TRIAL STATISTICAL ANALYSIS PLAN

c30393090 -01

BI Trial No.:	1275.0026
Title:	Post Marketing Surveillance in Japan on Long Term Drug Use of TRADIANCE® Combination Tablets AP and BP in Patients with type 2 Diabetes Mellitus
Investigational Product(s):	Empagliflozin + Linagliptin
Responsible trial statistician(s):	[redacted] Address: [redacted] Phone: [redacted] Fax: [redacted]
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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
ADS	Analysis Data Set
AE	Adverse Event
BICMQ	Boehringer Ingelheim Customised MedDRA Query
BMI	Body Mass Index
CRF	Case Report Form
DPP-IV	Dipeptidyl Peptidase-IV
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOT	End-of-Treatment
FPG	Fasting Plasma Glucose
GLP-1	Glucagon-Like Peptide-1
HbA1c	Glycosylated haemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-interventional Study
NYHA	New York Heart Association Functional Classification
PMS	Post-Marketing Surveillance
PT	Preferred Term
PV	Protocol Violation
Q1	Lower quartile
Q3	Upper quartile
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SD	Standard deviation
SGLT2	Sodium Glucose cotransporter 2
SMQ	Standardised MedDRA query
SOC	System organ class

Term	Definition / description
TSAP	Trial Statistical Analysis Plan

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 TSAP assumes familiarity with the Non-interventional Study Protocol (NIS Protocol), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in NIS Protocol Section 9.7 “DATA ANALYSIS”. 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 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

No change has been made in the planned analyses from the statistical methods described in the NIS Protocol.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

Incidences of adverse drug reactions (ADRs)

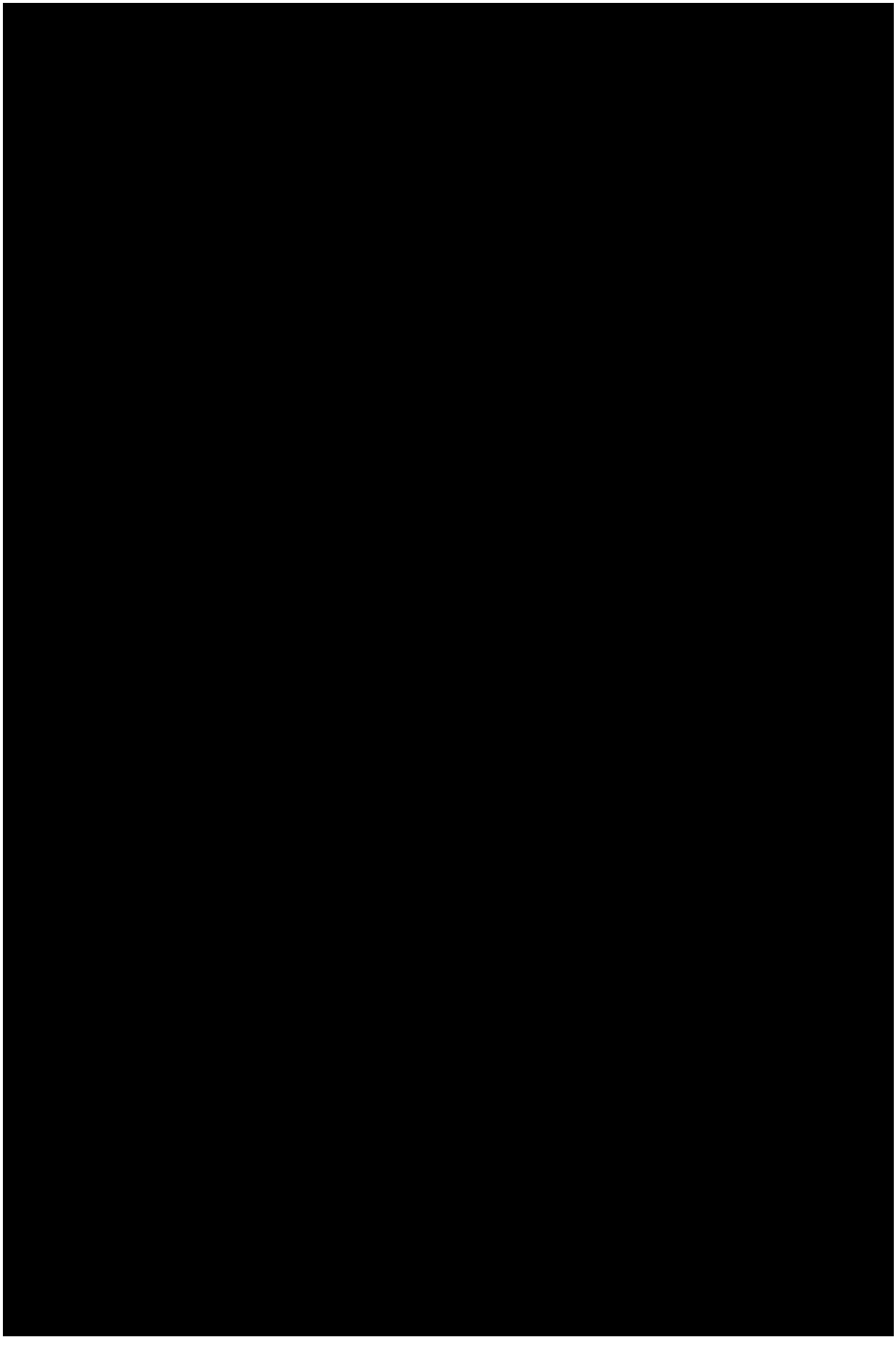
5.2 SECONDARY ENDPOINT(S)

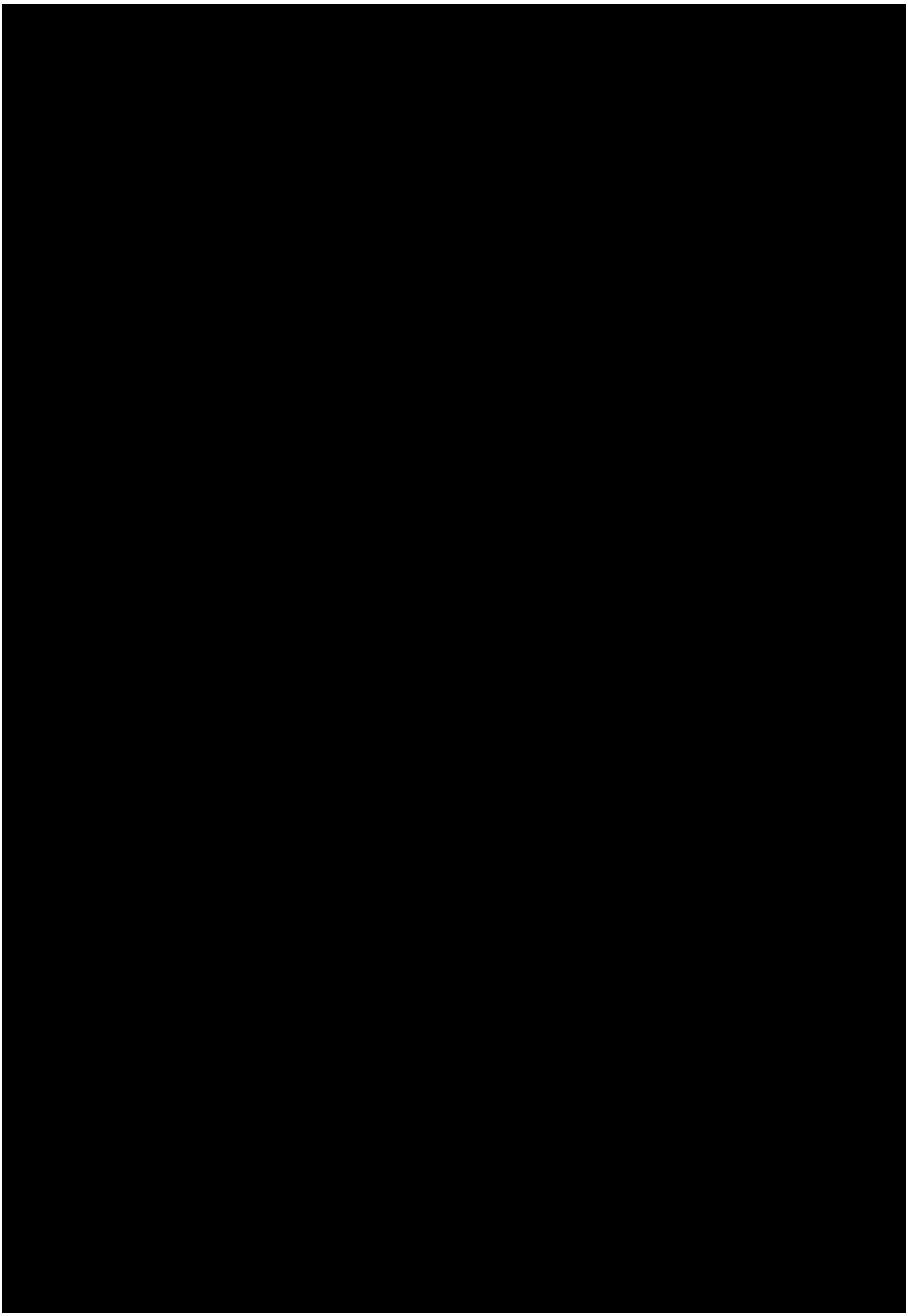
5.2.1 Key secondary endpoint(s)

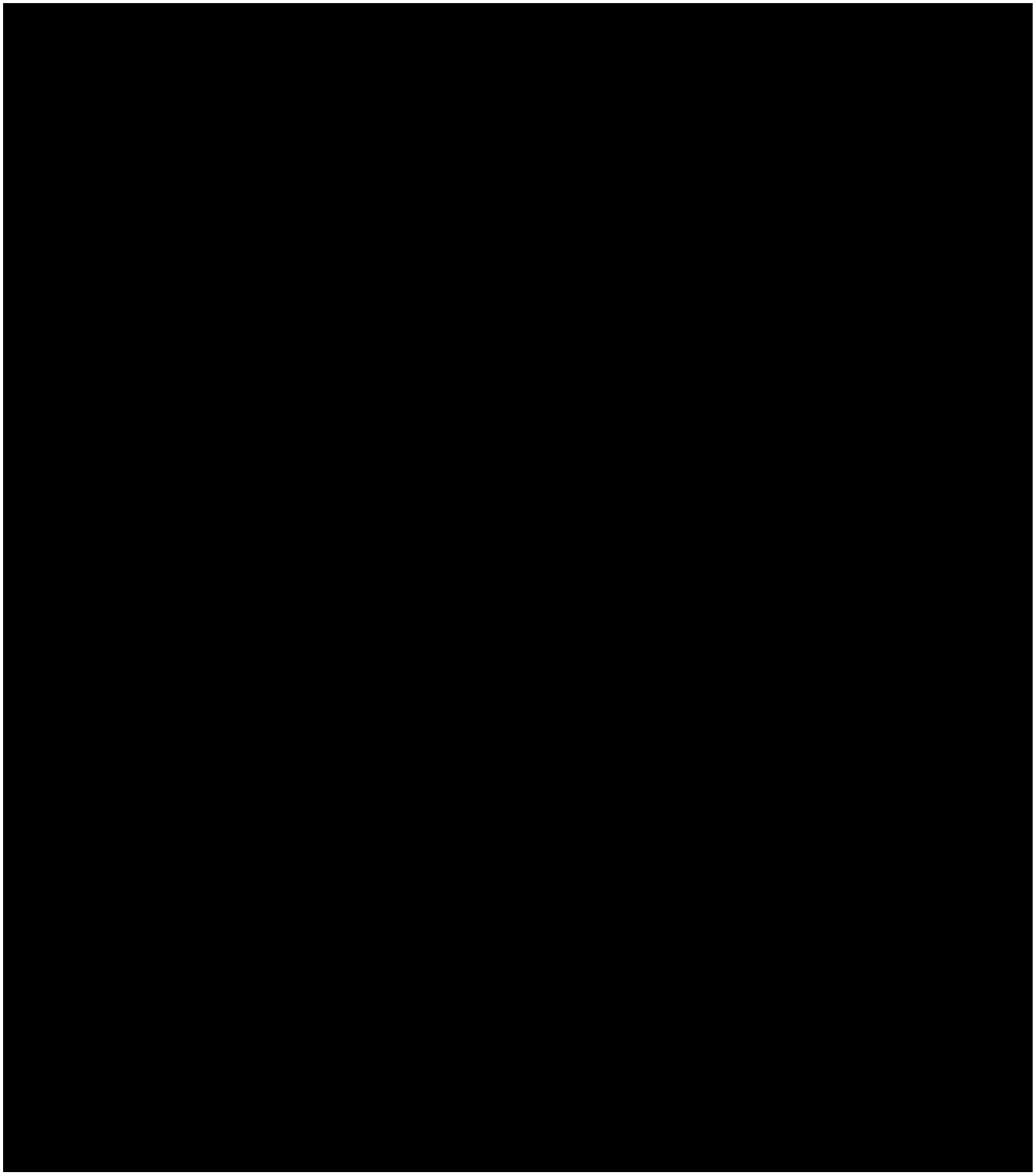
This section is not applicable as no key secondary endpoint has been specified in the protocol.

5.2.2 Secondary endpoint(s)

None







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 effectiveness 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 6.2:1 defines the different categories of important PVs. The final column describes which PVs will be used to exclude patients from each patient analysis sets. Observed PVs will be concluded as important or not important at report planning meetings before database lock at the latest.

Table 6.2:1 Important protocol violations

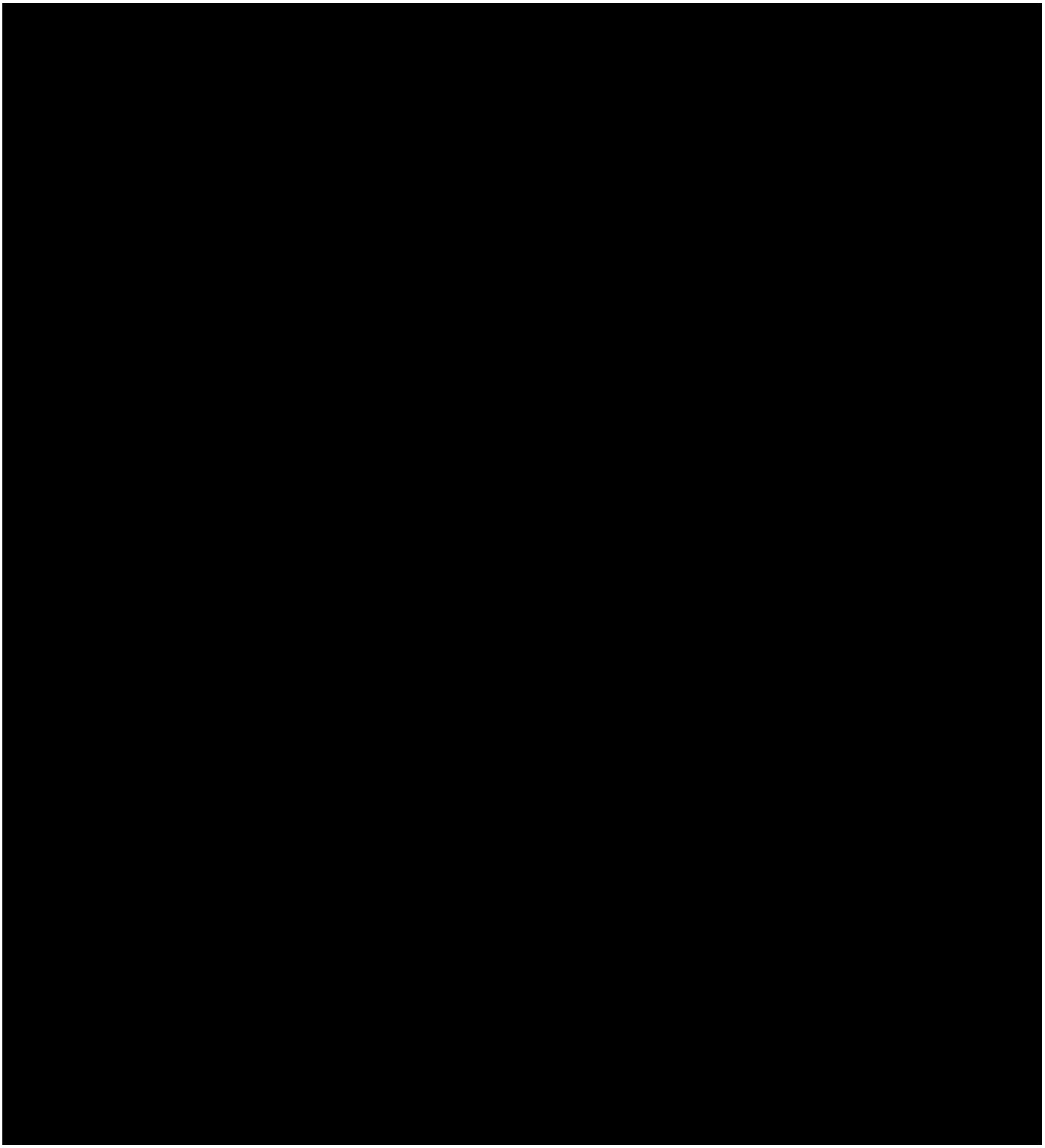
Category/ Code		Description	Example/Comment	Method	Excluded from
A		**Entrance criteria not met**			
	A1.1	No type 2 diabetes		Automated	Effectiveness
	A1.2	Patient received TRADIANCE ® treatment before registration		Automated	All
B		**Informed consent**			
C		**Trial medication and randomization**			
	C1	Incorrect trial medication taken			
	C1.1	No treatment with TRADIANCE ®		Automated	All
E		**Missing data**			
	E1	No values of both HbA1c and FPG at both baseline and visit except for baseline	No available values of both HbA1c and FPG at both baseline and visit except for baseline	Automated	Effectiveness
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 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 TRADIANCE ® treatment out of registration period		Manual	All
	G1.5	Not continuous investigation		Manual	All

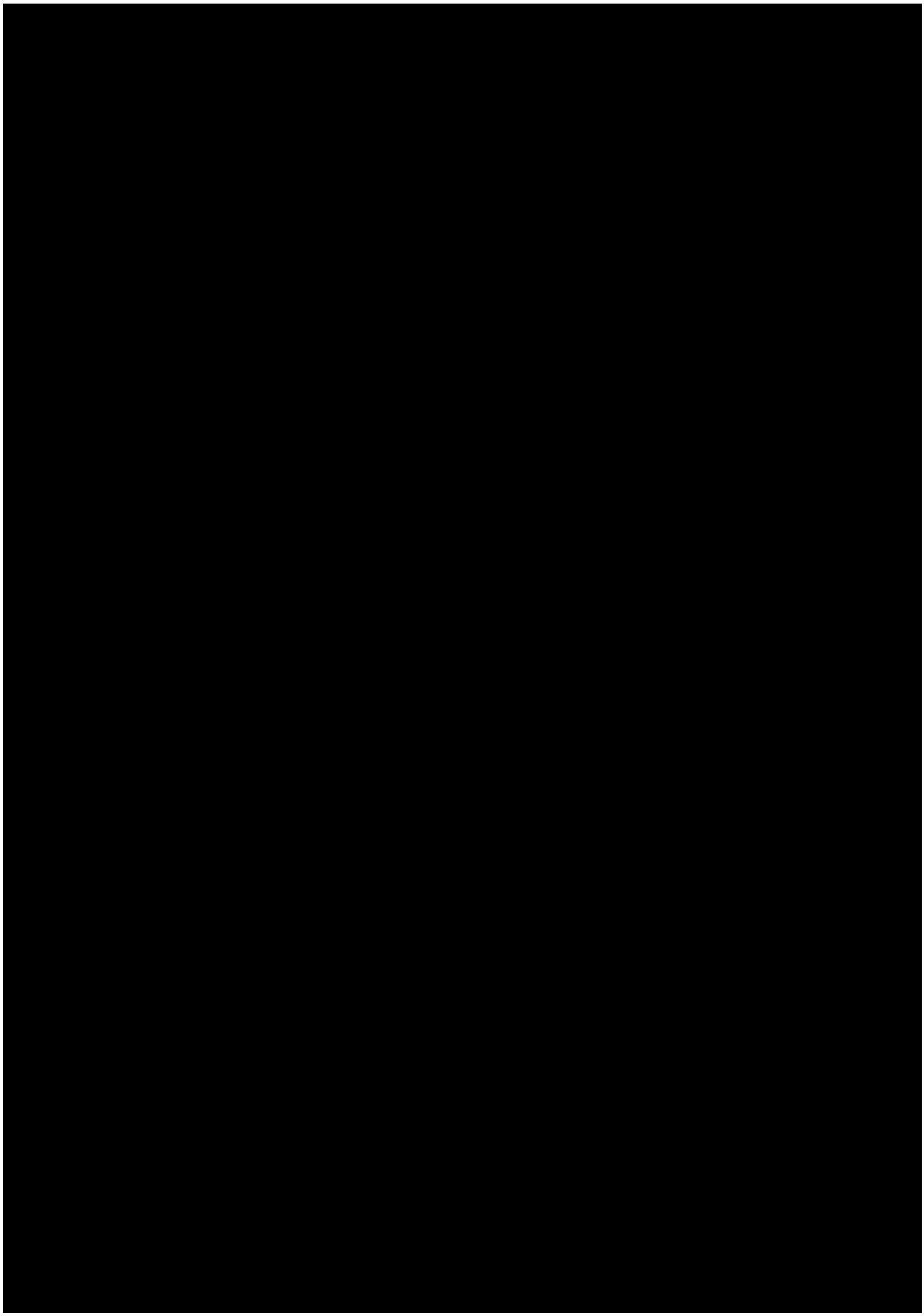
6.3 PATIENT SETS ANALYSED

The safety set and the effectiveness set are defined as follows. The safety set will be the basis of all demographic, baseline and safety analyses. Effectiveness analysis will be on basis of the effectiveness set.

- Safety set:
  This patient set includes all patients who had no invalid registration, who were documented to have taken at least one dose of TRADIANCE®.

- Effectiveness set:
  This patient set includes all patients with TRADIANCE® in the safety set who have a baseline and at least one available on-treatment HbA1c or FPG value.





6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

If only year of date is non-missing, then missing date are imputed 01 JUL of reported year. Else if only year and month of date are non-missing, then missing date is imputed 15 of the reported months.

Safety:

[redacted]

Effectiveness:
Missing effectiveness data will not be imputed.
Date of last TRADIANCE ® intake:
To calculate duration of TRADIANCE ® treatment at an interim analysis, the date is imputed with the date of the snapshot.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

With regard to effectiveness and safety endpoints, the term “baseline” refers to the last observed measurement prior to administration of TRADIANCE®. Observation on the same day as administration of TRADIANCE® is "baseline".

Effectiveness 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	0	NA	1
Week12	84	2	133
Week26	182	134	231
Week40	280	232	322
Week52/EOT	364	323	End of study

7. PLANNED ANALYSIS

For End-Of-Treatment (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 2 decimal places. The category missing will be displayed only if there are actually missing values.
Caution: Frequencies for combination drugs of antidiabetic medication must be tabulated by each active pharmaceutical ingredient.

In addition, individual values on demographics, safety and effectiveness will be presented in subject data listings.

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). Frequency of patients will be summarized by system organ class (SOC) and preferred term (PT).
Concomitant medication will be coded by latest version of “Nihon Iyakuhinshu” (2).

7.3 TREATMENT COMPLIANCE

Compliance data is not collected in this study

7.4 PRIMARY ENDPOINT (S)

The primary outcome of this study is the incidence of adverse drug reactions (ADRs).
For the analysis of the primary endpoint, see Section 7.8.

7.5 SECONDARY ENDPOINT (S)

None

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 treated set.

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events 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.

For further details on summarization of AE data, please refer to the guideline “Analysis and Presentation of Adverse Event Data from Clinical Trials” (3).

AE analyses will be carried out after integrating AE data from CRF and AE data from perceive system. In addition, AEs coded as "no adverse event" will not be included in the AE analyses.

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intakes till 7 days after last drug intake during observation period will be analysed. For details on the treatment definition, see Section 6.1.

An overall summary of adverse events will be presented.

The frequency of patients with AEs, severe AEs, drug related AEs, AEs leading to discontinuation, drug related AEs leading to discontinuation, outcome for serious AEs and outcome for serious drug related AEs are tabulated.

The frequency of patients with AEs, ADRs, SAEs and SADRs will be summarised by primary system organ class and preferred term. Patients with 'priority survey items' according to the drug's Risk Management Plan will be summarised separately. The analysis of "priority survey items", "Important identified risks", "Important potential risks" will be conducted for AEs, ADRs.

It is created that table of patient with ADRs in each subgroup defined in Section 6.4. Not only the frequency but also the odds ratios are displayed.

In addition summaries for the time to onset of first episode for the ADRs will be tabulated, by duration (<= 12 week, 12 to <=26 weeks, 26 to <=52 weeks, > 52), by primary system organ class and preferred term.

Adverse events leading to death and adverse events leading to discontinuation will be also summarised by treatment, primary system organ class and preferred term.

An ADR is defined as an AE for which either the investigator or the sponsor (or both) assess the causal relationship to TRADIANCE® as "Yes". A SAE is defined as an AE for which either the investigator or the sponsor (or both) assess the seriousness either as "Serious".

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).

The following AEs are detected on the basis of the Standardised MedDRA queries (SMQs) or Boehringer Ingelheim customised MedDRA query (BICMQ) (details are described in ADS plan).

Safety will be assessed by treatment exposure time adjusted incidence rate (n in 100 patient years) of ADRs.

Important identified risk, Important potential risk and significant ADRs.

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.
*: ADRs are also summarised.
Important identified risks
- Urinary tract infection *
- Genital infection *
- Volume depletion *
- Hypoglycaemia *
- Pancreatitis *
- Ketone body increase/Ketoacidosis *
- Polyuria/Pollakiuria *
- Intestinal obstruction *
- Hepatic function disorders *

Important potential risks
- Renal disorder *
- Bone fracture *
- Skin lesion *
- Bullous pemphigoid *
- Interstitial pneumonitis *
- Infection *
- Malignant tumour *
- Cardiac failure *
- Influence of weight decreased on safety *
- Lower limb amputation *

Risk ratios with 95% confidence intervals will be shown for subgroup analysis. In case that there will be the significant difference each factor, the frequency of patients with 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

Descriptive statistics (see summary statistics at 7. Planned analysis) of eGFR at each calculated visit will be summarized in the table.

7.8.3 Vital signs

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

7.8.4 ECG

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

7.8.5 Others

No plan for other safety parameters.

8. REFERENCES

10. HISTORY TABLE

Table 10:1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**24 –May-2021**	[redacted]	None	This is the final TSAP without any modification