BI Study Number:	**1245.286**
Title:	**POST MARKETING SURVEILLANCE ON LONG TERM DRUG USE OF** **JARDIANCE® TABLETS IN PATIENTS WITH CHRONIC HEART FAILURE IN JAPAN.**
NCT number:	NCT05262764
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This page has been added to the Statistical and Epidemiological Analysis Plan (SEAP) to reflect the requirements by ClinicalTrials.gov. This information is not part of the standard document.

STASTICAL AND EPIDEMIOLOGICAL ANALYSIS PLAN (SEAP)

Document Number:	c44536556-01
BI Study Number:	1245.286
BI Investigational Product(s)	Empagliflozin
Title:	Post Marketing Surveillance on Long Term Drug Use of JARDIANCE® Tablets in Patients with chronic heart failure in Japan.
Brief lay title:	PMS of JARDIANCE® Tablets in Patients with CHF
SEAP version identifier:	Version 1.0
Date of last version of SEAP:	NA
ONIS Statistician [SEAP author]	[redacted]
ONIS [redacted] [SEAP reviewer]	[redacted]
ONIS Data [redacted] [SEAP reviewer]	[redacted]

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1. LIST OF ABBREVIATIONS

ACE	Angiotensin-Converting-Enzyme inhibitor
ADR	Adverse Drug Reaction
ARNI	Angiotensin Receptor-Neprilysin Inhibitor
AE	Adverse Event
BI	Boehringer Ingelheim
BMI	Body mass index
BNP	Brain Natriuretic Peptide
CCB	Calcium Channel Blocker
CHF	Chronic Heart Failure
CI	Confidence Interval
CRF	Case Report Form
CV	Cardiovascular
DPP-IV	Dipeptidyl Peptidase IV
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EoT	End-Of-Text
E peak	Early diastolic left ventricular filling velocity
e’	Early diastolic mitral annular velocity
GLP-1	Glucagon‐Like Peptide 1
HF	Heart Failure
LAD	Left atrial dimension
LVEDD	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection rate
LVESD	Left ventricular end-systolic diameter
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRA	Mineralocorticoid Receptor Antagonist
NIS	Non-interventional study
NT-proBNP	N-Terminal pro-Brain Natriuretic Peptide
NYHA	New York Heart Association functional classification
PD	Protocol deviation
PMS	Post Marketing Surveillance
PT	Preferred term
RMP	Risk Management Plan
SAE	Serious Adverse event
SEAP	Statistical and epidemiological analysis plan
SMQ	Standardized MedDRA query
SOC	System organ class
T2DM	Type 2 Diabetes mellitus

2. RESPONSIBLE PARTIES

[redacted]

Contact details and the list of all investigators will be kept in a stand-alone document. This document will be managed in the Post Marketing Surveillance (PMS) tracking system which manages the contracts with site and investigators name.

3. PURPOSE AND SCOPE

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 PMS data.

This SEAP assumes familiarity with the Non-interventional Study (NIS) Protocol, including Protocol Amendments. In particular, the SEAP is based on the planned analysis specification as written in NIS Protocol Section 9.7 “DATA ANALYSIS”. Therefore, SEAP readers may consult the NIS Protocol 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.

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
None				

5. RESEARCH QUESTION AND OBJECTIVE

The primary objective is to evaluate the incidence of adverse drug reaction (ADR) (focus on hypoglycaemia, the events relevant volume depletion, influence of ketone body increased / ketoacidosis, renal impairment) of JARDIANCE Tablets under the real world setting in patients with CHF (Chronic Heart Failure).

6. RESEARCH METHODS

6.1 STUDY DESIGN

This is a non-interventional study based on newly collect data of patients under routine care to confirm safety and effectiveness of JARDIANCE® Tablets in real-world setting in Japanese patients with CHF.

6.2 SETTING

6.2.1 Study sites

Sites throughout entire country will be equally listed according to the size of the hospitals or general clinics at which JARDIANCE® Tablets are available for prescription.

Planned number of sites: Approximately 200 Sites (including CV (Cardio vascular) internal medicine)

A medical representative will explain the objective and design of this study to investigators at each study site and conclude a written contract with the head of the study site (e.g., hospital director).

6.2.2 Inclusion/ exclusion criteria

Inclusion criteria
- Patients with CHF who are prescribed with JARDIANCE® Tablets in Japan.
- Patients who have never been treated with Empagliflozin (including treatment for Type 2 Diabetes mellitus (T2DM)) before enrolment.

Exclusion criteria
None

6.2.3 Registration period

From April 2022 to March 2023

6.2.4 Patient registration method

The registration method will be a central registration system. Patients who begin treatment with JARDIANCE® Tablets after the conclusion of the contract will be registered by entering necessary information in the Electronic Data Capture (EDC) system within 14 days from the day of treatment initiation (inclusive).
Patient registration will be stopped when the overall target number of patients for the study is reached.

6.3 STUDY POPULATION

The following table defines the different categories of important Protocol Deviations (iPDs). The final column describes which iPDs will be used to exclude patients from each patient analysis sets. The final decision about which patients will be excluded from analysis sets will be taken during the study and at report planning meetings before database lock at the latest.

Table 6.3: 1 Important protocol deviations

Category / Code		Description	Requirements	Method	Excluded from
A		**Entrance criteria not met**			
	A1.1	Patient of non-CHF	Reason for use is not CHF	Automated	Effectiveness
	A1.2	Patient received Empagliflozin (JARDIANCE®) or Empagliflozin + Linagliptin (TRADIANCE®) treatment before registration	See Previous Medication code*:3969023, 3969108	Automated	All
C		**Trial medication and randomization**			
	C1	Incorrect trial mediation taken			
	C1.1	No treatment with JARDIANCE® Tablets	No treatment status	Automated	All
G		**Trial specific**			
	G1	**Invalid registration**			
	G1.1	No patient visits after entry	Administration status is "No visit since the first visit"	Automated	All
	G1.2	Duplicated registration	Patient who has been already registered in this study with another patient ID. In this case, all data for the later patient will not be used.	Manual	All
	G1.3	Registration rule not followed	Patient registered beyond 14 days since the administration of JARDIANCE® started. (See NIS Protocol section 9.2.2.1)	Automated	All
	G1.4	Patient started JARDIANCE® treatment out of registration period	Patient started JARDIANCE® treatment out of registration period. (See NIS Protocol section 9.2.2.1)	Automated	All
	G1.5	Patient started JARDIANCE® treatment out of contract period for each site	Patient started JARDIANCE® treatment out of contract period for each site. (See NIS Protocol section 9.2.2.1)	Manual	All

Note *Previous Medication code is coded by latest version of "Nihon-iyakuhinshu".

The safety set will be the basis of all demographics, baseline and safety analyses. Effectiveness analysis will be on basis of the effectiveness set.

- Safety set:

This patient set includes all patients who didn't have iPDs regarding safety and regulatory issues as marked as "All" in Table 6.3: 1.

- Effectiveness set:
  This patient set includes all patients in safety set with CHF and have effectiveness information. (Patients marked "Effectiveness" in Table 6.3: 1 should be excluded from effectiveness analysis.)

6.4 STUDY VISITS

The study will consist of a baseline visit and further visits in a 52-week follow-up for patients who have initiated JARDIANCE® Tablets treatment. The follow-up data (safety and administration of JARDIANCE®) from patients who change hospital and continue taking JARDIANCE® will be collected by participating investigators if possible.

With regard to effectiveness and safety endpoints, the term "baseline" refers to the last observed measurement before the first administration of JARDIANCE® Tablets. The first date of the administration of JARDIANCE® Tablets is included in "baseline".
The analyses of eGFR over time will be performed based on calculated visits as shown in Table 6.4: 1. If two or more data points of a patient fall into the same interval, the closest value to the planned 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 first value will be used.

Table 6.4: 1 Baseline, time windows and calculated visits

		Time window (actual days on treatment)	
Week label	Planned days	Start	End
Baseline	1	The last observed measurement before administration of JARDIANCE®	
Week 12	84	2	133
Week 26	182	134	231
Week 40	280	232	322
Week 52	364	323	End of study

7. VARIABLES

7.1 EXPOSURES

Exposure to JARDIANCE® Tablets is estimated as time from the day JARDIANCE® Tablets is initiated until the day the drug is last administrated on a patient-level (or the final contact with the patient during the regular observation period).
Patients newly initiating JARDIANCE® Tablets will be followed up to 52 weeks.

7.2 OUTCOMES

7.2.1 Primary outcomes

The primary endpoint of this study is the incidence of ADRs (focus on hypoglycaemia, the events relevant volume depletion, influence of ketone body increased / ketoacidosis and renal impairment).
There is no primary outcome for effectiveness as the primary objective of a PMS is evaluating safety.

7.2.2 Secondary outcomes

- Incidence of all-cause death
- Incidence of CV death
- Incidence of hospitalizations for heart failure

[redacted]

7.3 COVARIATES

The covariates included in the model analysis are described at Table 10.3.1: 1 in Section 10.3.

8. DATA SOURCES

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via the EDC system.

In EDC system, two casebooks will be set:
Book 1 includes baseline, 12 weeks and 26 weeks.
Book 2 includes 40 weeks and 52 weeks.

The data are to be transmitted immediately after being entered into EDC at 26 weeks (Book 1) and 52 weeks (Book 2) after the start of treatment or at discontinuation.
For any adverse events, the data should be immediately entered into EDC and transmitted.

9. DATA MANAGEMENT AND SOFTWARE / TOOLS

9.1 SOFTWARE/TOOLS

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

9.2 HANDLING OF MISSING VALUES

Safety:
Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and Incomplete AE dates" (1))

Missing or partial date information will be replaced according to following rules.

YEAR	MONTH	DAY	YMD	DT
"Unknown" (tick-box)			UNKNOWN	.
yyyy	Null or "Unknown"	Null	yyyy	yyyy/01/01
yyyy	mm	Null or "Unknown"	yyyymm	yyyy/mm/01

In general, when tabulating AEs, and demographic and baseline characteristics variables reported as unknown will be treated as such; otherwise treated as missing data.
eGFR, Blood pressure (Systolic blood pressure and Diastolic blood pressure), Pulse rate, Weight, Grip Strength and Echocardiography (LVEF, LVEDD, LVESD, LAD, E peak, A peak and e'): For the missing values in these items, no imputation methods will be employed.

9.3 HANDLING OF INCONSISTENCIES IN DATA AND OUTLIERS

Outliers will not be excluded from analyses unless otherwise noted.

10. DATA ANALYSIS

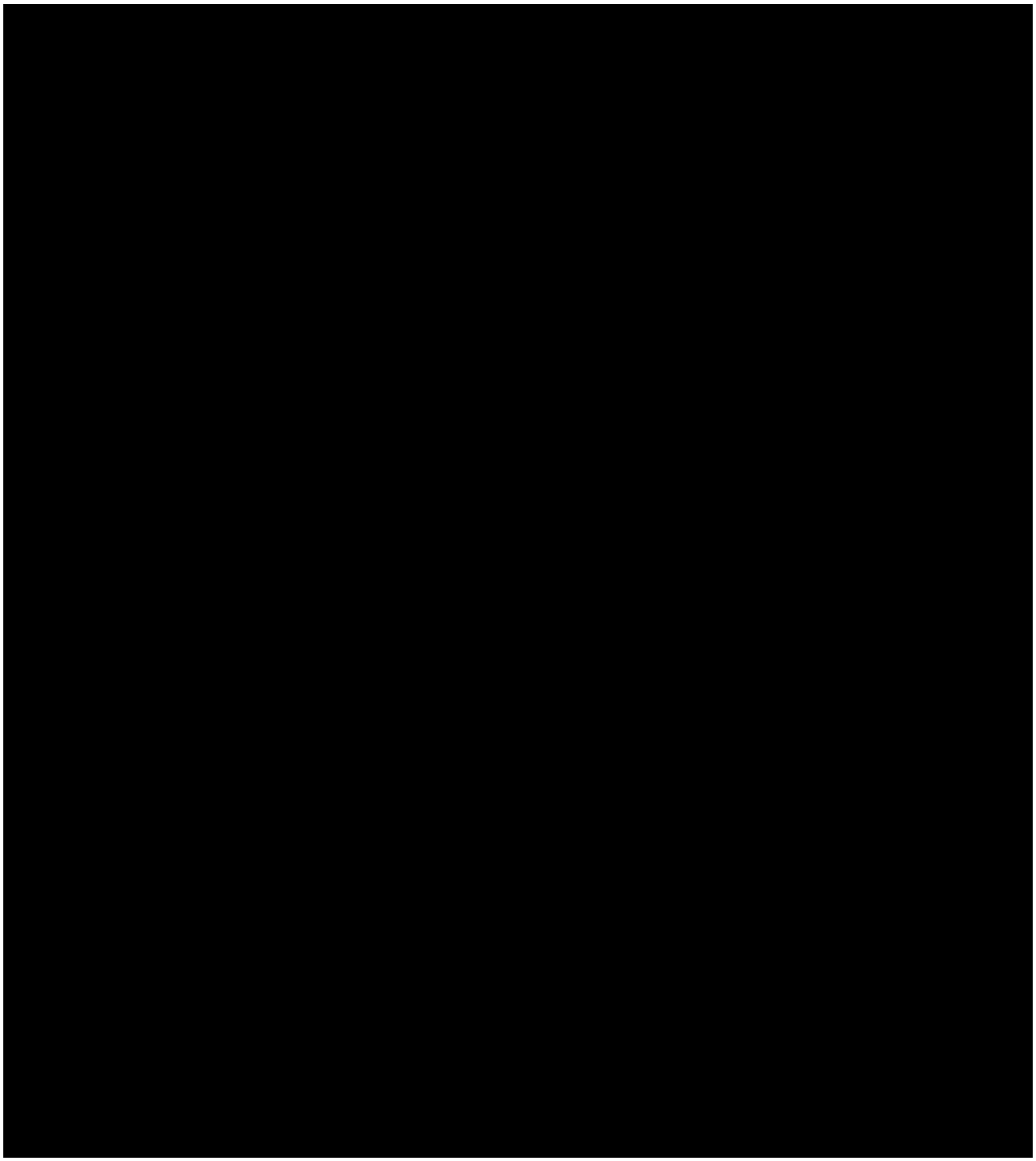
For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Q1 / Median / Q3 / Max.

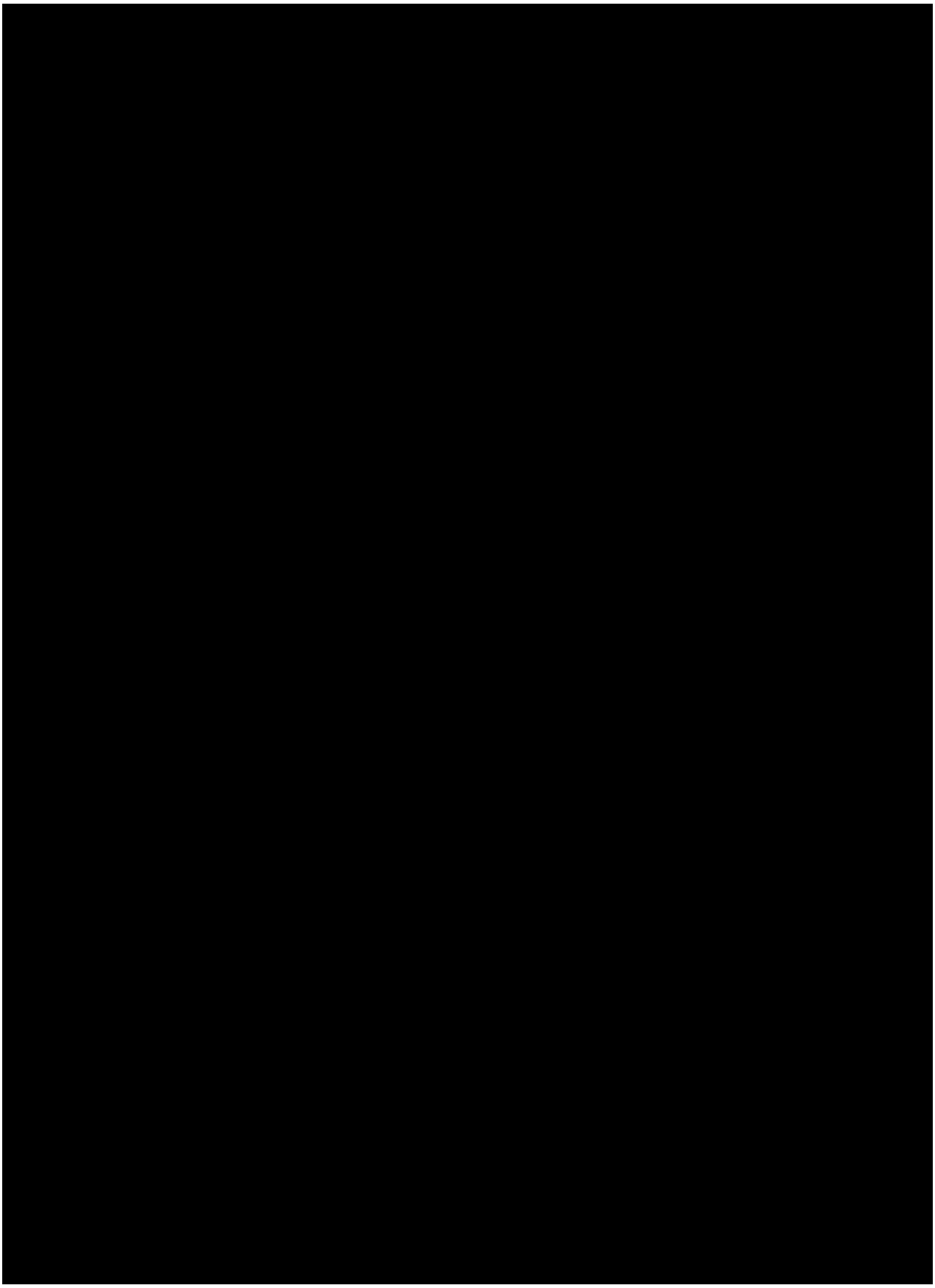
For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

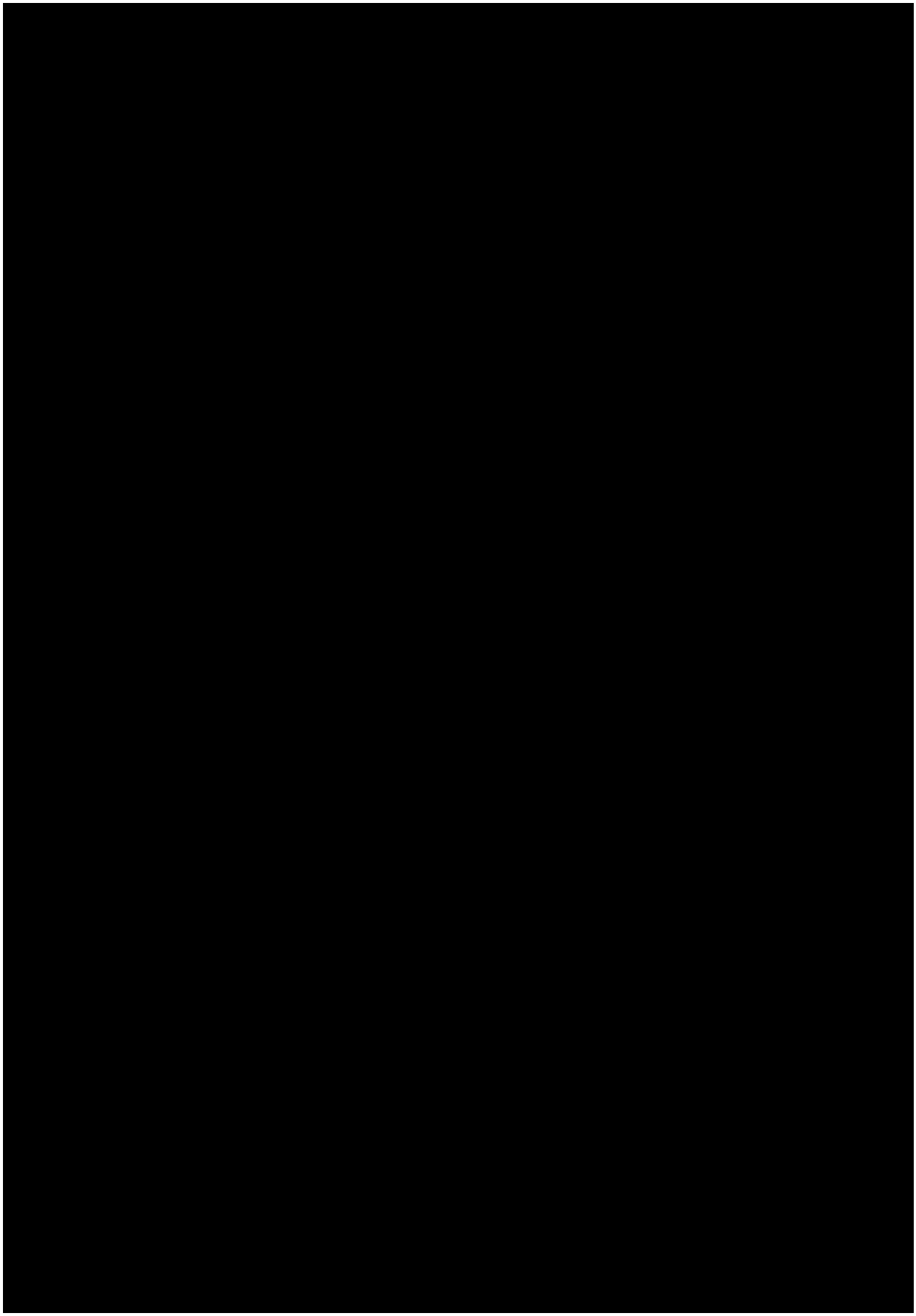
Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they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

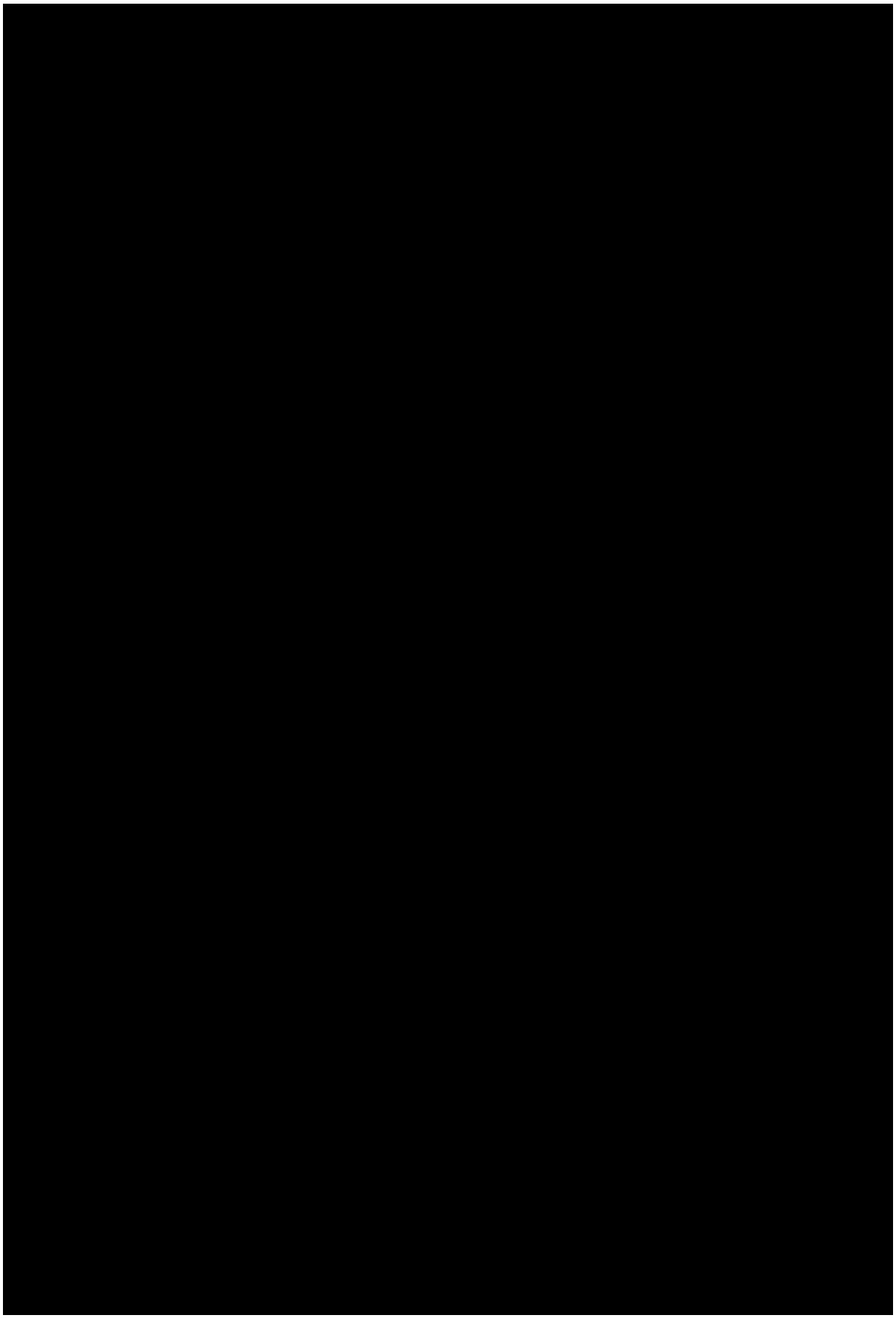
10.1 MAIN ANALYSIS

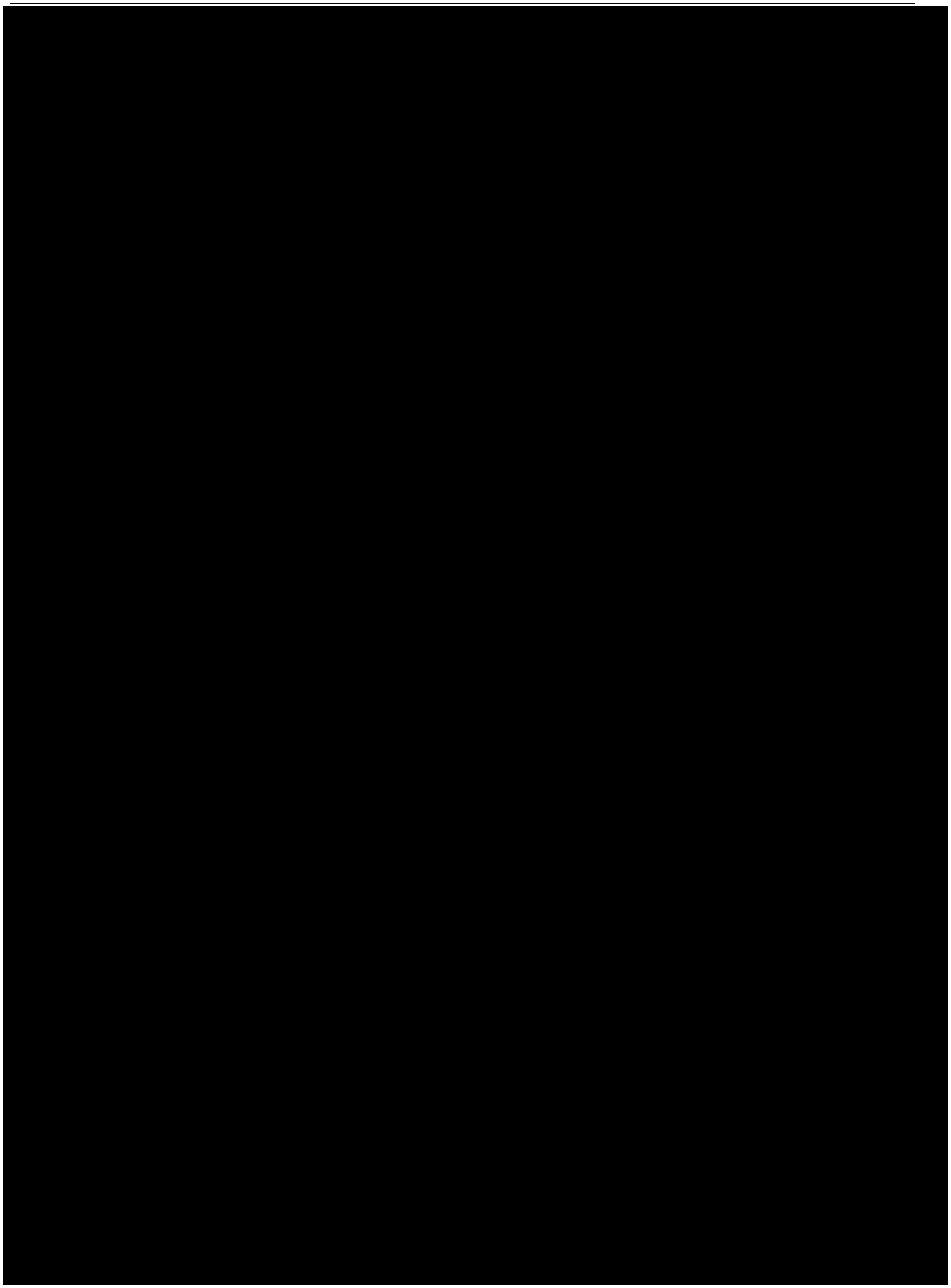
The analysis of the primary outcomes is described in Section 10.3.1.
In this PMS, since the primary endpoint is the incidence of ADRs (focus on hypoglycaemia, the events relevant volume depletion, influence of ketone body increased / ketoacidosis and renal impairment), the main analysis is to show frequency, proportion and its corresponding confidence interval (CI). The details are given in Section 10.3.1.

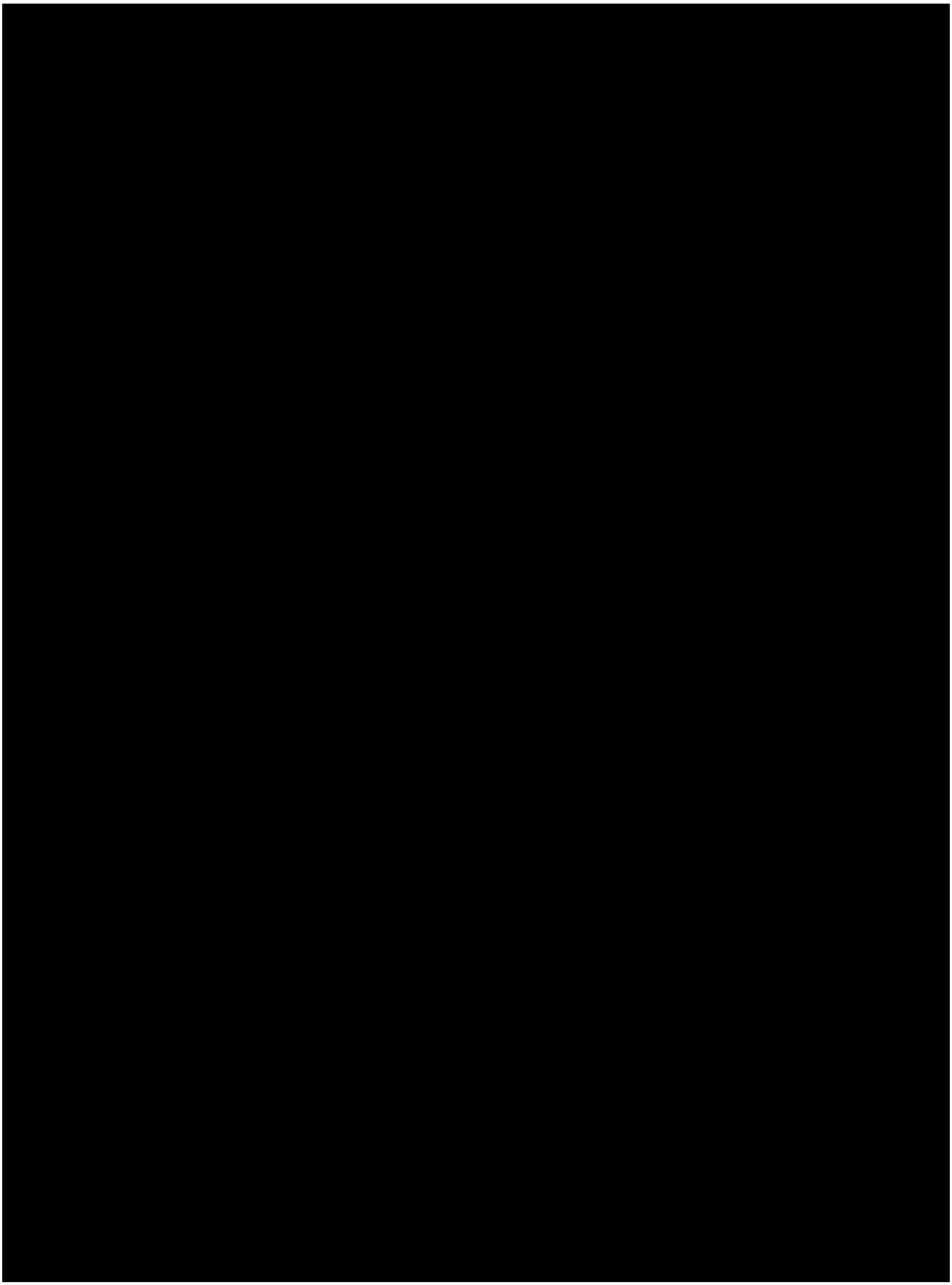


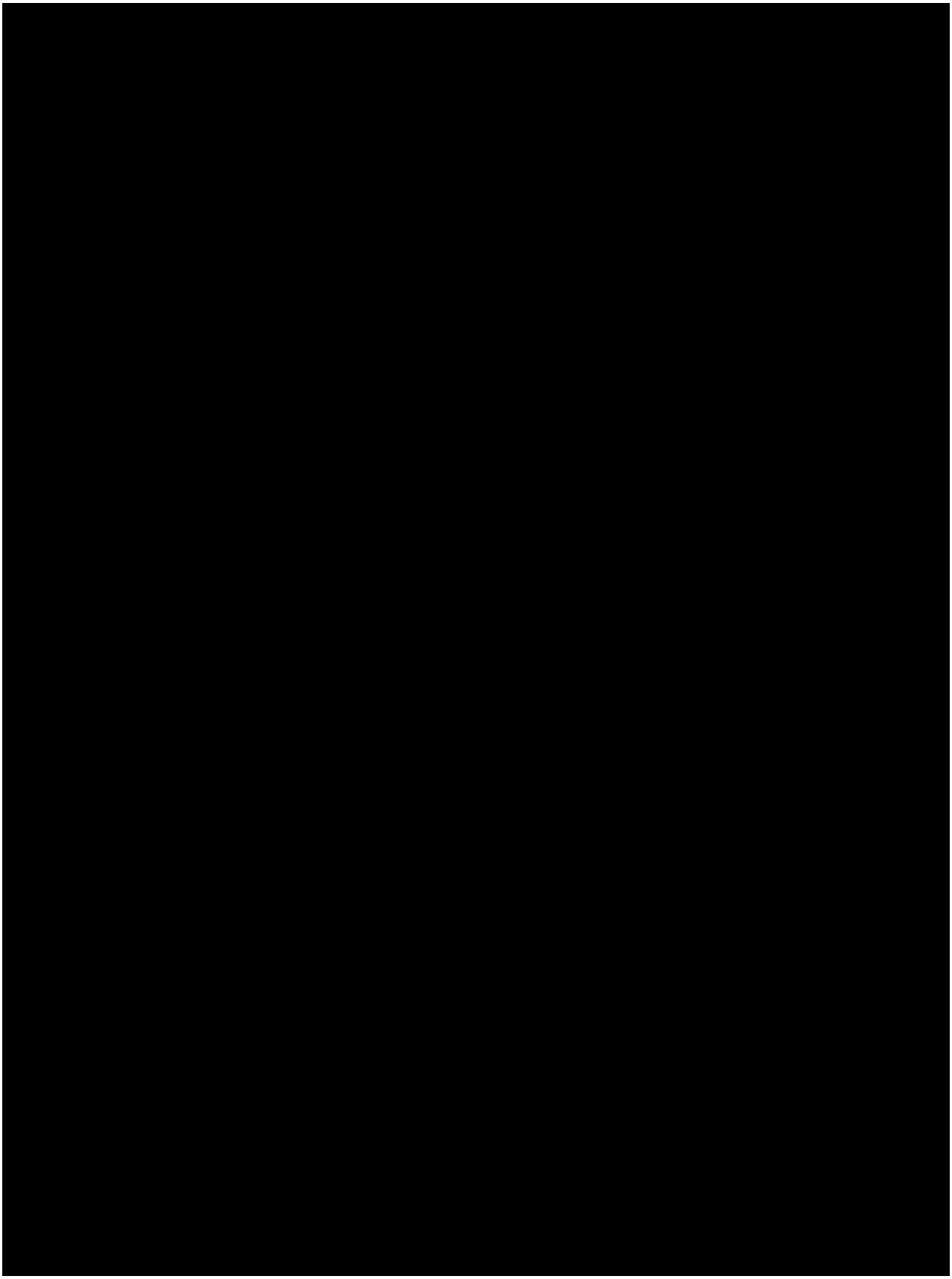


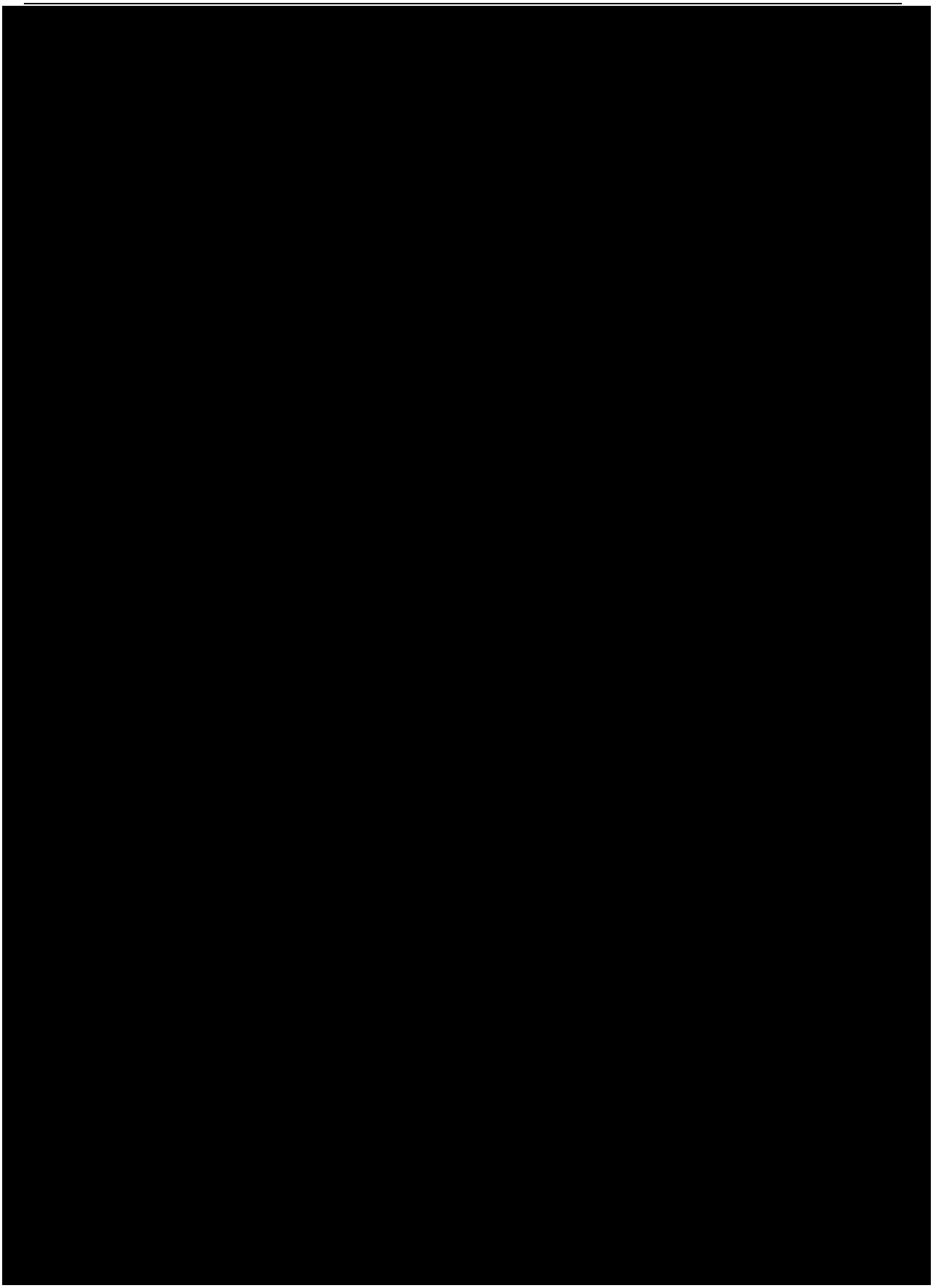












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10.3 SAFETY ANALYSIS

All safety analyses will be performed on the safety set.

10.3.1 Adverse events

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

All AEs occurring between the initiation of JARDIANCE® Tablets prescribed at baseline visit and 7 days (inclusive) after the last administration will be considered 'treatment emergent'.

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

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

For further details on summarization of AE data, please refer to BI standards ('Analysis and Presentation of Adverse Event Data from Clinical Trials' (2)).

Unless otherwise specified, AE analyses will be used AE data from safety database.

An Adverse Drug reaction (ADR) is defined as an AE for which either the investigator or the sponsor (or both) assesses the causal relationship to JARDIANCE® as "Yes." A serious AE is defined as an AE for which either the investigator or the sponsor (or both) assesses the seriousness as "Serious."

The SOCs will be sorted according to the standard sort order specified by European medicines agency. PTs will be sorted by frequency (within SOC).

The frequency of patients with the following items will be summarized.

- AEs
- ADRs
- Severe AEs
- Severe ADRs (Dr)
- AEs leading to discontinuation
- ADRs (Dr) leading to discontinuation
- AEs leading to all-cause death
- ADRs leading to all-cause death
- AEs leading to CV death
- ADRs leading to CV death
- AEs leading to hospitalization for HF
- ADRs leading to hospitalization for HF
- Serious AEs
- Serious ADRs

Note1: Severe AEs/ADRs and AEs/ADRs leading to discontinuation will be used AE data from CRF.

Note2: For the definition of all-cause death, CV death and HF, refer to note in Section 10.2.5.

Note3: ADRs (Dr) is defined as an AE for which only the investigator assesses the causal relationship to JARDIANCE® as "Yes".

The frequency of patients with the following items will be summarized by primary SOC and PT.

- AEs
- ADRs
- AEs leading to discontinuation
- ADRs (Dr) leading to discontinuation
- AEs leading to all-cause death
- ADRs leading to all-cause death
- AEs leading to CV death
- ADRs leading to CV death
- AEs leading to hospitalization for HF
- ADRs leading to hospitalization for HF
- Serious AEs
- Serious ADRs

Note1: AEs/ADRs leading to discontinuation will be used AE data from CRF.

Note2: For the definition of all-cause death, CV death and HF, refer to note in Section 10.2.5.

Note3: ADRs (Dr) is defined as an AE for which only the investigator assesses the causal relationship to JARDIANCE® as "Yes".

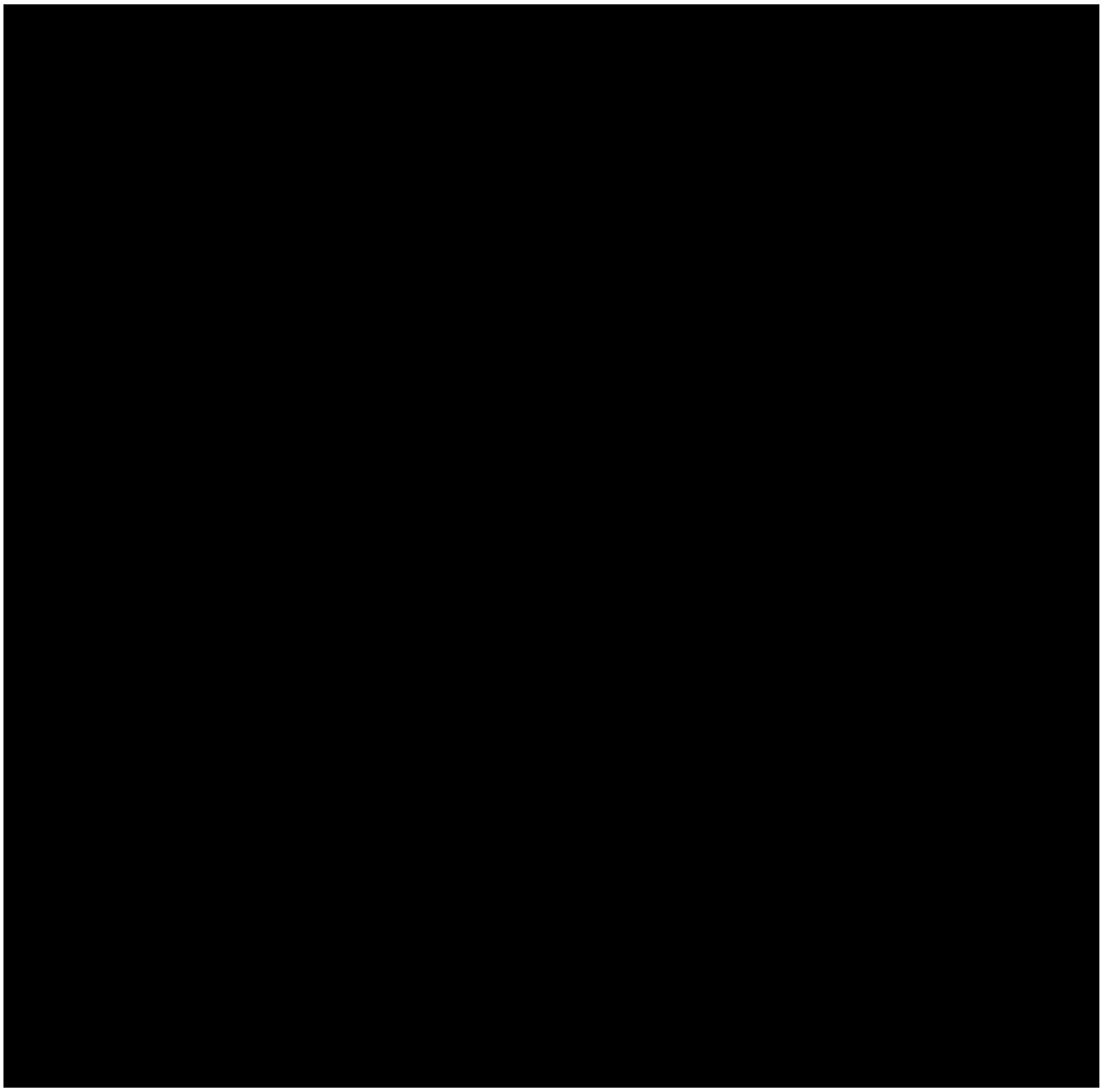
The listings in the following items are presented.

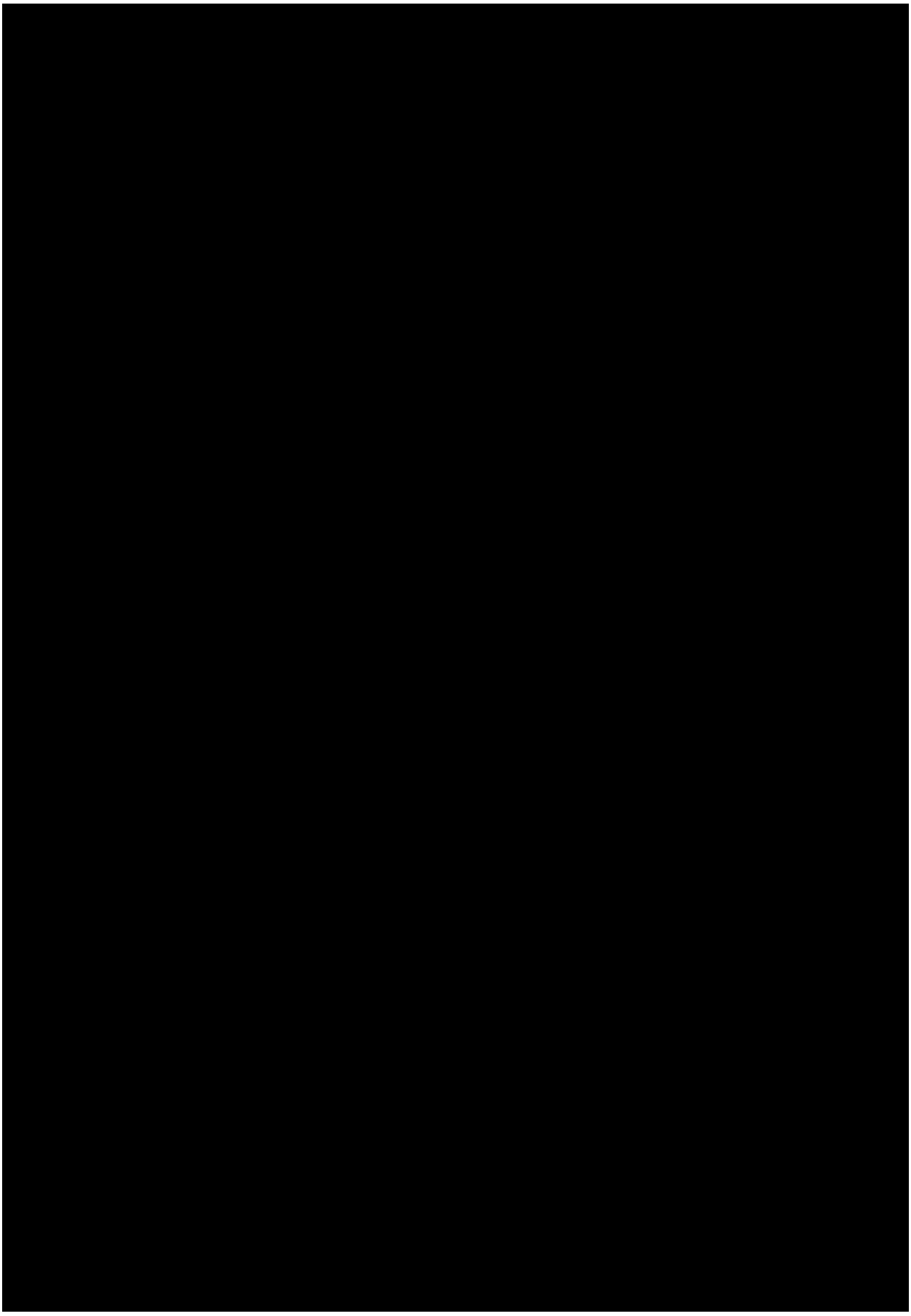
- AEs leading to discontinuation used AE data from CRF.

- AEs obtained from the safety database with different assessments of the causal relationship to JARDIANCE® judged by between the sponsor and the investigator.

Summaries for the time to onset of first episode for the ADRs will be tabulated, by duration (0 to <12, 12 to <26, 26 to <40, 40 to <52, ≥52, Unknown [weeks]), by primary SOC, and PT.

To compare risks of overall ADR in different patient subgroups, frequency tabulation stratified by the subgroups will be provided with odds ratios for the incidence of ADR and 95% confidence intervals for the odds ratios whenever specified (see Table 10.3.1: 1). The odds ratio and the 95% confidence intervals for the odds ratios will be calculated by use of Logistic regression. In case that there will be a significant difference between each factor in the subgroups (i. e. in the case that the confidence interval for the odds ratio will not include the number 1), the frequency of patients with ADR will be summarized by the factor, primary SOC and PT.





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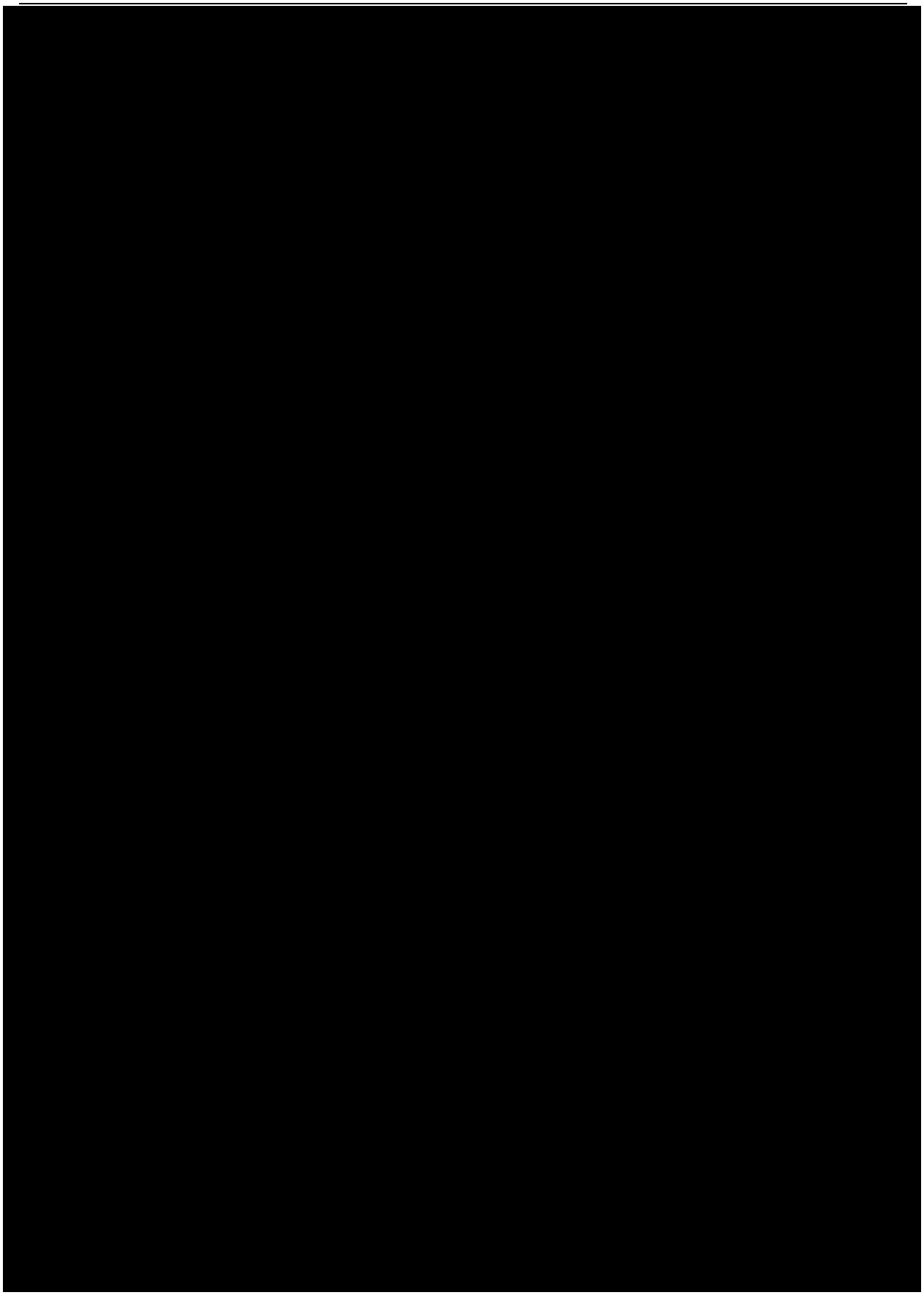

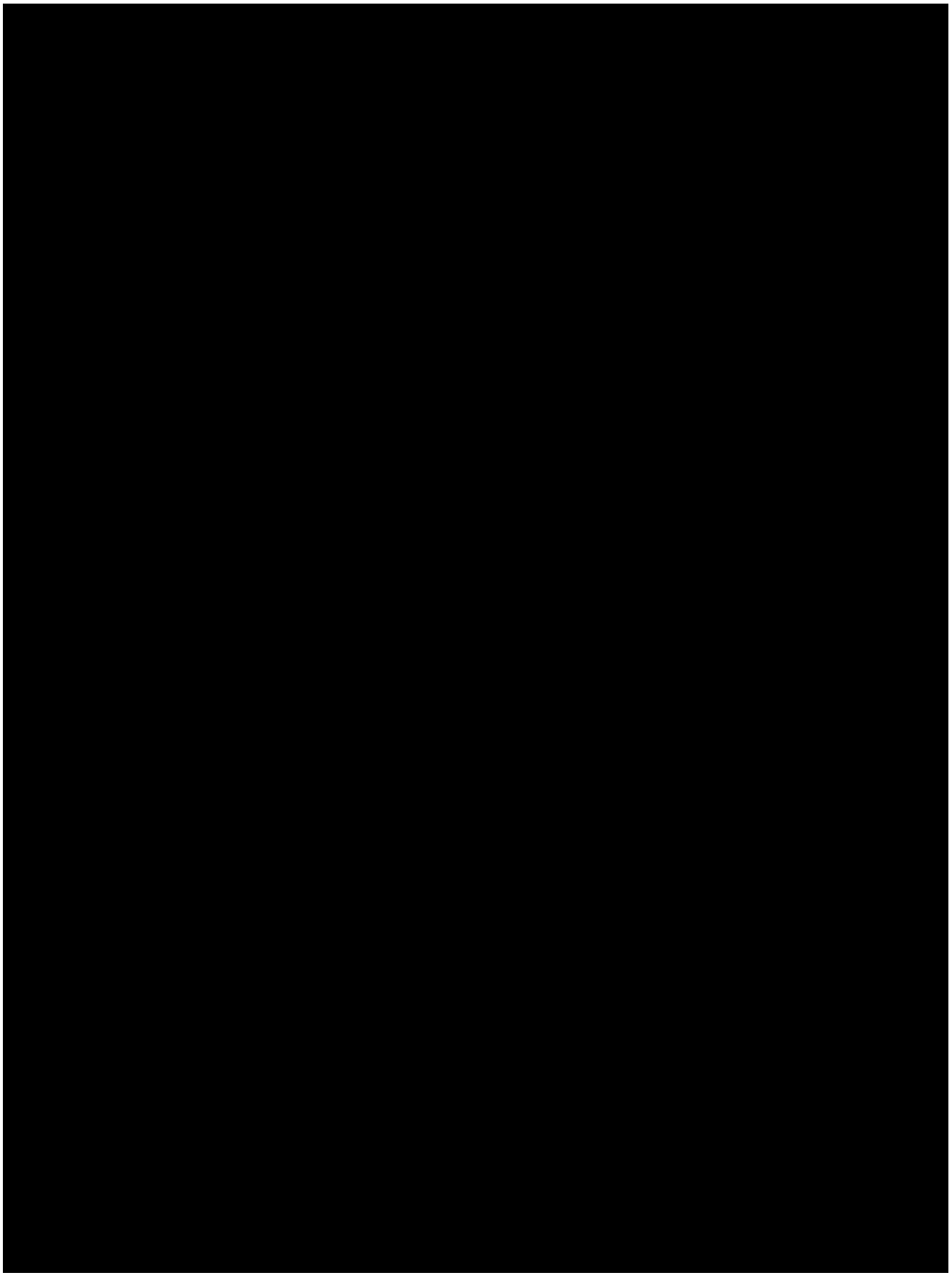

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10.3.2 Endpoints related to safety

For safety set, duration of treatment exposure adjusted incidence rate, frequency, proportion and its corresponding confidence interval (CI) in all-cause death, incidence of CV death, incidence of initial hospitalizations for HF and Safety specifications will be shown in the same way as Table 10.2.5: 1.

Kaplan-Meier analysis will be used to estimate incidence of all-cause death, incidence of CV death, incidence of initial hospitalizations for HF rate and incidence of CV death or initial hospitalizations for HF and a Kaplan-Meier plot and Safety specifications will be constructed.

10.3.3 Laboratory data

Descriptive statistics of eGFR at each calculated visit will be summarized in the table. Also, change from baseline in eGFR over time by the calculated visit will be displayed.

11. QUALITY CONTROL

All processes are conducted according to GPSP Standard Operating Procedures (SOP) (3). Appropriate records and documents are stored based on the GPSP SOPs and these processes are checked by internal self-check.

12. REFERENCES

12.1 PUBLISHED REFERENCES

Not applicable.

[redacted]

ANNEX 1. ADDITIONAL INFORMATION

Not applicable.

ANNEX 2. REVIEWERS AND APPROVAL SIGNATURES

Not applicable (this study will be stored in the DMS for submission documents).