TRIAL STATISTICAL ANALYSIS PLAN

c08935851-01

BI Trial No.:	1245.94
Title:	Post Marketing Surveillance in Japan on Long Term Drug Use of JARDIANCE® Tablets in Patients with type 2 Diabetes Mellitus
Investigational Product(s):	Empagliflozin, BI 10773
Responsible trial statistician(s):	[redacted] Address: [redacted] Phone: [redacted], Fax: [redacted]
Date of statistical analysis plan:	22 OCT 2020 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
ADR	Adverse drug reaction
AE	Adverse event
BICMQ	Boehringer Ingelheim customised MedDRA query
BMI	Body-mass index
CRF	Case Report Form
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eGFR	Estimated Glomerular filtration Rate
FPG	Fasting plasma glucose
MedDRA	Medical Dictionary for Regulatory Activities
NGSP	National Glycohemoglobin Standardization Program
NIS	Non-interventional Study
PMS	Post Marketing Surveillance
PT	Preferred term
PV	Protocol violation
SBP	Systolic blood pressure
SD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System organ class

3. INTRODUCTION

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 post-marketing surveillance (PMS) data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Non-interventional Study (NIS) Protocol, including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in NIS Protocol Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP 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.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There has been no change in the planned analysis from the statistical methods described in the NIS Protocol.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

There is no primary endpoint for efficacy, the primary objective of the PMS study is the evaluation of safety (see the NIS Protocol Section 5.2.1).

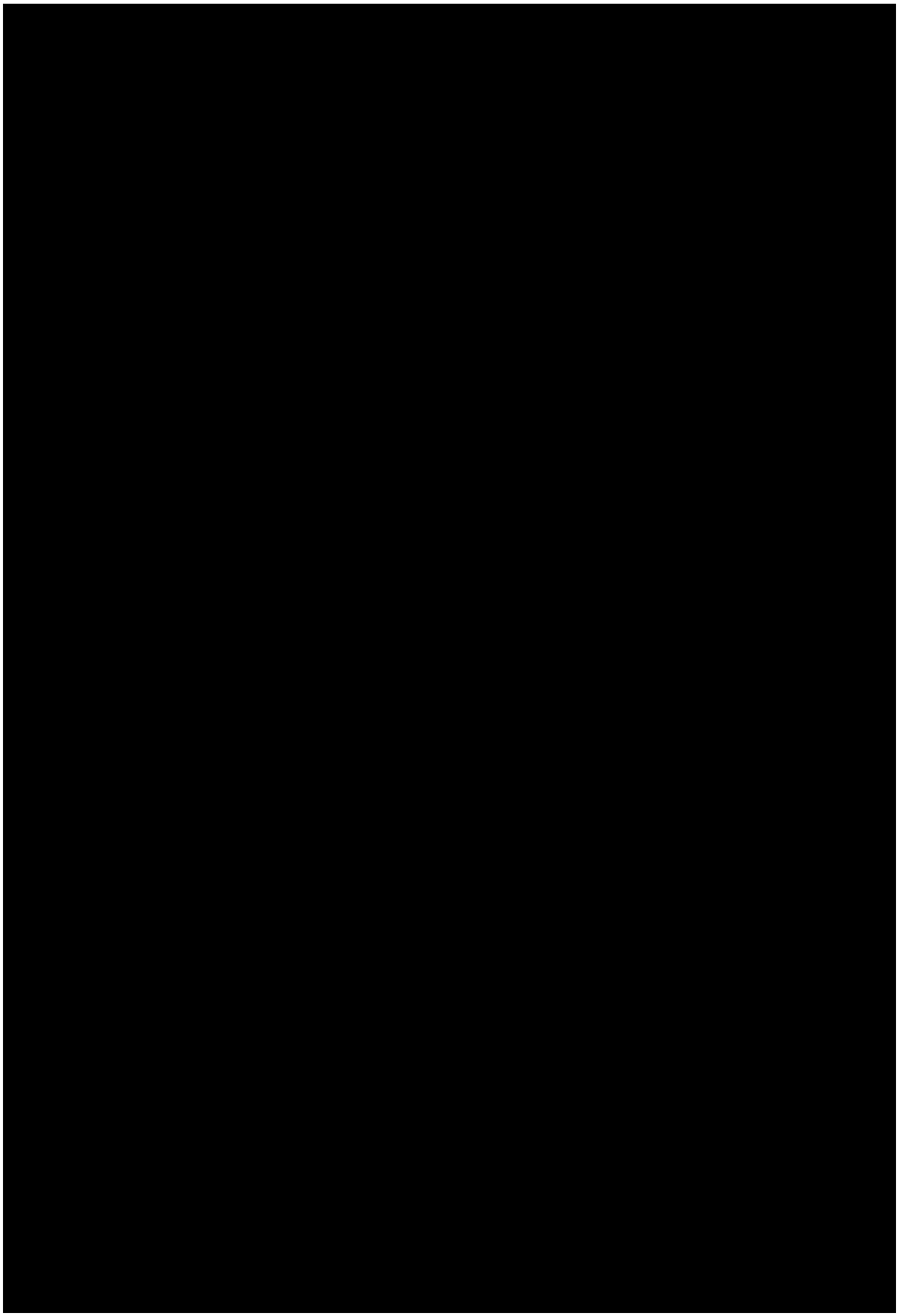
5.2 SECONDARY ENDPOINT(S)

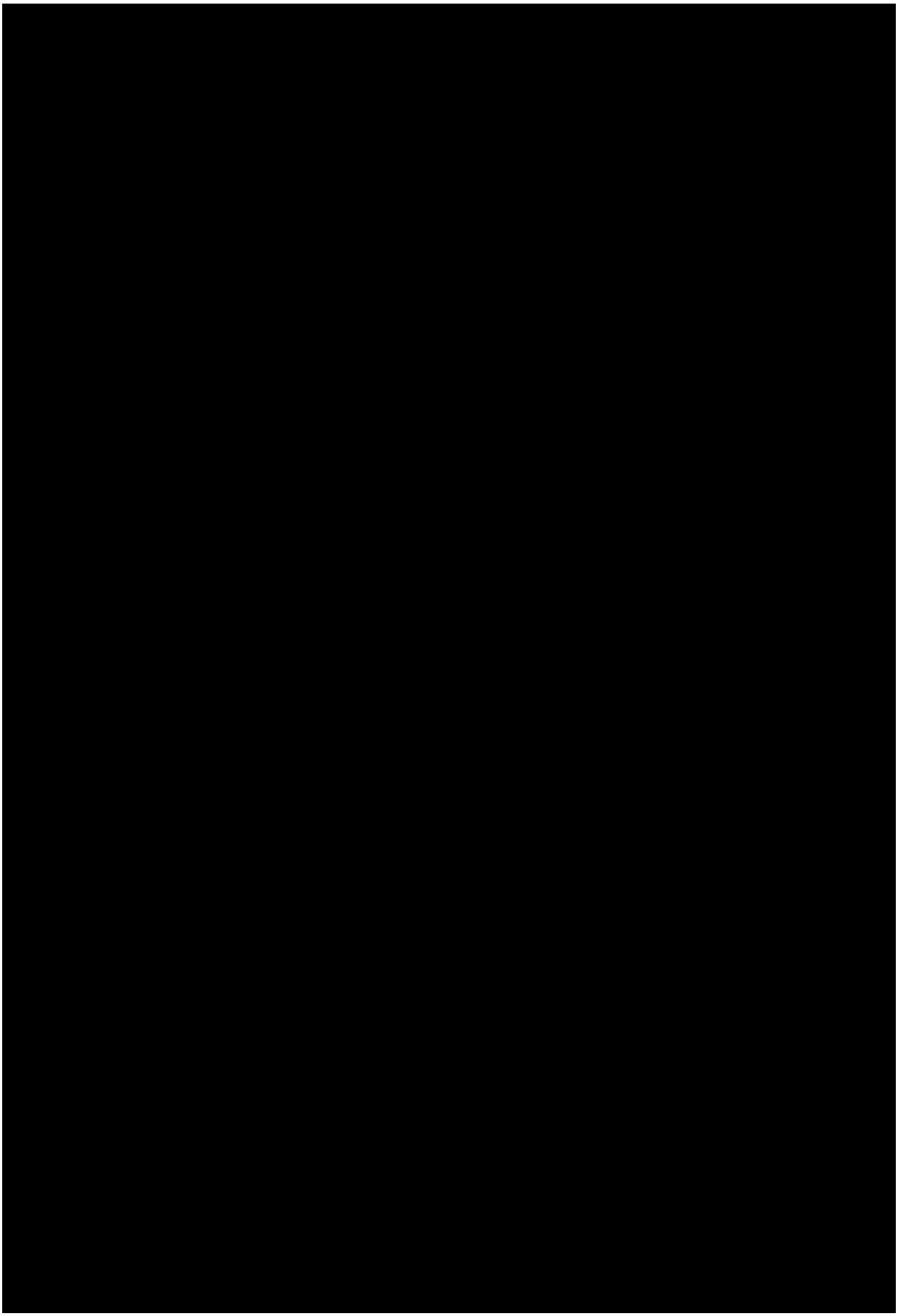
5.2.1 Key secondary endpoint(s)

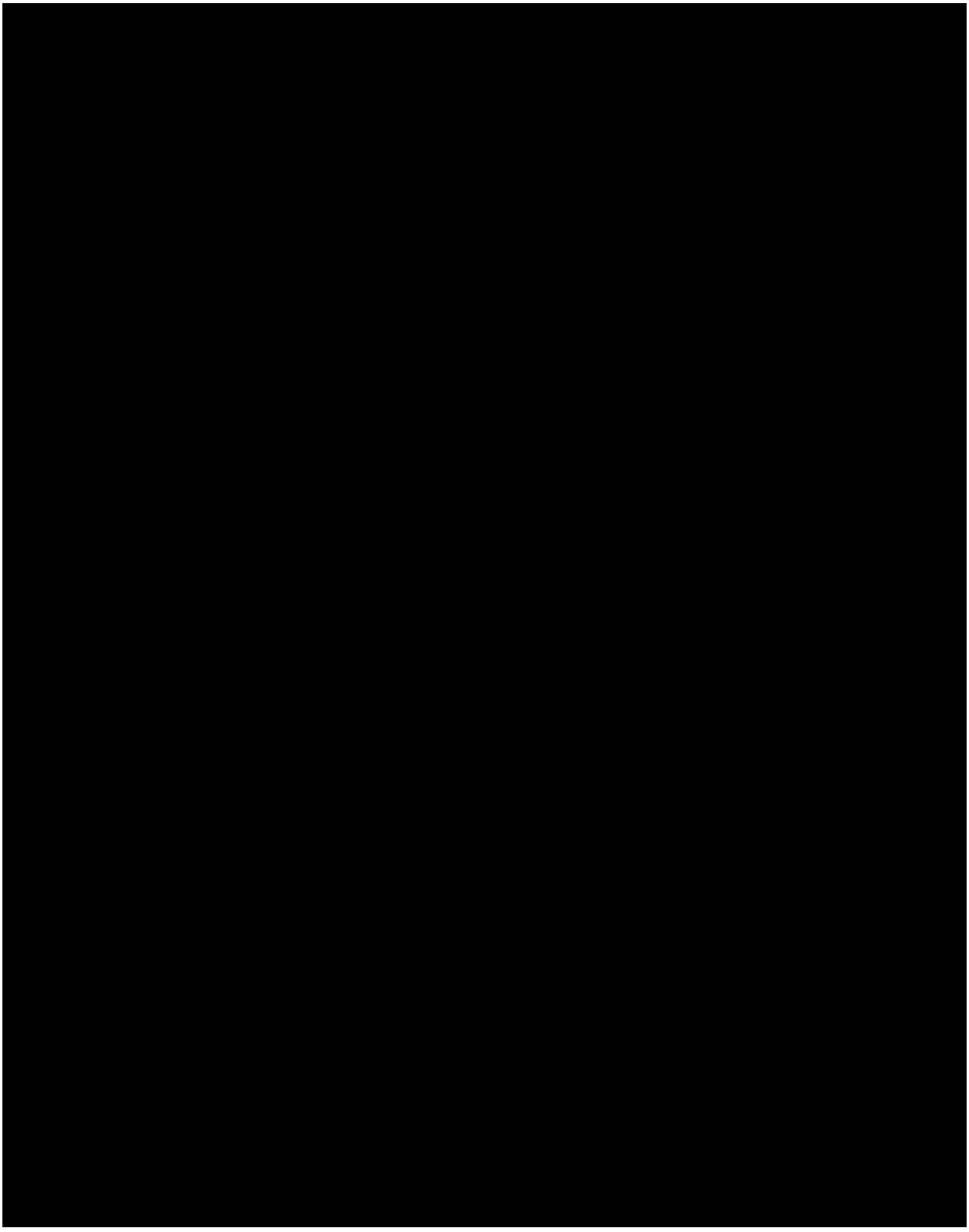
This section is not applicable as no key secondary endpoint has been specified in the NIS protocol.

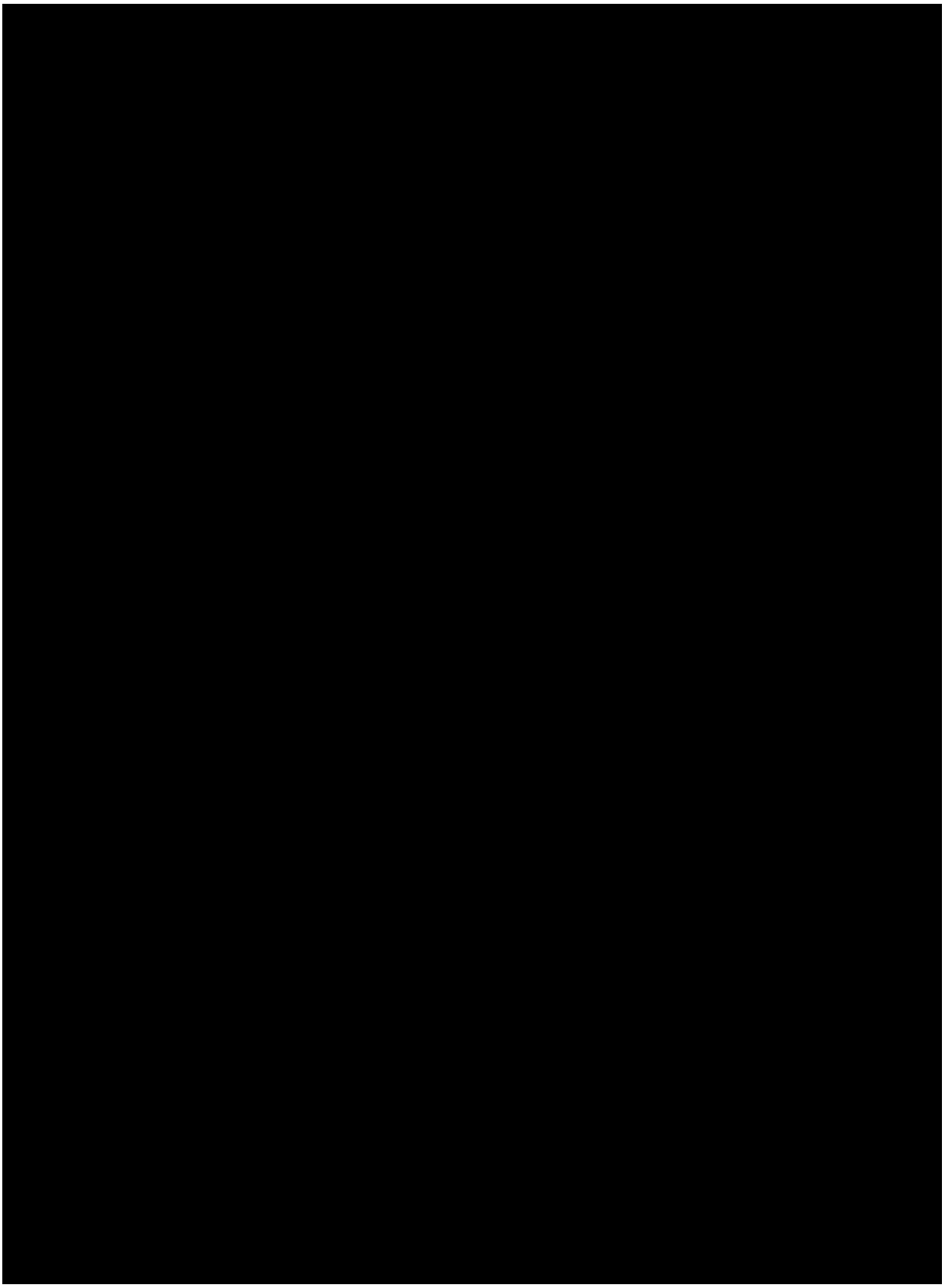
5.2.2 Secondary endpoint(s)

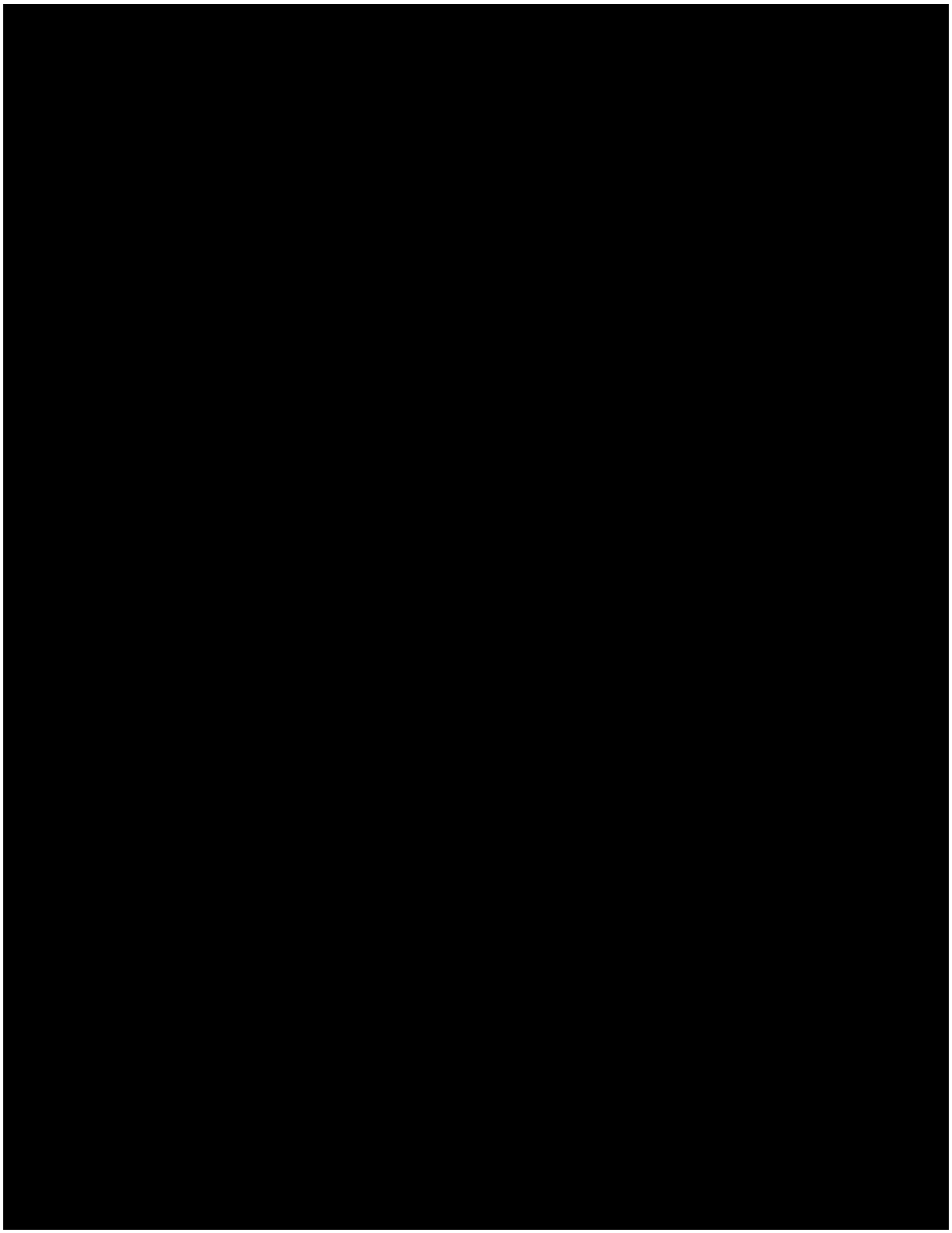
The secondary endpoints will be used as stated in the NIS Protocol Section 5.1.1.

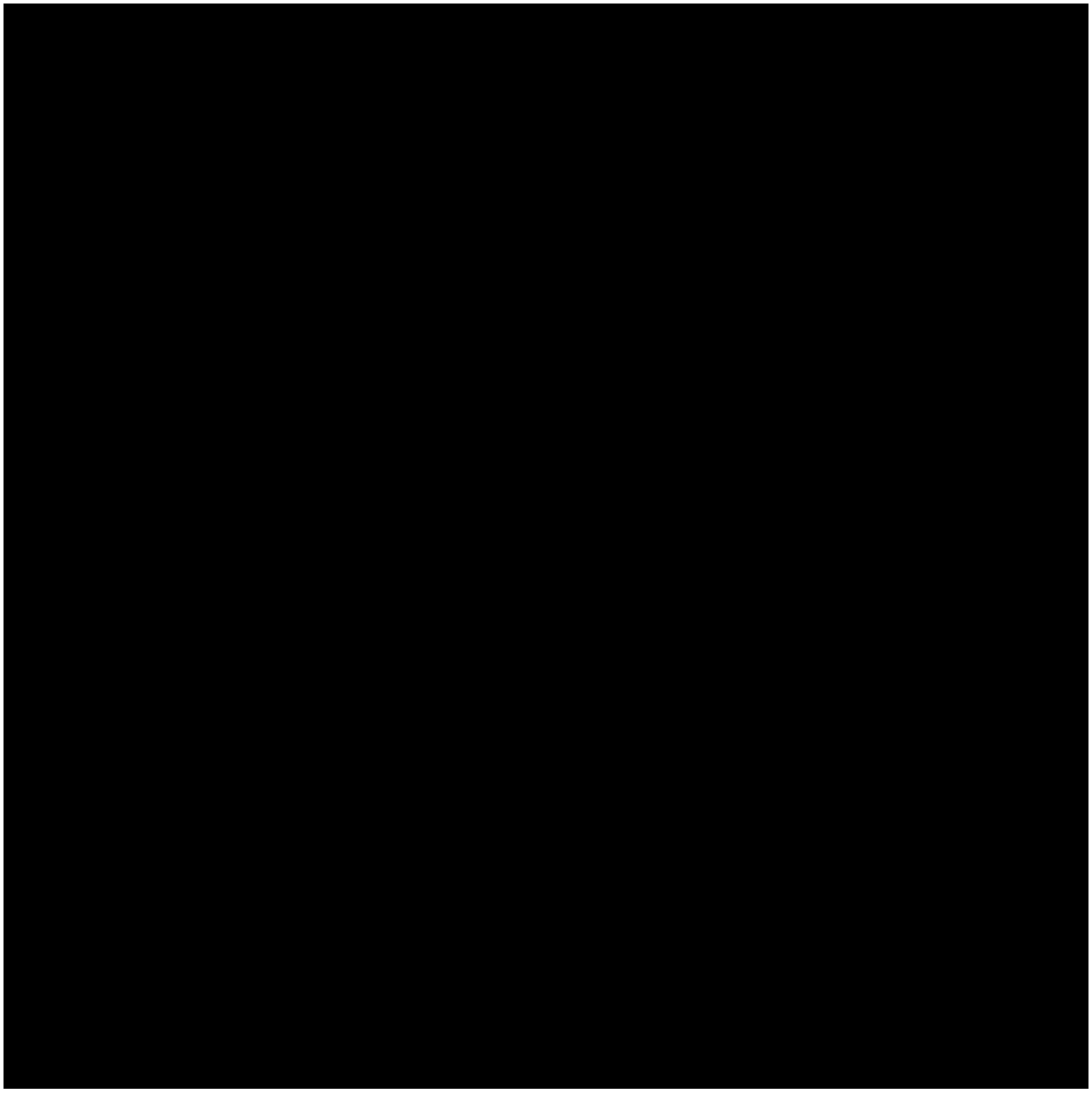












6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatments, please refer to NIS Protocol Section 4. The technical specification for treatment set-up is described in the analysis data set (ADS) plan. For efficacy analyses, data up to 7 days after last treatment intake will be considered as on treatment for HbA1c and 1 day for FPG. For safety analyses, data up to 7 days after last treatment intake will be considered as on treatment for AE, 1 day for weight, blood pressure and pulse and 3 days for laboratory measurements.

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important PVs. The right-most column describes which PVs will be used to exclude patients from the different patient analysis sets. The final decision about which patients will be excluded from analysis sets will be taken during the course of the study and at report planning meetings before database lock at the latest.

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Example/Comment	Method	Excluded from
A		**Entrance criteria not met**			
	A1.1	No type 2 diabetes		Automated	Efficacy
	A1.2	Patient received JARDIANCE® treatment before registration		Manual	All
B		**Informed consent**			
C		**Trial medication and randomisation**			
	C1	Incorrect trial medication taken			
	C1.1	No treatment with JARDIANCE®		Automated	All
E		**Missing data**			
	E1	No baseline value	No available baseline value of HbA1c and FPG for efficacy analysis	Automated	Efficacy
G		**Trial specific**			
	G1	**Invalid registration**			
	G1.1	No patient visit after entry	Patient made no visit after the entry	Automated	All
	G1.2	Multiple registration	Patient who were already registered in this trial or over the two trials(1245.94 and 1245.98) 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		Manual	All
	G1.4	Patient started JARDIANCE® treatment out of registration period	Patients who started treatment after the end of registration period(31May2017) *Patients who started before contract period are not entered.	Automated	All
	G1.5	Not continuous investigation		Manual	All

6.3 PATIENT SETS ANALYSED

The following two analysis sets are defined as in NIS Protocol Section 7.3. The safety set will be the basis of all demographic, baseline and safety analyses. Efficacy analysis will be on basis of the efficacy set.

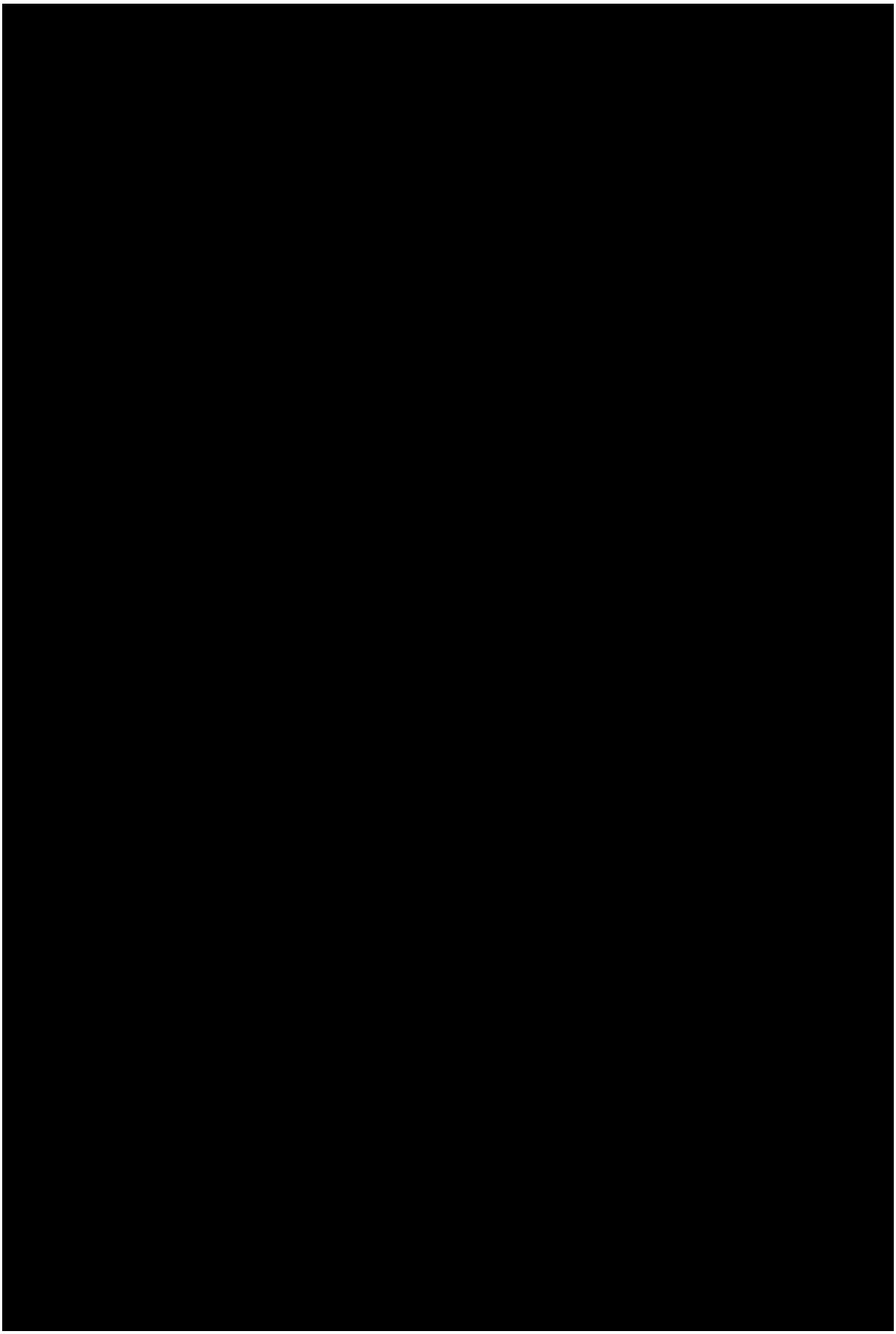
- Safety set:
  This patient set includes all patients who didn't have important PVs regarding safety and regulatory issues as marked "All" in Table 6.2: 1.

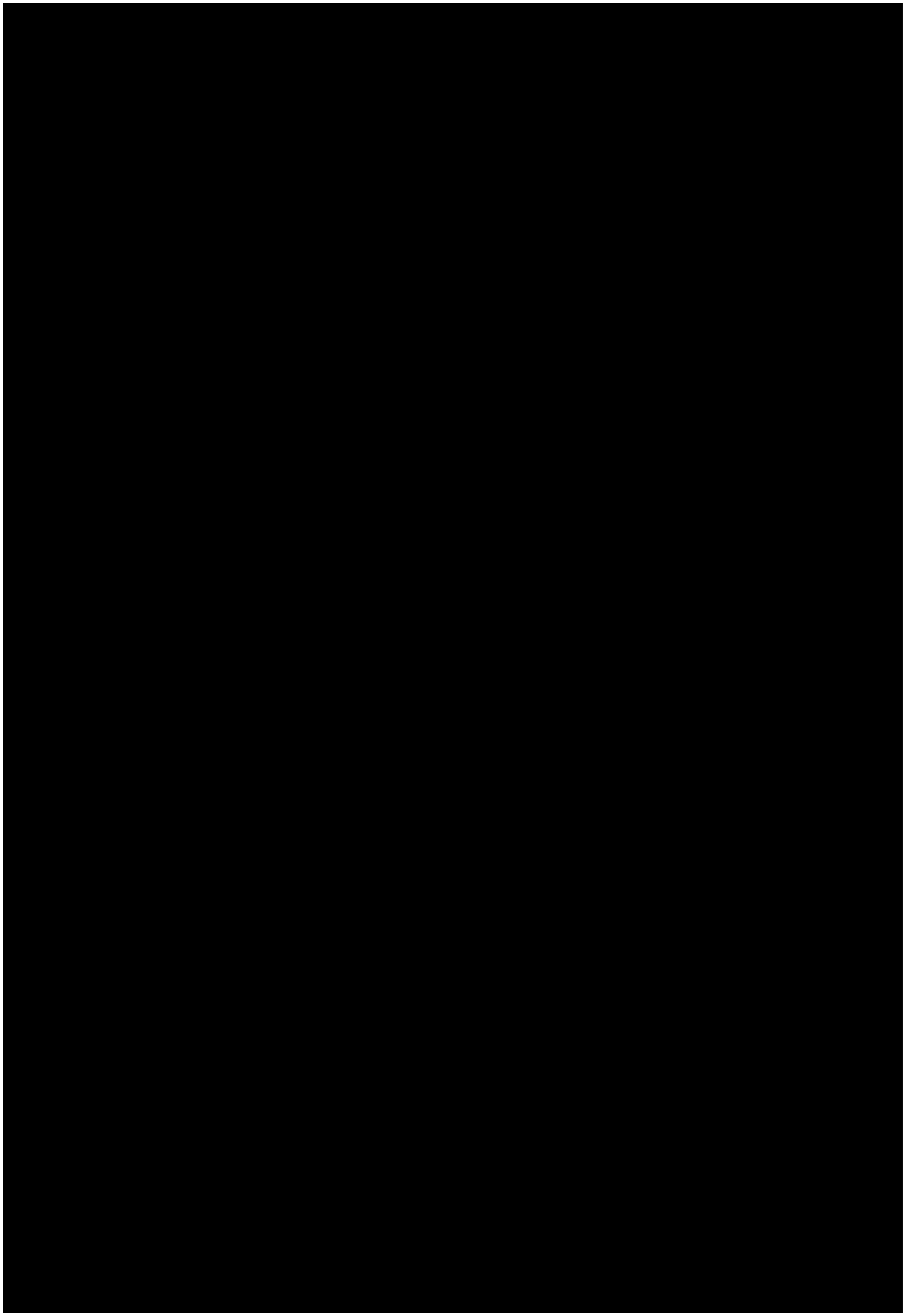
- Efficacy set:
  This patient set includes all patients with JARDIANCE® in the safety set who have at least one available on-treatment HbA1c or FPG value with Type II diabetes mellitus.

Table 6.3: 1 Patient sets analysed

	Patient set	
Class of endpoint	Safety set	Efficacy set
Secondary endpoints		X
Primary endpoints, safety endpoints, demographic/baseline endpoints & treatment exposure	X	

[redacted]





[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because centre is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

No imputation will be performed in efficacy and safety analyses. This rule will not apply for AEs. Missing or incomplete AE dates are imputed according to BI standards ('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/07/01
yyyy	mm	Null or "Unknown"	yyyymm	yyyy/mm/15

If the date of data which is collected as after treatment of JARDIANCE® in the CRF is before start of JARDIANCE®, they will be set to missing. This rule is not to be applied for AEs.

Date of last JARDIANCE® intake:
To calculate duration of JARDIANCE® treatment at an interim analysis, the date is imputed with the following date according to the book number.

Book1: the first treatment date + 83 days (Week 12)
Book2: the first treatment date +363 days (Week 52)
Book3: the first treatment date +727 days (Week 104)
Book4: the first treatment date +1091 days (Week 156).

At DBL, the last date in the book is imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

With regard to efficacy and safety endpoints, the term "baseline" refers to the last observed measurement prior to administration of JARDIANCE®.
Efficacy analyses will be performed based on calculated visits as shown in Table 6.7: 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 6.7: 1 Baseline, time windows and calculated visits

		Time window (actual days on treatment)	
Week label	Planned days	Start	End
Baseline		The last observed measurement prior to or on the first administration of JARDIANCE®	
Week 12	84	1	133
Week 26	182	134	231
Week 40	280	232	322
Week 52	364	323	406
Week 64	448	407	497
Week 78	546	498	637
Week 104	728	638	819
Week 130	910	820	1001
Week 156	1092	1002	End of study

7. PLANNED ANALYSIS

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

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

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to 2 decimal places. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded by the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Only descriptive statistics are planned for concomitant diseases.

Concomitant medication will be coded by latest version of “Nihon-iyakuhinshu”.

7.3 TREATMENT COMPLIANCE

It is not planned to analyse treatment compliance.

7.4 PRIMARY ENDPOINT(S)

There is no primary endpoint for efficacy as the primary objective of the PMS study is the evaluation of safety.

7.4.1 Primary analysis of the primary endpoint(s)

The analysis will be performed as defined in the NIS Protocol (see the NIS Protocol Section 7.3.1).

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint(s)

The subgroup analysis will be performed (see Section 6.4).

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

7.5.1.1 Primary analysis of the key secondary endpoint(s)

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

7.5.1.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

For the change from baseline in HbA1c and FPG at the last observation, descriptive statistics will be calculated based on the efficacy set. A 95% confidence interval for the mean change from baseline will also be calculated.

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the safety set.

7.8.1 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.

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)).

An overall summary of adverse events will be presented.
The frequency of patients with the following items will be summarized by primary SOC and PT.

- AEs
- ADRs
- serious AEs
- serious ADRs
- AEs leading to death
- ADRs leading to death
- AEs leading to discontinuation
- ADRs leading to discontinuation

AEs will also be reported by intensity. The frequency of patients with ADRs occurred in summer (the onset date is in June, July, August, or September) will also be summarized.

In addition, summaries for the time to onset of first episode for the ADRs will be tabulated, by duration (<2weeks, 2 to <4 weeks, 4 to <6 weeks, 6 to <8 weeks, 8 to <10 weeks, 10 to <12 weeks, 12 to <36 weeks , 36 to <60 weeks, 60 weeks to <72weeks, 72 weeks to 84 weeks

to <96weeks, 96 weeks to <108weeks, 108 weeks to <120weeks, 120 weeks to <132weeks, 132 weeks to <144weeks, 144 weeks to <156weeks, ≥156 weeks), by primary SOC, and PT.

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

An ADR is defined as an AE for which either the investigator or the sponsor (or both) assess the causal relationship to JARDIANCE® either as "Possibility high", "Possibility low", or "Unknown".

A serious AE is defined as an AE for which either the investigator or the sponsor (or both) assess the seriousness as "Serious".

AE analyses will be carried out after integrating AE data from CRF and AE data from Local PV safety database (Perceive).

In addition, events coded as "no adverse event", etc. will not be included in the AE analyses. The list of codes will be provided by Drug Safety.

<u>Priority survey items, Important identified risk, Important potential risks and Significant ADRs</u>

The following AEs are summarised on the basis of the Standardised MedDRA queries (SMQs) or Boehringer Ingelheim customised MedDRA query (BICMQ) by primary SOC and PT.
*:1 ADRs are also summarised.
*2: ADRs occurred in summer (the onset date is in June, July, August, or September) are also summarized.

Risk ratios with 95% confidence intervals will be shown for subgroup analyses. In case that there will be the significant difference between each factor, the frequency of patients with drug related AEs (ADRs) and with serious AEs will be summarized by primary SOC and PT. Due to the high number of exploratory subgroup analyses, it is recognised that the likelihood of chance findings is high and therefore subgroup results should be interpreted with caution.

7.8.2 Laboratory data

Mean +- SD table and figure by visit of hematocrit, hemoglobin, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride and eGFR. To calculate eGFR, see the NIS Protocol Section 5.3.3. Change from baseline of weight by visit will be also displayed.

7.8.3 Vital signs

Change from baseline of blood pressure (SBP and DBP) and pulse by visit.

7.8.4 ECG

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

7.8.5 Others

No plan for other safety parameters.

8. REFERENCES

1 *BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version; KMED.
2 *BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
1	**22-Oct-20**	[redacted]	None	This is the final TSAP