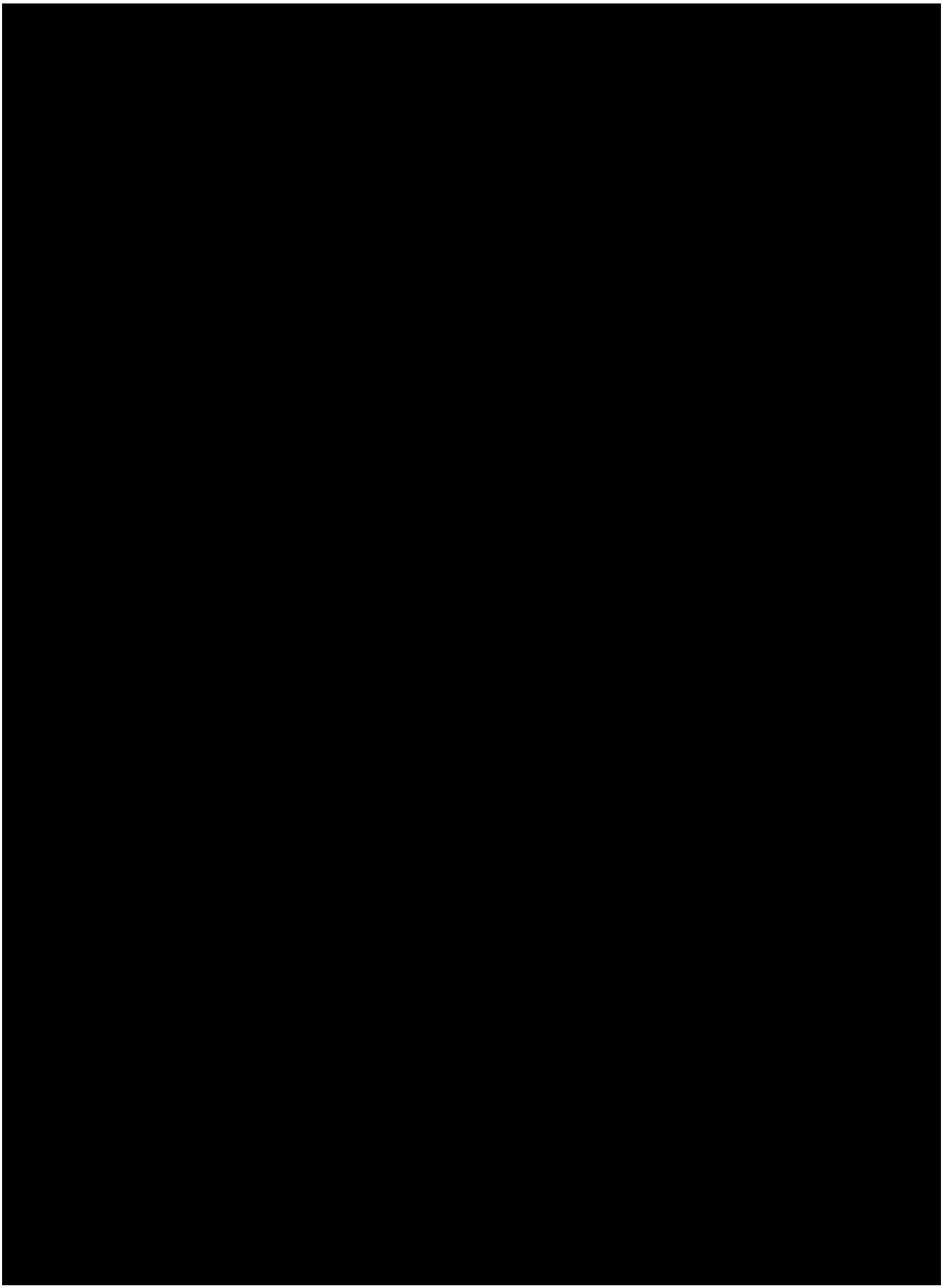
2 MI and PMM are applied to all randomised patients with a baseline measurement.











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6.5 POOLING OF CENTERS

For descriptive statistics by centre, data from small centres within the same country will be pooled. The data from centres with fewer than 8 patients will be combined into the category 'Fewer than 8 patients' for each individual country that has centres with fewer than 8 patients. Analysis to explore centre effects includes the calculation of descriptive statistics of the primary endpoint.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Based on the different reasons of patients' data missing for different endpoints, various methods will be used to assess the impact of missing data on the efficacy endpoints of this trial, depending upon the type of the endpoint.

6.6.1 Imputation methods

6.6.1.1 Original results (OR) analysis

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

6.6.1.2 Observed cases (OC) analysis

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

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

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

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

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

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

Values for total daily insulin dose at each visit will be calculated as the mean total daily dose over the 14 days immediately prior to the visit (excluding the visit day). If there are <4 days

of valid insulin data during the 14 day period, the mean will not be calculated and the visit value will be set to missing. The same rule will apply for total daily bolus, total daily basal and number of injections per day endpoints as well. Subsequent handling of missing data will be performed via a likelihood-based method and will use the mixed-effect model repeated measures (MMRM).

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

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

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

[redacted]

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

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

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

[redacted]

6.6.1.5 Last observation carried forward (LOCF)

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

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

Missing values within a course of measurements on-treatment will be interpolated based on the last observed value before the missing visit and the first observed value after the missing visit. This is independent from the selection of a value as the picked visit value to be used in the descriptive analysis by visit (as described in Section 6.7).

Let:

D0 = date of a visit with a missing endpoint value;

D1 = date of the next visit (with endpoint value non-missing) after the visit with missing endpoint;

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

Ei = endpoint values for visits Di for i= -1, 0 and 1

Then the missing endpoint value can be interpolated as:

E0 = E-1 + ((E1 - E-1) x (D0 - D-1) / (D1 - D-1)).

Missing data will only be imputed up to the planned visit to be reached by all randomised patients (week 26).

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

6.6.1.6 Multiple imputation (MI)

A multiple imputation approach will be used as a sensitivity analysis for the primary endpoint. Further details can be found in Section 7.4.2.

6.6.1.7 Non-completers considered failure (NCF)

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

6.6.2 Safety and other variables

Missing safety data will not be replaced.

An analysis of the changes from baseline to the last available value under treatment and the minimum and maximum post baseline will be determined for quantitative safety laboratory variables.

6.6.3 Missing dates and times

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

[redacted]

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

A missing time of first drug administration will be imputed as 08:00 o'clock in the morning, missing administration times at on-treatment visits will be imputed by 08:00 o'clock in the morning.

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

- If an End of Treatment (EoT) visit or visit 11 is documented, it should be the date of the EoT visit.
- If the date is incomplete with only month and year and the EoT visit is missing, it should be the first day of the following month.
- If the patient is lost to follow-up it should be the date of the last visit + the longest treatment duration based on drug supply + 1 day.
- If a patient died during the course of the trial and no additional information about drug stop date are available, the date of death will be used as drug stop date assuming that the patient took the medication until the day of death.
- All other cases need to be assessed by the trial team on an individual basis, trying to use the points above as guidance.

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

For partial start and stop dates for concomitant therapies (CT) the following derivations will be used to impute 'worst case' values:

- If the day of the end date is missing then the end date is set to last day of the month.
- If the day and month of the end date are missing then end date is set to 31st December of the year.
- If the day of the start date is missing the start date is set to first day of the month.
- If the day and month of the start date are missing then the start date is set to 1st January of the year.

For other incomplete date information (except to assess the overall compliance, see below) always the midpoint of the possible interval will be used. If only the year is present the day and month will be imputed as 01 July, if year and month is present the day will be imputed as 15. If the year is missing, the date will be considered missing.

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

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

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

6.7 BASELINE, TIME WINDOW, AND CALCULATED VISITS

With regard to efficacy and safety endpoints, the term "baseline" refers to the last observed measurement prior to administration of any randomised study medication. For specific endpoints, baseline definitions are as follows:

Serum beta-hydroxybutyrate (BHB)

- Serum BHB sampled at the site and analysed at the central laboratory

Baseline will be defined as the fasted measurement observed at Visit 6, before first drug intake.

- Capillary patient self-measured BHB via the ketone meter and reported in the diary

For the analysis on morning or daily measurements (see Section 7.8.2.5), baseline will be defined as the mean of morning or daily measurements reported during the run-in period, respectively (Visit 5 to Visit 6, including the day of first administration of trial drug).

[redacted]

Hypoglycaemia rate

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

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

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

[redacted]

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
MDG	1
CGM	*
Body weight	1
Blood pressure	1
Waist circumference	7
Insulin dose	0
Hypoglycaemia	1
UACR	1
Health economics and QoL	1
Safety	
Adverse events	7
Hypoglycaemia [1]	1
Hepatic injury [2]	30
Safety laboratory measurements	3
AST/ALT/TBL [3]	30
Pulse rate	1

*Refer to Section 5.4.4 for the assignment of CGM measurements to the on-treatment period
[1] Refer to all hypoglycaemia analyses except the general hypoglycaemia AE analysis by SOC and PT.
[2] Refer to a sensitivity analysis including all hepatic injuries with an onset date up to 30 days after the study treatment stop (see Section 7.8.1.4).
[3] Refer to a sensitivity analysis on elevated liver enzymes, for which events with an onset date up to 30 days after the study treatment stop will be included in the analysis.

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

Efficacy, safety, [redacted] will be assigned to visits based on time windows around the planned visit dates. These time windows are defined based on the planned number of days after the date of first administration of study drug (see Table 6.7: 2).

Table 6.7: 2 Time windows for HbA1c measurements at scheduled visits after randomisation

			Time window (actual days on treatment)	
Visit number	Visit label	Planned days	Start	End[A]
6	Baseline	0	NA	1[B]
8	Week 4	28	2	56
9	Week 12	84	57	105
10	Week 18	126	106	154
11	Week 26	182	155	Study drug stop date + X days

[A] In case of premature discontinuation of the study drug an eEOT visit has to be performed. Measurements from the eEOT visit will be assigned to the appropriate visit according to the table. In this case the time window for the visit that includes the eEOT visit will end X days after the study drug stop date, including Day X. The definition of X is endpoint specific, cf. Table 6.7: 1. Patients will then be asked to continue in the study according to the visit schedule. Off-treatment measurements will be assigned to visits in the same manner. No time window for optional visit is planned.

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

The mid-point between two visits defines the end of a time window, with the midpoint being included in the time window of the preceding visit. The end of the time window of the last on-treatment visit (end of treatment (EoT)) is endpoint dependent (cf. Table 6.7: 1). As endpoints are planned to be measured according to different visit schedules, this midpoint algorithm will be applied and the time windows modifed accordingly.

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

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

			Time window (actual days on treatment)	
Visit number	Visit label	Planned days	Start	End[A]
6	Baseline	0	NA	1[B]
7	Week 1	7	2	17
8	Week 4	28	18	56
9	Week 12	84	57	105
10	Week 18	126	106	154
11 EOT	Week 26/EoT	182	155	Study drug stop date + X days

[A] In case of premature discontinuation of the study drug an eEOT visit has to be performed. Measurements from the eEOT visit will be assigned to the appropriate visit according to the table. In this case the time window for the visit that includes the eEOT visit will end X days after the study drug stop date, including Day X. The definition of X is endpoint specific, cf. Table 6.7: 1. Patients will then be asked to continue in the study according to the visit schedule. Off-treatment measurements will be assigned to visits in the same manner. No time window for optional visit is planned.

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

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

[redacted]

[redacted]

Repeated and unscheduled efficacy and safety measurements will be assigned to the nominal visits and listed in the subject data listings according to the time windows described above. Only one observation per time window will be selected for analysis. For OC analyses, only on-treatment values will be considered. For OC-AD analyses, both on- and off-treatment values will be considered. If there are multiple values within a time-window, the value closest to the protocol planned visit day will be selected. If there are two observations which have the same difference in days to the planned day or if there are two observations on the same day, the earliest value will be used. If an observation is available on the last day of treatment, this observation will be preferably selected over any later observation that is still within the time window. If there are multiple values within the time window of the last visit, including a

value on the last day of drug intake, the value on the last day of drug intake is used as the value of the last visit.

For pre-treatment time points, data will be assigned to nominal visits. Unscheduled visits will only be considered if the data would otherwise be missing for that time point.

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

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

Note: for LOCF imputation, the last observed on-treatment value will be carried forward, whether or not it was selected in the previous time window. Also for interpolation any valid values can be used, regardless of whether they were selected as visit values. For more details on LOCF refer to Section 6.6.

7 PLANNED ANALYSES

Disposition of the patient population participating in the trial will be analysed by treatment groups and presented in the clinical trial report as a frequency-distribution.

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

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

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

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

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

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

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

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

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Reporting of Clinical Trials and Project Summaries" (7).

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

Treatment comparison

In all specified statistical analyses, treatment comparisons will be made between each randomised Empagliflozin group (2.5, 10 and 25 mg) and placebo.

7.1 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

7.1.1 Baseline evaluation

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

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

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

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

HbA1c (%) (continuous and in categories), FPG (mg/dL) (continuous and in categories), weight (kg) (continuous and in categories), waist circumference (cm), blood pressure (mmHg) (continuous and in categories), UACR (mg/gcrea) (continuous and in categories), fasted serum BHB (mmol/L) (continuous and in categories), capillary daily patient self-measured BHB (mmol/L) (continuous and in categories) and capillary morning patient self-measured BHB (mmol/L) (continuous and in categories).

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

[redacted]

Categories for baseline characteristics are defined in Section 6.4.

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

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

[redacted]

[redacted]

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant medication use will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3) and preferred name. Summaries will be presented for concomitant therapies taken during randomised treatment and those taken at baseline.

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

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

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

7.3 TREATMENT COMPLIANCE

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

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

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

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

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

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

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

The FAS patient set will be considered.

7.4 PRIMARY ENDPOINT

7.4.1 Primary analysis

The primary endpoint in this trial is the change from baseline in HbA1c (%) at 26 weeks. Efficacy and effectiveness will be tested in a hierarchical manner.

The primary efficacy analysis will be performed on the FAS (OC). Patients will be assigned to the treatment they were randomised to. Only on-treatment HbA1c values will be included

in the primary analysis. Only data up to the Week 26 timepoint will be included. All randomised treatment groups will be included in the same analysis.

Mean changes from baseline in HbA1c after 26 weeks will be analysed using a restricted maximum likelihood-based repeated measures approach (MMRM analysis). Analyses will include the fixed categorical effects of treatment, pre-existing insulin therapy, week and treatment by week interaction, as well as the continuous, fixed covariates of baseline HbA1c, baseline eGFR and baseline HbA1c by week interaction. Patient will be included as random effect. An unstructured (co)variance structure will be used to model the within patient measurements.

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

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

The statistical model will be:

HbA1c change from baseline = overall mean + continuous baseline HbA1c + pre-existing insulin therapy + continuous baseline eGFR + treatment + week + baseline HbA1c by week interaction + treatment by week interaction + random error

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

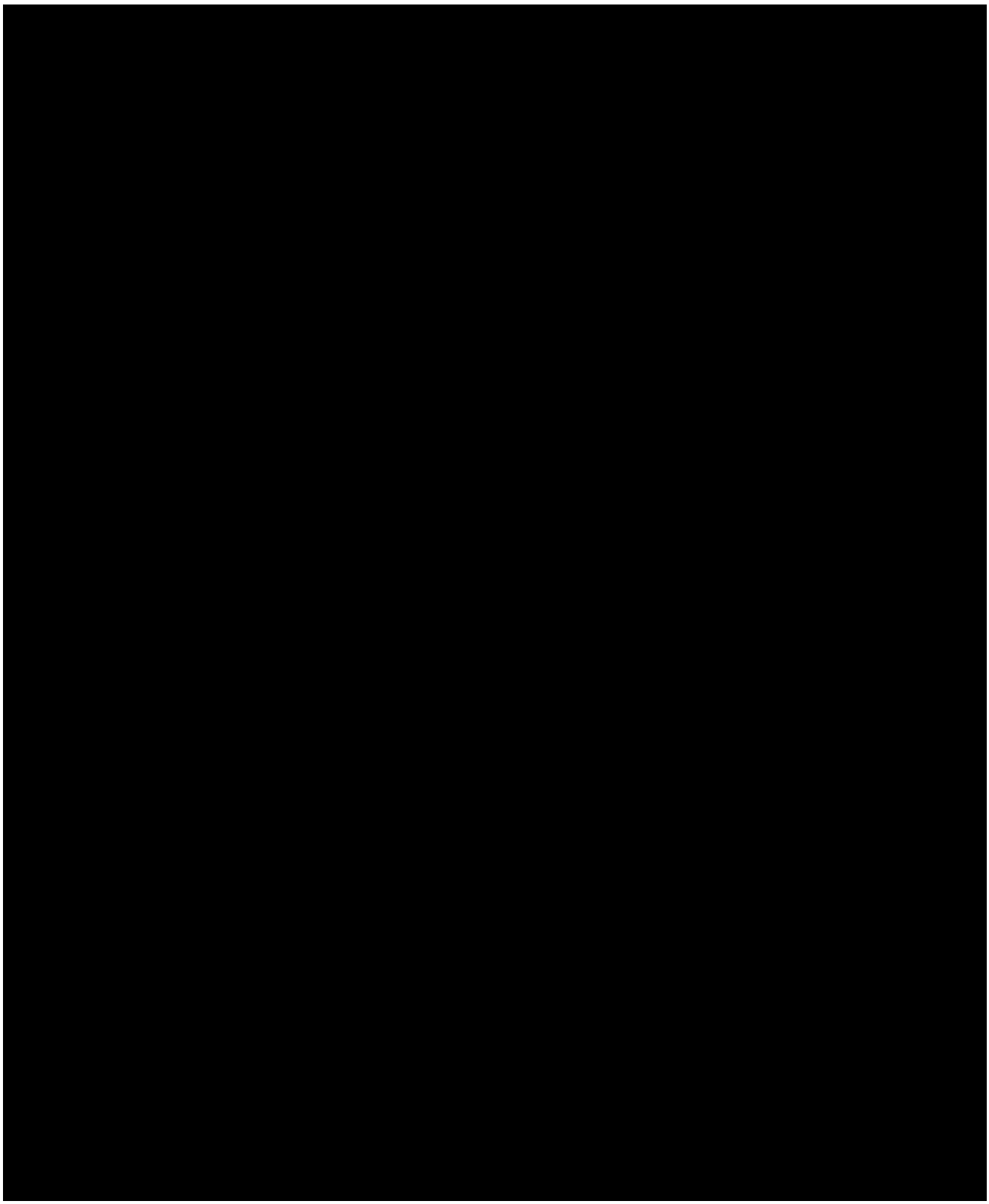
7.4.2 Model diagnostics

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

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

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

[redacted]



7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

Confirmatory analysis

The analysis of the rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose <54 mg/dL and/or severe hypoglycaemic events confirmed by adjudication will utilise a negative binomial model, with terms for treatment, continuous baseline rate, continuous baseline HbA1c, continuous baseline eGFR and pre-existing insulin therapy as fixed effects and log(time at risk) as an offset. The results will be presented as a rate per patient-year. This analysis will be performed on the FAS (OC).

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

The analysis of the rate from Week 5 to Week 26 will include all on-treatment events from the start of Week 5 (Day 29) until one day after treatment stop date. This period will also define the time at risk.

The analysis of the rate from Week 1 to Week 26 will include all on-treatment events from the date of first study drug intake until one day after treatment stop date. This period will also define the time at risk.

[redacted]

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

Confirmatory analysis

The analysis of change from baseline in body weight after 26 weeks will follow the strategy for the primary endpoint, MMRM. The model will include the fixed categorical effects of treatment, pre-existing insulin therapy, week and treatment by week interaction, as well as the continuous, fixed covariates of baseline HbA1c, baseline eGFR, baseline body weight and baseline body weight by week interaction. This analysis will be performed on the FAS (OC), including all available on-treatment data up to the Week 26 timepoint.

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

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

[redacted]

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

Confirmatory analysis

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

effects of treatment, pre-existing insulin therapy, week and treatment by week interaction, as well as the continuous, fixed covariates of baseline HbA1c, baseline eGFR, baseline total daily insulin dose and baseline total daily insulin dose by week interaction. This analysis will be performed on the FAS (OC), including all available on-treatment data up to the Week 26 timepoint.

The baseline total daily insulin dose will be calculated based on the mean daily insulin requirement during the run-in period (Visit 5 to Visit 6). The total daily insulin dose will be calculated for each visit, based on the mean daily insulin requirement over the 14 days prior to the visit (excluding the day of the visit). If <4 days of valid insulin data is available, the visit value will be set to missing. The source data for the total daily insulin dose is the e-diary and this does not undergo a cleaning process. For data handling rules, see Section 5.4.6.

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

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

[redacted]

7.5.1.4 Change from baseline in blood pressure after 26 weeks

Confirmatory analysis

The analysis of change from baseline in blood pressure after 26 weeks will follow the strategy for the primary endpoint, MMRM. The model will include the fixed categorical effects of treatment, pre-existing insulin therapy, week and treatment by week interaction, as well as the continuous, fixed covariates of baseline HbA1c, baseline eGFR, baseline blood pressure and baseline blood pressure by week interaction. This analysis will be performed on the FAS (OC), including all available on-treatment data up to the Week 26 timepoint.

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

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

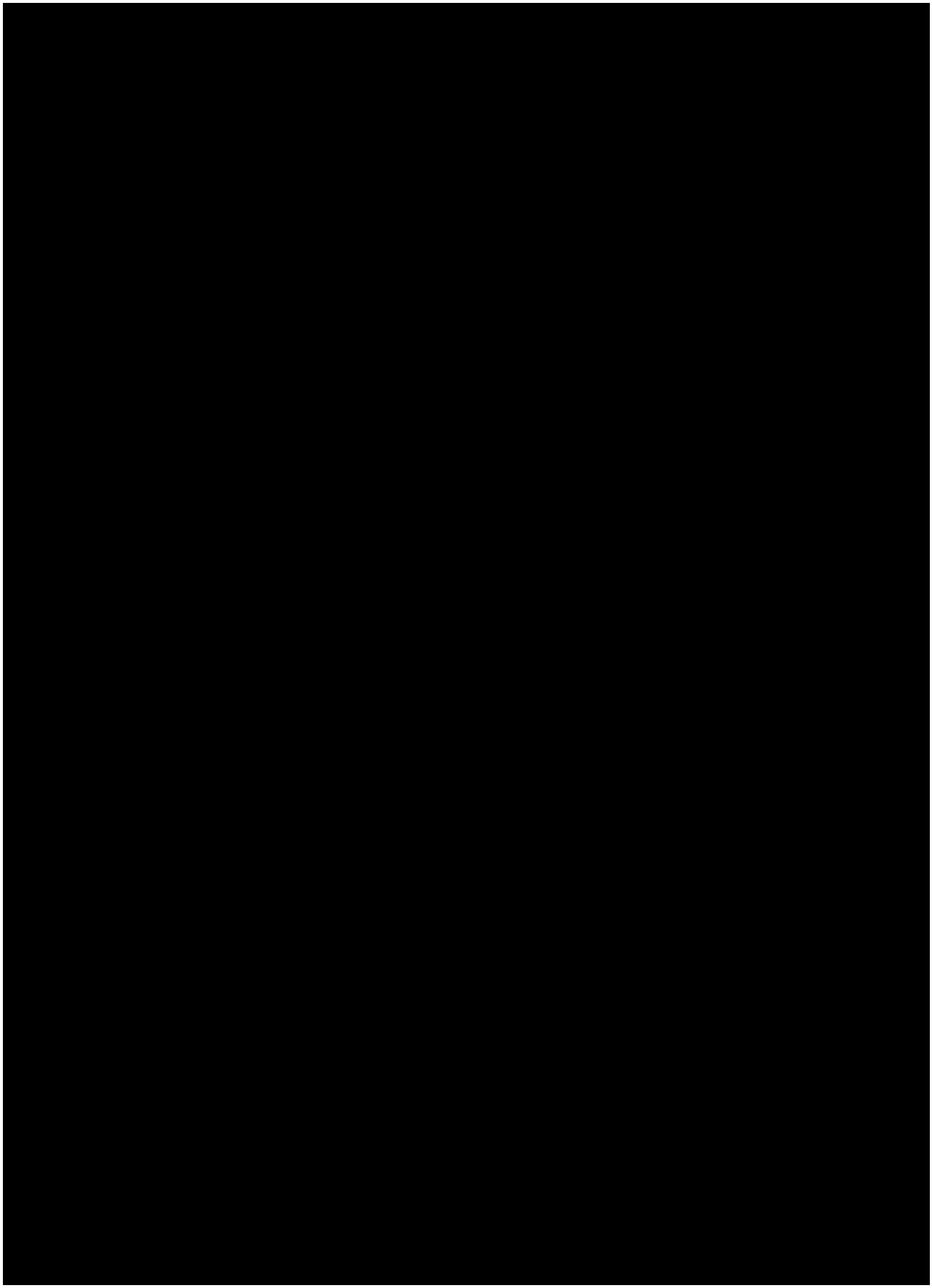
All analyses will be performed separately for SBP and DBP.

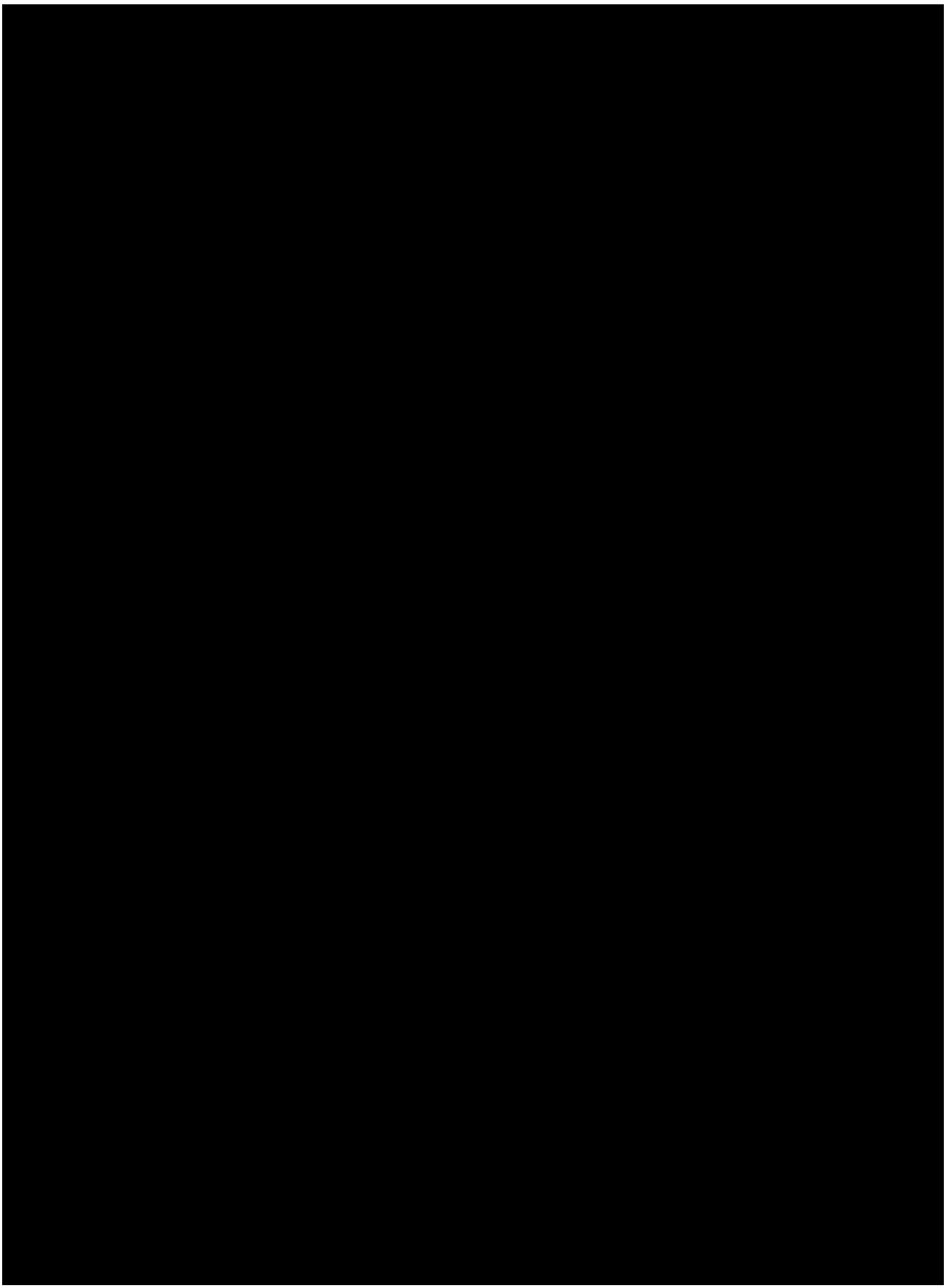
[redacted]

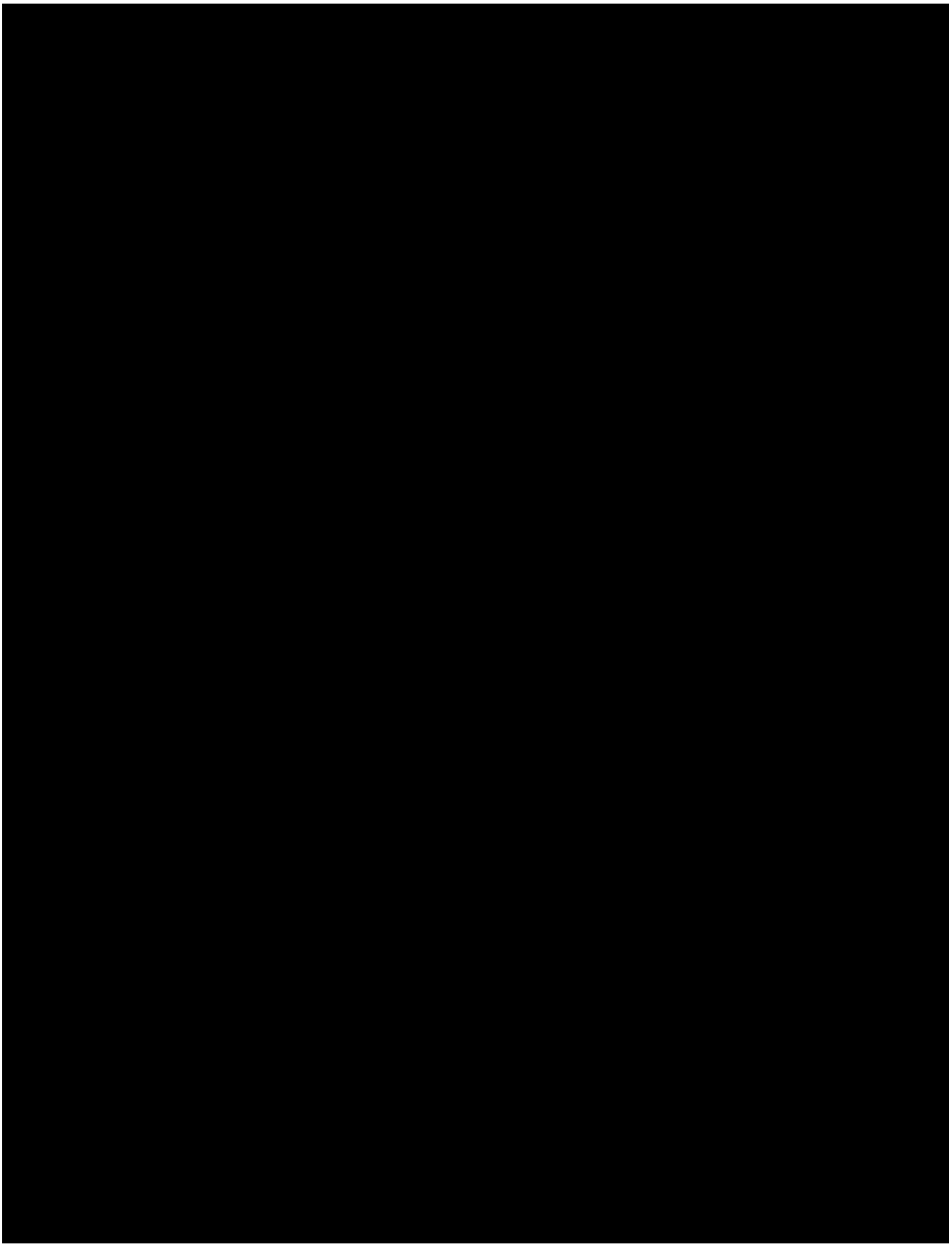
7.5.2 (Other) Secondary endpoint

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

[redacted]







7.7 EXTENT OF EXPOSURE

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

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

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

> 0 to 1 week, > 1 to 4 weeks, > 4 to 8 weeks, > 8 to 16 weeks, > 16 to 24 weeks, > 24 to 28 weeks, > 28 weeks. Note that "> 1 to 4 weeks" stands for 8 to 28 days.

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

≥1 day, ≥1 week, ≥4 weeks, ≥8 weeks, ≥16 weeks, ≥24 weeks, ≥28 weeks. Note that "≥1 week" category refers to 7 days.

7.8 SAFETY ANALYSIS

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

7.8.1 Adverse events

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

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

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

For analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences.
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).
- In addition certain analyses (other than the general analyses by SOC and PT produced by the XAE macro) will have their own collapsing rules. This concerns the following endpoints:
    - Genital infection events will not be collapsed if they are representative of different types (i.e. fungal balanitis or vulvovaginitis versus other than fungal balinitis or vulvovaginitis);

- Sepsis events will not be collapsed if they are representative of different sources of infection (i.e. urinary tract (urosepsis) versus other than urinary tract);
- Severe hypoglycaemia endpoint confirmed by adjudication will not be collapsed;
- Hypoglycaemia adverse events will not be collapsed (except in case of occurrences with identical onset date, time and glucose value);
- Lower limb amputation endpoint will not be collapsed

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

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

7.8.1.1 Assignment of AEs to treatment

In general, the analysis of adverse events will be based on the concept of treatment emergent adverse events. Exceptions are: malignancy events, bone fractures and lower limb amputation (see below). This means that all adverse events occurring between first drug intake until 7 days after last drug intake will be assigned to the randomised treatment. All adverse events occurring before first drug intake will be assigned to 'screening' and all adverse events occurring after last drug intake + 7 days will be assigned to 'post-treatment'. For details on the treatment definition, see Section 6.1.

Malignancy, bone fracture and lower limb amputation events

For malignancy (and respectively bone fracture and lower limb amputation), in addition to the standard ‘7-day-on-treatment approach’ detailed above, all malignancy adverse events (respectively bone fracture and lower limb amputation adverse events) that occurred between first study drug intake up to the trial termination date, will be pooled and analysed together in Section 15 of the trial report.

In general, in-text AE tables will only present AEs assigned to the randomised treatment taken except drug-related AEs which will also be presented as actual treatment taken at each given timepoint. Appendix 16.1.9.2 will display in addition AEs observed 'pre-treatment' (including AEs observed during screening, T1DM therapy optimisation and placebo run-in regardless of treatment group). In particular, summaries will be created to include an analysis where AEs and SAEs are assigned to the following phases: Screening, each treatment group, and post-treatment for each treatment group.

7.8.1.2 Analysis of other significant AEs

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

- ‘action taken = discontinuation’ or ‘action taken = reduced’, or

- Marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review meeting or Blinded Report Planning Meeting.

7.8.1.3 AE summaries

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. AEs will also be reported by intensity. Separate tables will be provided for patients with other significant adverse events according to ICH E3 (9), for patients with adverse events of special interest (AESI), for patients with serious adverse events, for patients with AEs leading to discontinuation, and for patients with drug-related AEs.

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

Appendix 16.1.9.2 will include the following analyses:

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

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

- AEs per treatment arm

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

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

7.8.1.4 AEs of special interest (AESI)

The protocol defines the following adverse events that for analysis purposes will be considered as AESIs:

- Decreased renal function
- Hepatic injury
- Ketoacidosis
- Severe hypoglycaemia (i.e. severe hypoglycaemic episodes as defined in the CTP)
- Lower limb amputation

Events of these AESIs are identified through the AE being flagged by the investigator as an AESI on the case report form (CRF). For further details on the definition of these events, refer to Section 5.3.6.1 of the CTP.

The AESI decreased renal function will be summarised by SOC and PT based on the following narrow SMQ:

Renal:

- Acute renal failure: 20000003 (narrow SMQ)

This display will be replicated to present serious events and then events leading to discontinuation.

The acute renal kidney injury will also be discussed based on the creatinine laboratory data increase as detailed in Section 7.8.2.4.

The AESI hepatic event will be summarised by SOC and PT based on the following narrow SMQs:

Hepatic:

- Liver related investigations, signs and symptoms: 20000008 (narrow SMQ)
- Cholestasis and jaundice of hepatic origin: 20000009 (narrow SMQ)
- Hepatitis, non-infectious: 20000010 (narrow SMQ)
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions: 20000013 (narrow SMQ)

This display will be replicated to present serious events and then events leading to discontinuation. A final display will summarise the AEs related to hepatic injury that occurred from baseline up to 30 days after the last dose of study medication.

Further laboratory analyses will support the hepatic evaluation. See Section 7.8.2.2 for further details on elevated liver enzyme analyses.

Ketoacidosis:

- CEC confirmed ketoacidosis and ketosis endpoints
    - Analysis of number of patients with ketoacidosis

A frequency table will first summarize the results of the CEC adjudication committee for ketoacidosis events (refer to Section 7.8.1.6 for further details on the adjudication process). This summary will present the number of patients with CEC confirmed certain ketoacidosis, potential ketoacidosis, unlikely ketoacidosis, unlikely ketoacidosis but ketosis, or unclassifiable events, by worst severity and requirement of hospitalisation.

A second frequency analysis will be created and will display the characteristics of ketoacidosis for patients with CEC certain ketoacidosis. These characteristics will include outcome, severity of the worst episode, time to onset of first episode, and lowest blood pH. This analysis will be successively repeated for ketoacidosis endpoints considered by the CEC as potential, as well as for ketoacidosis endpoints considered by the CEC as certain or potential.

Time to onset of the first CEC certain ketoacidosis event will be analysed by Kaplan-Meier estimates. The onset date determined by the adjudication committee will be used as date of event. The time to the occurrence of the event will be computed as date of the event minus date of first drug intake plus one day.

The Kaplan-Meier graph will present data up to the end of the treatment period.

Patient without an event will be considered censored at the date of the last trial drug intake plus seven day.

A log-rank test will be then computed to test the equality of the survival curves.

The Kaplan-Meier analysis and the log-rank test will then be performed for CEC certain or potential ketoacidosis event.

Frequency of patients with CEC certain ketoacidosis (and respectively CEC potential ketoacidosis) will be planned by preferred term from the specified trigger search terms for DKA.

- Analysis of frequency of ketoacidosis episodes

An overview table will first summarize the results of the CEC adjudication committee on ketoacidosis episodes by worst severity.

The CEC certain ketoacidosis episodes will be tabulated by treatment and characteristics of ketoacidosis (e.g. outcome, severity, pre-existing factors, blood pH).

When appropriate, the number of episodes per 100 patient-years will be calculated in addition to the number of episodes according to the following formula:

100*(number of ketoacidosis events /time at risk [patient-years] to report a diabetic ketoacidosis event)

Where time at risk [patient-years] is calculated as time from first administration of study drug until last administration of study drug + 7 days, summed up over all patients per treatment group, and divided by 365.25.

The same ketoacidosis episode analysis will be presented for CEC potential ketoacidosis, as well as for CEC certain or potential ketoacidosis.

- Other ketoacidosis endpoints

Patients with investigator defined AESI ketoacidosis will be tabulated by event characteristics; as well as the number of investigator defined AESI ketoacidosis episodes.

Frequency of patients with investigator defined AESI ketoacidosis will in addition be tabulated by SOC and PT, as well as using specified trigger search terms for DKA.

- Ketosis endpoints

Additional analyses will be produced to assess the risk of ketosis. Patient with ketosis are patients with either:

- CEC unlikely ketoacidosis but ketosis, or

- Single or multiple BHB readings (i.e. capillary patient-self measures or serum measurements) between >1.5 and < 3.8 mmol/L without accompanying typical ketoacidosis symptoms, hospitalisation or serious adverse event. As documented in the DKA CEC charter, these types of events are not considered trigger events for the adjudication

The number of patients with any ketosis events will be summarised as well as the number of ketosis episodes.

Ketosis episodes are defined as:

- CEC unlikely ketoacidosis but ketosis, or
- Single or multiple consecutive BHB readings >1.5 (i.e. capillary patient-self measures or serum measurements, within 24 hours of the previous reading for consecutive measurements) that do not trigger adjudication and that are not followed by an event triggering adjudication within 24 hours.

Severe hypoglycaemia adverse events:

In this section, only severe hypoglycaemia reported by the investigators as AESI, or severe hypoglycaemia that have been confirmed by the adjudication committee will be considered. Also note that 'CEC confirmed severe hypoglycaemia' refers to the exact same endpoint as 'severe hypoglycaemia confirmed by adjudication' that was the terminology used in the efficacy section.

Refer to Section 9.3 for further details on the derivation of the severe hypoglycaemia adverse event endpoints analysed in this section.

- CEC confirmed severe hypoglycaemia endpoint
  - Analysis of number of patients with severe hypoglycaemia adverse event

A frequency table will first summarize the results of the adjudication committee on hypoglycaemic events that had been sent to the CEC for adjudication.

Kaplan-Meier graphs will be plotted for the time to first onset of CEC confirmed severe hypoglycaemia. The onset date determined by the adjudication committee will be used as date of event. The time to the occurrence of the event will be computed as date of the event minus date of first drug intake plus one day.

The Kaplan-Meier graph will present data up to the end of the treatment period.

Patient without an event will be considered censored at the date of the last trial drug intake plus one day.

A log-rank test will be computed to test the equality of the survival curves.

Patients with CEC confirmed severe hypoglycaemia will be tabulated by treatment and characteristics of hypoglycaemia including minimum glucose level and time to onset of first episode. The frequency of severe nocturnal hypoglycaemia AE (i.e. any hypoglycaemia event with an onset from 0:00 midnight to 5:59 a.m.) will also be evaluated as part of these characteristics.

Finally, the severe hypoglycaemia considered serious or requiring third person assistance will be tabulated using the narrow SMQ Hypoglycaemia. This analysis will be restricted to patients with CEC confirmed severe hypoglycaemia.

- Analysis of frequency of hypoglycaemia adverse events

The number of CEC confirmed severe hypoglycaemic episodes will be first tabulated by treatment and characteristics of hypoglycaemia. When appropriate, the number of episodes per patient-year will be provided in this analysis. The time at risk for severe hypoglycaemia [patient-years] will be derived similarly as for ketoacidosis, but in using 1 day of washout instead of 7 days in the calculation.

A negative binomial model will be fitted to analyse the event rate of CEC confirmed severe hypoglycaemia per patient-years, with terms for treatment, continuous baseline rate, continuous baseline HbA1c, continuous baseline eGFR (CKD-EPI, creatinine) and pre-existing insulin therapy as fixed effects and log(time at risk) as an offset.

In addition, the severe hypoglycaemic episodes that have been confirmed by the adjudication committee will we represented on a graph by hour of the day (from midnight to 11:59 pm).

- Investigator defined AESI severe hypoglycaemia adverse event endpoint

Patients with investigator defined AESI severe hypoglycaemia will also be summarised by treatment and event characteristics, as well as the investigator defined AESI severe hypoglycaemic episodes.

Patients with investigator defined AESI severe hypoglycaemia will additionally be summarised by SOC, PT and treatment group.

Lower limb amputation

A frequency table summarising the investigator defined AESI lower limb amputation events will be created by SOC and PT. The table will be then repeated for serious events, and for events leading to treatment discontinuation.

Patients with events detected based on project-defined preferred term lists for respectively vascular AEs, wound/infections, diabetic foot related AEs, nervous system disorders and volume depletion will be additionally summarised. All PTs associated to these events occurring before (<=) the lower limb amputation procedure will be included in this analysis.

Finally, the characteristics of the lower limb amputation procedures (associated to the investigator defined AE) will be summarised. The reasons of the amputation and the level of the amputation will be the main characteristics of interest. All procedures that occurred between first study drug intake up to the later between the trial termination and the last AE onset date will be summarised.

7.8.1.5 Other specific adverse events

Hypoglycaemia

- Hypoglycaemia adverse events

In this sub-section, only hypoglycaemia reported by the investigator as adverse events will be discussed. For specifications on analyses on severe hypoglycaemia adverse event, refer to Section 7.8.1.4.

Refer to Section 9.3 for details on the derivation of the hypoglycaemia adverse event endpoints listed below.

Every episode of PG ≤ 70 mg/dL should be documented with the respective time and date of occurrence. This includes hypoglycaemia with glucose values < 54 mg/dL and all symptomatic and all severe hypoglycaemic events. On the basis of this information the hypoglycaemic adverse event will be classified according to the following protocol defined categories:

- Asymptomatic hypoglycaemia with PG ≤ 70 mg/dL

- Documented symptomatic hypoglycaemia with 54 mg/dL ≤ PG ≤ 70 mg/dL and typical symptoms

- Documented symptomatic hypoglycaemia with PG < 54 mg/dL and typical symptoms and no need for external assistance

- Severe hypoglycaemia, events requiring assistance

- Analysis of number of patients with hypoglycaemia adverse events

The frequency of patients with protocol defined hypoglycaemia adverse event will be presented by treatment.

The frequency of patients with hypoglycaemia adverse event according to investigator's judgment will be tabulated by treatment, SOC and preferred term.

- Analysis of frequency of hypoglycaemic adverse events

Similarly as for the analysis on patient level, a summary on the number of protocol defined hypoglycaemia adverse event episodes will be produced per patient-years.

Then, descriptive statistics will be produced for the predefined protocol further safety endpoint “rate of symptomatic hypoglycemic AE with confirmed PG<54 mg/dL and/or severe hypoglycaemic AE confirmed by the adjudication, per 30 days, from Week 1 to Week 4”. A negative binomial model with terms for treatment, baseline rate, continuous baseline HbA1c, continuous baseline eGFR (CKD-EPI, creatinine) and pre-existing insulin therapy as fixed effects and log (time at risk [30 days]) as an offset will also be prepared. These two analyses will furthermore be replicated on the FAS.

Step 1 and Step 2 of the TSAP Section 5.4.7 collapsing rules will apply, in order to avoid the double-counting of episodes between adjudicated severe hypoglycaemia data and hypoglycamia AE data.

- Patient-reported hypoglycaemia events

The endpoints describe in this sub-section will be exclusively based on patient-reported hypoglycaemia data.

A summary presenting the number of patients with the following endpoints will be tabulated:

- Asymptomatic hypoglycaemia with PG ≤ 70 mg/dL
- Symptomatic hypoglycaemia with PG ≤ 70 mg/dL
- Asymptomatic hypoglycaemia with PG < 54 mg/dL
- Symptomatic hypoglycaemia with PG < 54 mg/dL
- Nocturnal symptomatic hypoglycaemia with PG ≤ 70 mg/dL
- Nocturnal symptomatic hypoglycaemia with PG ≤ 70 mg/dL
- Nocturnal asymptomatic hypoglycaemia with PG < 54 mg/dL
- Nocturnal asymptomatic hypoglycaemia with PG < 54 mg/dL

The number of episodes per patient-year will be analysed for these endpoints as well, for which the TSAP Section 5.4.6.3 collapsing rules will apply.

A negative binomial model will be fitted to analyse the symptomatic hypoglycaemia with PG < 54 mg/dL, with terms for treatment, continuous baseline HbA1c, continuous baseline eGFR (CKD-EPI, creatinine) and pre-existing insulin therapy as fixed effects and log(time at risk) as an offset.

Urinary and genital infections

The following additional specific adverse events will also be assessed and be tabulated by treatment group:

- Genital tract infections (narrow BIcMQ, investigator assessment)
- Urinary tract infections (UTI) (narrow BIcMQ, investigator assessment)

The serious genital infection events as well as the genital infection events leading to treatment discontinuation will additionally be summarised using the narrow project defined PT list.

Similarly, the serious UTI events as well as the UTIs leading to treatment discontinuation will be summarised using the BIcMQ.

A frequency table for complicated urinary tract infections/pyelonephritis/urosepsis where ‘complicated urinary tract infections’ are defined as serious AEs from the narrow BIcMQ UTI, all events included in the sub-BIcMQ pyelonephritis and all events of preferred term urosepsis will in addition be provided .

Genital infections based on investigator assessment will additionally be summarised by type (fungal balanitis or fungal vulvovaginitis, genital infection other than fungal balanitis or fungal vulvovaginits), intensity (mild, moderate or severe), time to onset of first episode (within the first 3 months of treatment or after), duration (<7 days, 7-14 days and >14 days), how the event was treated (no treatment, therapy assigned, hospitalisation), treatment (0, 1, 2, >2 antimicrobials needed to treat), duration of treatment (≤7 days, >7 days), whether leading to discontinuation of treatment, and the number of episodes per patient.

Furthermore, the above mentioned displays on genital infections based on investigator assessment will be repeated by the type of infection (fungal balanitis or fungal vulvovaginitis, or genital infection other than fungal balanitis or fungal vulvovaginitis).

UTIs based on investigator assessment will additionally be summarised by intensity (mild, moderate or severe), time to onset of first episode (within the first 3 months of treatment or after), duration (<7 days, 7-14 days and >14 days), anatomical location (upper UTI, lower UTI), how the event was treated (no treatment, therapy assigned, hospitalisation), treatment (0, 1, 2, >2 antimicrobials needed to treat), duration of treatment (≤7 days, >7 days), whether leading to discontinuation of treatment, and the number of episodes per patient.

Kaplan-Meier graphs will also be created for time to onset of the first investigator defined UTI and for time to onset of the first investigator defined genital infections. For both endpoints, the time to the occurrence of the event will be computed as date of the event minus date of first drug intake plus one day. The same censoring date rules as the ones defined in Section 7.8.1.4 for time to onset to ketoacidosis endpoint will be used for patient without an event. The onset date of the first UTI episode will be used in case of multiple episodes.

The Kaplan-Meier graph will present data up to the end of the treatment period.

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

Acute pyelonephritis, sepsis, and asymptomatic bacteriuria

The following specific adverse event based on investigator assessment will be tabulated by treatment group:

- Acute Pyelonephritis: patient incidence overall and by intensity, and treatment required (0, 1, 2, >2 antimicrobials needed to treat)
- Sepsis: patient incidence overall and by source of infection
- Asymptomatic Bacteriuria: patient incidence overall

Bone fractures

Frequency of patients with bone fracture will be provided by event characteristics (e.g.type of fracture, intensity, and time to onset of first fracture). Bone fracture will also be displayed by SOC and PT using the BIcMQ. The BIcMQ analysis will be repeated for serious bone fracture events and for bone fractures leading to treatment discontinuation. Finally, the bone fracture events that occurred between first study drug intake and up to study end will be pooled together and analysed based on the BIcMQ in a separate analysis.

Volume depletion

Frequency table of patients with volume depletion will be constructed based on preferred terms:

- Volume depletion: (BIcMQ)

Malignancy

AE frequency table will be created for malignancies based on the following narrow SMQs:

- Malignancies: The following Sub-SMQs of SMQ Malignancies (20000090) will be used: Sub-SMQ Malignant or unspecified tumors (20000091) and Sub-SMQ Malignancy related conditions (20000092).

This analysis will be then replicated for serious malignancy, and for malignancy leading to treatment discontinuation.

Finally, all malignancy adverse events that occurred between first study drug intake up to study end will be pooled together and analysed based on the narrow SMQ search in a separate analysis.

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

Independent external CECs regularly review cardiovascular, neurovascular, hepatic, severe hypoglycaemia, and ketoacidosis events and evaluate whether pre-specified criteria for these adjudication endpoints are met. Details on composition of the CECs, responsibilities and clinical event definitions are provided in separate CEC charters. Events qualifying for adjudication will be selected based on the latest CEC charter versions.

The CECs will be provided with additional, specified background material on the patients with these events and perform an assessment of the events. Adjudication assessments will be incorporated to the database.

Refer to Section 7.8.1.4 for details on analyses for severe hypoglycaemia and ketoacidosis events confirmed by adjudication.

Frequency table by treatment group will be provided for the adjudicated cardiovascular and neurological endpoints and for the preferred terms in the specified SMQs of events. Table will also be provided for events that were confirmed or non-assessable.

The cardiovascular and neurovascular events qualifying for adjudication will be selected based on the following SMQs:

- Ischemic heart disease, excluding PTs “Blood creatine phosphokinase abnormal” and “Blood creatine phosphokinase increased”
- Cardiac failure, excluding PTs “Oedema”, “Oedema peripheral” and “Peripheral swelling” unless there are reported as serious events
- Torsade de pointes / QT prolongation
- Cerebrovascular disorders, excluding PT “Fahr's disease”

- Further simple preferred terms
- All fatal cases

7.8.1.7 AEs while patients taking wrong medication

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

7.8.2 Laboratory data

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

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

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

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

Only patients with at least one available on-treatment value will be included in the analysis of an individual laboratory parameter. All individual data will be presented in listings.

7.8.2.1 General laboratory evaluation

Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range at baseline and the last measurement on treatment. Descriptive statistics will be provided by treatment group for baseline, on-treatment values and for changes from baseline based on normalised values, as well as on the basis of standardized values for parameters with an incomplete reference range (e.g. ALT).

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

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

7.8.2.2 Elevated liver enzymes

Special attention will be paid to parameters characterising liver function. These include liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP)) and total bilirubin.

The frequency of the number of patients with AST/ALT elevations >= 3xULN, >= 5xULN, >= 10xULN, and >= 20xULN will be displayed.

To support analyses of liver related adverse drug effects, patients with AST and/or ALT >=3xULN with concomitant or subsequent TBILI>=2xULN in a 30 day period after AST/ALT elevation are of special interest. The start of the 30 day time span is triggered by each liver enzyme elevation above the defined thresholds. Patients who fulfil one or two of the criteria for AST/ALT or total bilirubin elevations above and has no information available for the remaining parameter(s) at the same time-point or within the 30 day time window will not be listed under "ALT and/or AST >= 3xULN with Total Bilirubin >= 2xULN".

Patients with elevations as defined above by ALT and/or AST, total bilirubin and AP combinations, will be summarised and stratified by Alkaline phosphatase < 2xULN and >=2xULN.

Details on patients with elevated liver enzymes will be listed.

In addition to the standard '3-day-on-treatment approach' detailed above, all liver enzyme elevation with an onset date up to 30 days after the treatment stop will be analysed for further displays in Section 15 of the CTR.

7.8.2.3 Lipid parameters

Descriptive statistics will be shown over time for the treated set (LOCF and OC) including change from baseline and percent change from baseline. For each lipid parameter, separate ANCOVA models will be fitted on the treated set (OC) for both change from baseline at week 26 and percent change from baseline at week 26 as dependent variables. The models will include treatment and pre-existing insulin therapy as fixed effects, and baseline lipid, baseline HbA1c, baseline eGFR (CKD-EPI, creatinine) are linear covariates.

The residuals from the ANCOVA models will be checked for normality using a Q-Q plot and documented in Appendix 16.1.9.2.

7.8.2.4 Renal laboratory parameters

<u>Creatinine and eGFR</u>

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

The glomerular filtration rate will be first estimated according to the following CKD-EPI creatinine equation, and stored in the trial database:

$$\text{eGFR (ml/min/1.73 m2)} = 141 \times \min(\text{serum creatinine [umol/L]}/88.4/k, 1)^{a} \times \max(\text{serum creatinine [umol/L]}/88.4/k, 1)^{-1.209} \times 0.993^{\text{Age}} \times [1.018 \text{ if female}] \times [1.159 \text{ if of African origin}]$$

Where:

- k is 0.7 for females and 0.9 for males,

- a is -0.329 for females and -0.411 for males,

- min indicates the minimum between (serum creatinine/k) and 1,

- max indicates the maximum between (serum creatinine/k) and 1.

For the analysis of eGFR (CKD-EPI, creatinine) and for the covariates in the efficacy statistical modelling the values calculated from the above formula using the serum creatinine values from the central laboratory will be used, and not the eGFR values provided by the central laboratory.

The glomerular filtration rate will also be derived according to the following CKD-EPI creatinine-cystatin C equation:

$$\begin{aligned}\text{eGFR (mL/min/1.73 m2)} = \; & 135 \times \min(\text{serum creatinine [mg/dL]}/\,k, 1)^{a} \\ & \times \max(\text{serum creatinine [mg/dL]}/\,k, 1)^{-0.601} \\ & \times \min(\text{standardized serum cystatin C [mg/L]}/0.8, 1)^{-0.375} \\ & \times \max(\text{standardized serum cystatin C [mg/L]}/0.8, 1)^{-0.711} \\ & \times 0.995^{\text{Age}} \\ & \times 0.969 \text{ [if female]} \\ & \times 1.08 \text{ [if black]}\end{aligned}$$

Where:

- k is 0.7 for females and 0.9 for males,

- a is 0.248 for females and -0.207 for males,

- min (serum creatinine/ k, 1) indicates the minimum between (serum creatinine/k) and 1,

- max (serum creatinine/ k, 1) indicates the maximum between (serum creatinine/k) and 1,

- min (standardized serum cystatin C / 0.8, 1) indicates the minimum between (standardized serum cystatin C /0.8) and 1,

- max (standardized serum cystatin C / 0.8, 1) indicates the maximum between (standardized serum cystatin C /0.8) and 1

- Age is expressed in years.

The endpoint eGFR (CKD-EPI, creatinine-cystatin C) will be derived at the visits where both serum creatinine and serum cystatin C are measured at the central laboratory.

The following additional rules will apply to derive these two eGFR renal endpoints:

- In case of mixed race, if 'Black or African American' is one of the patient races, eGFR will be by default derived as if the patient is of African origin.
- Age will be considered as a discrete variable for the above calculations, and the age will be from the same visit as the other variables. The age at a specific visit where eGFR is calculated will be derived as follows:

age [years] = (date of eGFR laboratory measurement – birth date + 1) / 365.25

A shift table from baseline to last value on treatment, (and from baseline to minimum value on treatment) will be provided for eGFR (CKD-EPI, creatinine) and for eGFR (CKD-EPI, creatinine-cystatin C) endpoints.

Descriptive statistics will also be created for creatinine, eGFR (CKD-EPI, creatinine) and eGFR (CKD-EPI, creatinine-cystatin C) values over time by treatment and presented in tables.

Additionally, a summary will be created representing the number of patients per treatment group that experienced a doubling in creatinine on treatment that was out of the normal range as compared to baseline.

Other renal endpoints

The following renal endpoint will be analysed:

- Doubling of serum creatinine accompanied by eGFR (CKD-EPI, creatinine) <= 45 mL/min/1.73m2. For this endpoint, the doubling of serum creatinine level corresponds to the increase of serum creatinine level to 2.0 fold from baseline.

Patients who already fulfil the above condition at baseline or without post-baseline laboratory measurements are not considered in the number of patients at risk for this endpoint. If a baseline laboratory measurement is not available for the parameter of interest, it is assumed that the patient did not experience the condition corresponding to the endpoint at baseline.

The number of patients with the event will be provided.

7.8.2.5 Blood beta-hydroxybutyrate (BHB)

Refer to Section 6.7 for the baseline definition of BHB endpoints.

- Serum BHB sampled at the site and analysed at the central laboratory

All the analyses described for this endpoint will be performed on fasted measurements only.

Descriptive statistics for baseline, actual values and change from baseline over time will be calculated. Descriptive statistics will also be provided to characterize the follow-up period.

The median and the corresponding confidence interval using SD will be plotted over time including the follow-up period. A box-plot presenting the value at baseline and over time will also be produced per treatment group.

A shift table from baseline to last value on treatment, (and from baseline to maximum value on-treatment) will also be provided by baseline values (<0.6 mmol/L, 0.6 to <=1.5 mmol/L, >1.5 to <3.8 mmol/L, >=3.8 to ≤8.0 mmol/L, > 8.0 mmol/L).

An additional shift table will display the number of patients in these BHB categories over time.

- Capillary self-measured BHB via the ketone meter and reported in the diary

Elevated ketone readings above >1.5 mmol/L that have not been confirmed by the investigator will not be included in any analysis of this section. Refer to Section 5.4.6.1 for further details on the ketone reading confirmation process.

Morning and daily endpoints

For all analyses specified in this section, capillary BHB readings reported as “HI” will be imputed to 8.1 mmol/L.

The periods of time of interest will be the following ones: week 1, week 2, week 3, week 4, week 5 to week 6, week 7 to week 8, week 12, week 18, week 22 and week 26.

Descriptive statistics will be produced on the average of morning BHB measurement values over the specific periods of time defined above.

The same descriptive statistics will be produced on the average of daily BHB measurement values over time, using the same periods of time defined above.

High BHB measurements

The analysis described in this paragraph will focus on high BHB measurement values that a patient may have reported in the diary. For this analysis, "HI" readings will be considered as such and not be replaced by a numerical value (for instance 8.1 mmol/L).

7.8.2.6 Urine ketone

Refer to Section 6.7 for the baseline definition of urine ketone endpoints.

The analyses described for this endpoint will be performed on fasted measurements only.

Analysis of categorical urine ketone data (negative, trace, 1+/small, 2+/moderate, 3+/large, 4+/large+) will be performed by value at baseline, over time, and worst value on treatment. The analysis will be presented as frequency table and graphically on pie charts.

7.8.3 Vital signs

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

7.8.4 ECG

12-lead ECG measurements will be taken at baseline (visit 6) and at EOT (visit 11). ECG-findings before first intake of trial drug will be considered as baseline condition. Any clinically significant new findings in the ECG measurement after the first ECG will be considered as AEs and analysed as planned in Section 7.8.1.

7.8.5 Others

Not applicable

8 REFERENCES

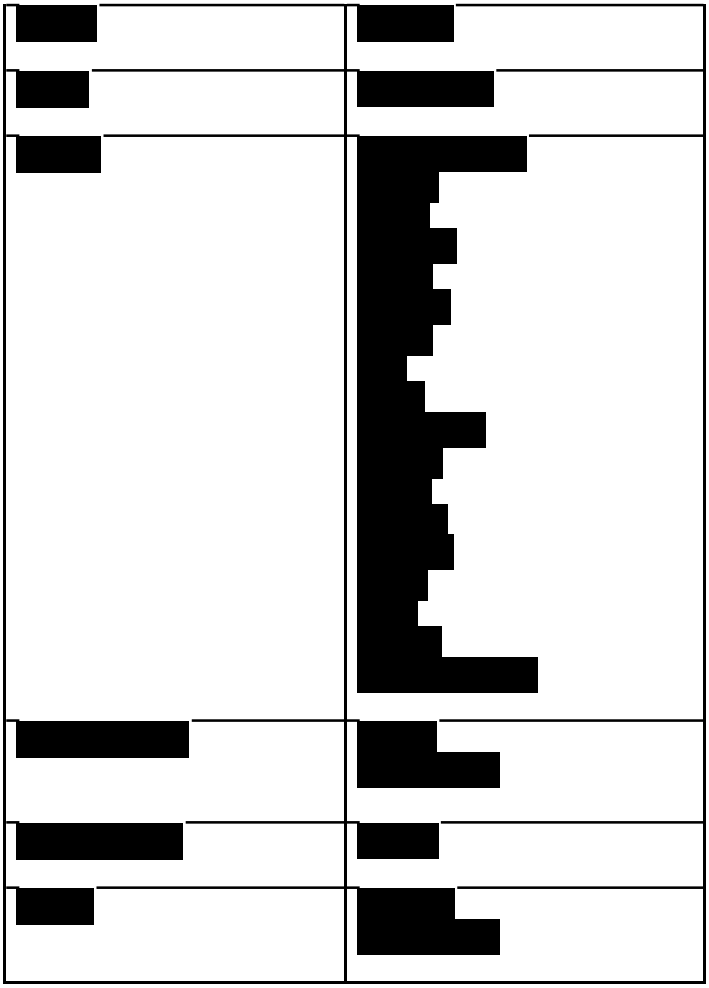
1	CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2	Service FJ; Glucose Variability; Diabetes 62:1398-1404, 2013 [R14-4138]
3	Baghurst PA.; Calculating the mean amplitude of glycemic excursion from continuous glucose monitoring data: an automated algorithm; Diabetes Technology & Therapeutics 2011; 13(3):296-302 [R14-4136]
4	Fritzsche G, Kohnert KD, Heinke P, Vogt L, and Salzsieder E; The use of a computer program to calculate the mean amplitude of glycemic excursions; Diabetes Technology & Therapeutics 2011; 13(3)L319-325 [R14-4137]
5	001-MCS 36-472: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
6	001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", version 2.0; IDEA FOR CON.
7	001-MCG-159, "Reporting of clinical trials and project summaries", current version; IDEA FOR CON.
8	001-MCG-156: «Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA FOR CON.
9	CPMP/ICH/137/95: "Structure and content of clinical study reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.
10	001-MCG-157: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

9 ADDITIONAL SECTIONS

[redacted]

[redacted]

[redacted]



9.2 SPECIAL SEARCH CATEGORIES AND ATC LEVELS FOR CONCOMITANT MEDICATION

The defining ATC levels and ATC codes of the WHO DD special search categories for the use of antihypertensives, ASA and lipid lowering drugs and are shown in Table 9.2:1.

Medications in the categories C02, C03, C07, C08 and C09 that have a missing ATC3 code will also be considered antihypertensives and will be presented in the respective table by their preferred name under antihypertensives.

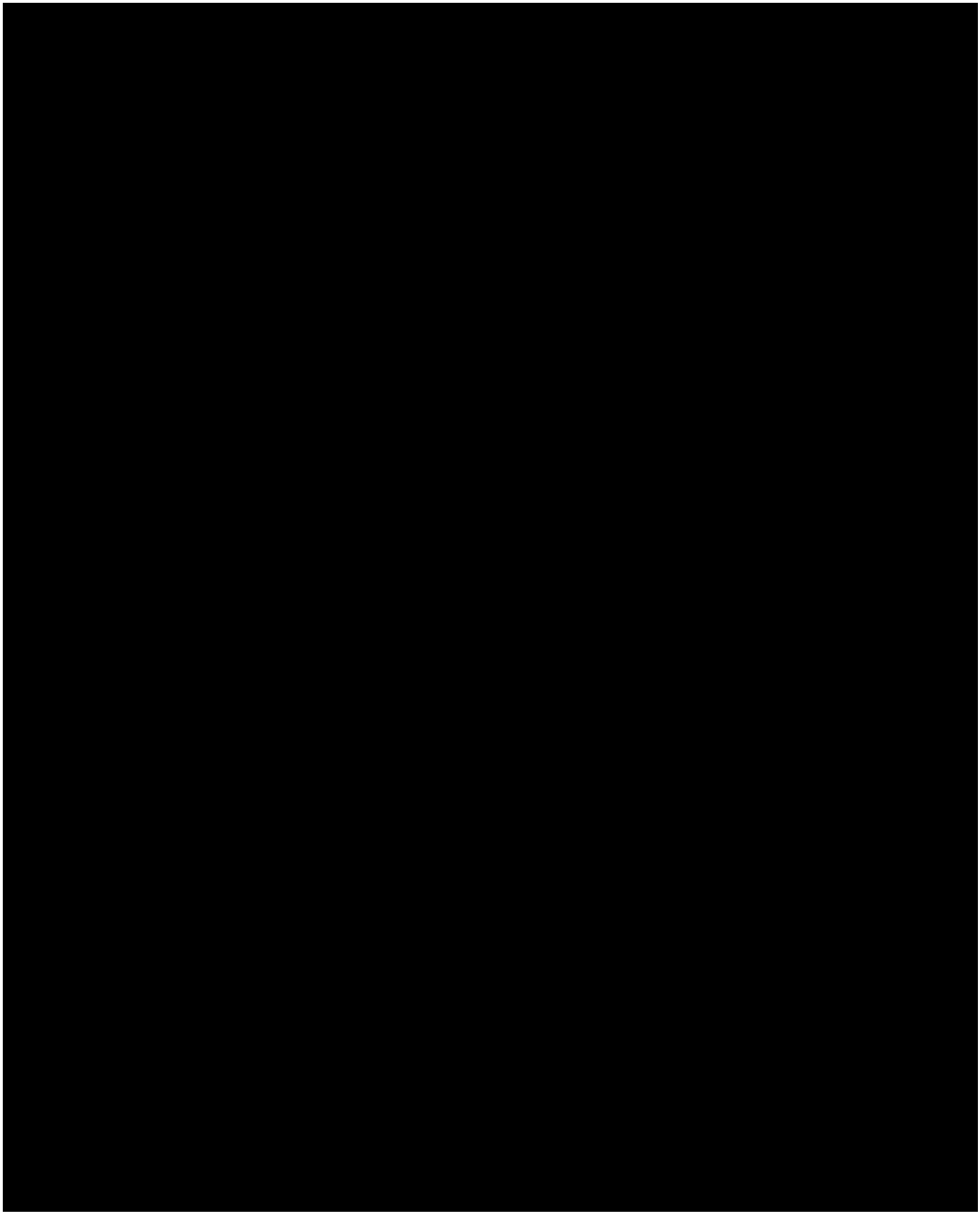
Table 9.2: 1 WHO DD special search categories

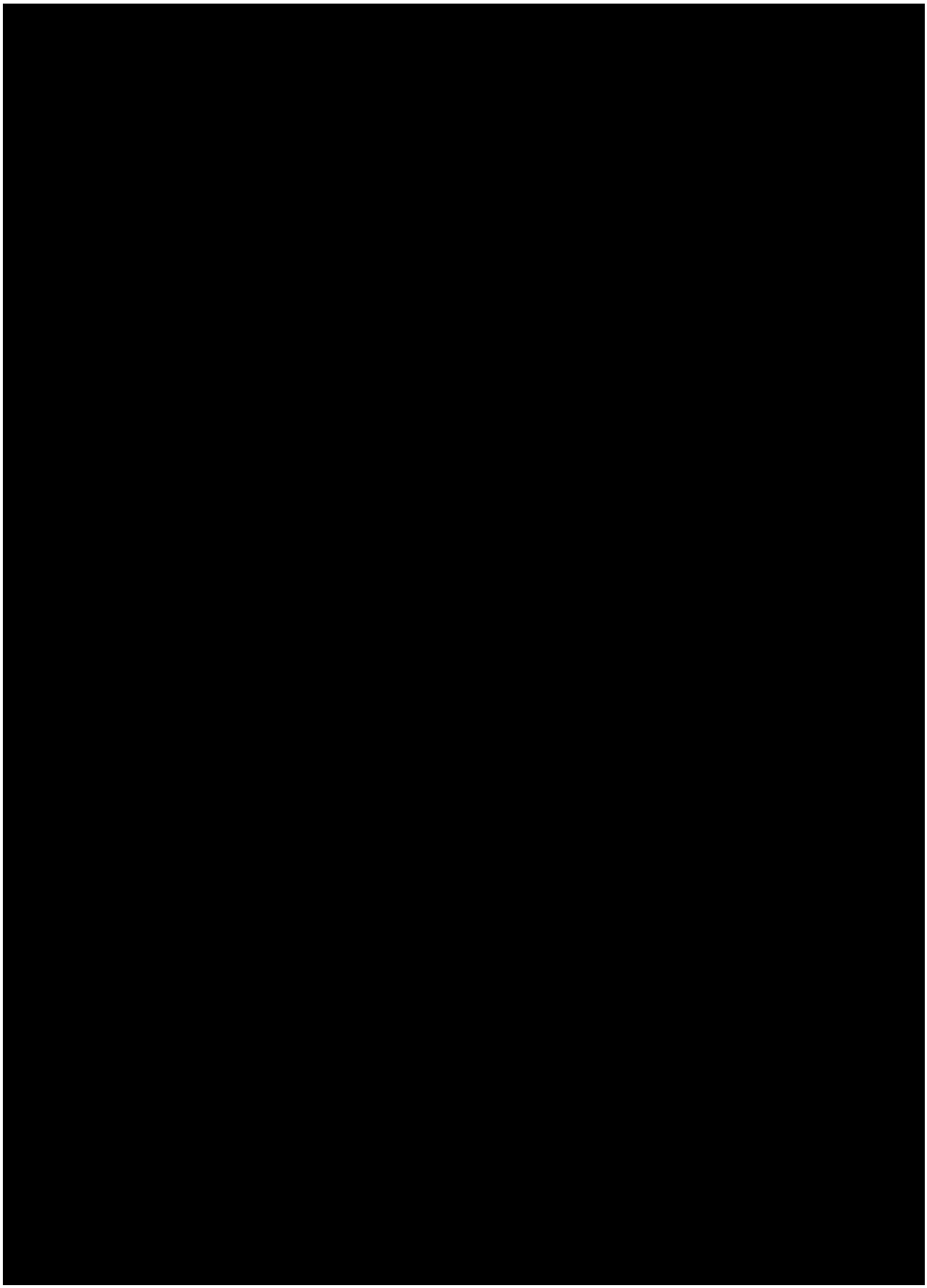
WHO DD special search categories			
SSC	**Displayed category**	**ATC level**	**ATC code**
ASA	ASA	ATC4	B01AC
Antihypertensives	Antiadrenergic agents, centrally acting	ATC3	C02A
	Antiadrenergic agents, ganglion-blocking	ATC3	C02B
	Antiadrenergic agents, peripherally acting	ATC3	C02C
	Arteriolar smooth muscle, agents acting on	ATC3	C02D
	Other antihypertensives excluding magnesium and magnesium sulfate	ATC3	C02K*
	Antihypertensives and diuretics in combination	ATC3	C02L
	Combinations of antihypertensives in atc-gr. C02	ATC3	C02N
	Low-ceiling diuretics, thiazides	ATC3	C03A
	Low-ceiling diuretics, excl. thiazides	ATC3	C03B
	High-ceiling diuretics	ATC3	C03C
	Potassium-sparing agents	ATC3	C03D

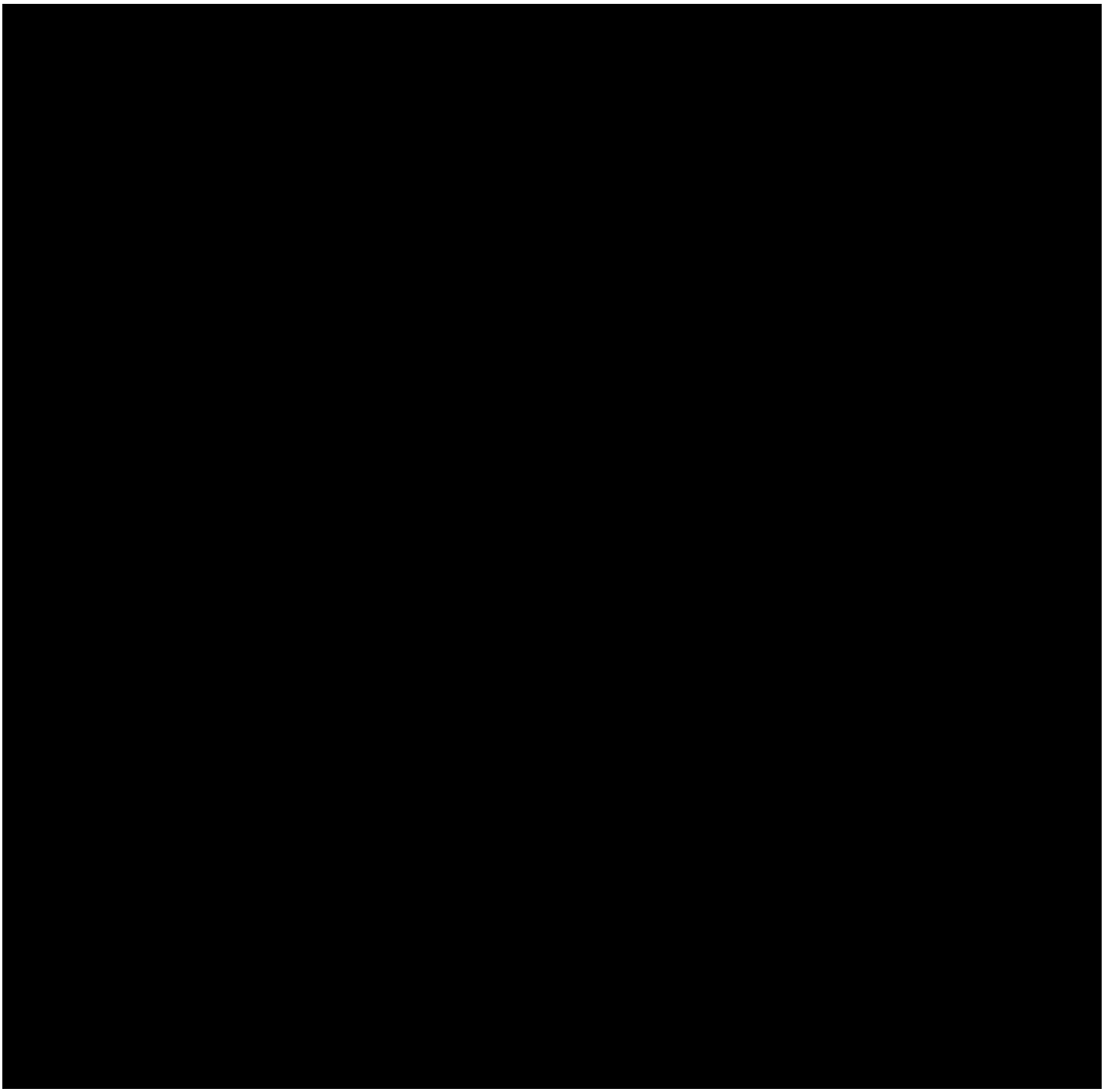
* C02K excluding the terms magnesium and magnesium sulphate

WHO DD special search categories (cont.)

SSC	Displayed category	ATC level	ATC code
	Diuretics and potassium-sparing agents in combination	ATC3	C03E
	Other diuretics	ATC3	C03X
	Beta blocking agents	ATC3	C07A
	Beta blocking agents and thiazides	ATC3	C07B
	Beta blocking agents and other diuretics	ATC3	C07C
	Beta blocking agents, thiazides and other diuretic	ATC3	C07D
	Beta blocking agents and vasodilators	ATC3	C07E
	Beta blocking agents and other antihypertensives	ATC3	C07F
	Selective calcium channel blockers with mainly vas	ATC3	C08C
	Selective calcium channel blockers with direct car	ATC3	C08D
	Non-selective calcium channel blockers	ATC3	C08E
	Calcium channel blockers and diuretics	ATC3	C08G
	ACE inhibitor, plain	ATC3	C09A
	ACE inhibitor, combinations	ATC3	C09B
	Angiotensin II antagonists, plain	ATC3	C09C
	Angiotensin II antagonists, combinations	ATC3	C09D
	Other agents acting on the 86ennin-angiotensin system	ATC3	C09X
Lipid lowering drugs	Niacin	ATC4 [nicotinic acid and derivatives]	C10AD
	Fibrates	ATC4 [Fibrates]	C10AB
	Statins	ATC4 [HMG COA reductase inhibitors]	C10AA
	Other	Other lipid modifying agents	C10AX
		Bile acid sequestrants	C10AC







10 HISTORY TABLE

Table 10: 1 History table

Version	Date	Author	Sections changed	Brief description of change
Final	17-MAY-17	[redacted]	None	This is the final TSAP without any modification
Revised	11-OCT-17	[redacted]	6.7 7.5.1.2 7.5.1.4 [redacted] 7.8.1.4 7.8.1.5	• [redacted] • [redacted] • Follow-up period for the assignment to active treatment for hepatic injury added • Multiple imputation analysis for body weight and blood pressure adapted • [redacted] • Definition of ketosis episodes added • A negative binomial model will be fitted to analyse the symptomatic hypoglycaemia with PG < 54 mg/dL • Minor changes in the wording and correction of typos