Trial Statistical Analysis Plan

c02160768-01

BI Trial No.:	1218.147
Title:	Post Marketing Surveillance on Long Term Drug Use of Trazenta Tablets as add-on therapy in Patients with type 2 Diabetes Mellitus
Investigational Product(s):	Linagliptin, BI 1356
Responsible trial statistician(s):	Address: Phone: Fax:
Date of statistical analysis plan:	12 October2018 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADR	Adverse Drug Reactions
ADS	Analysis data set
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	body mass index
eGFR	Estimated Glomerular Filtration Rate
HbA1c	Glycosylated haemoglobin
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
SMQ	Standardised MedDRA query
SOC	System organ class
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

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 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 5.1.1). The primary endpoint for safety is incidence 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 NIS protocol.

5.2.2 Secondary endpoint(s)

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

5.3 FURTHER ENDPOINT(S)

Further endpoints are the other endpoints as stated in the NIS Protocol Section 5.1.1.

5.4 OTHER VARIABLE(S)

Demographic and baseline characteristics

- Sex (Male, Female)
- Age [years]
  Actual age based on first administration of Trazenta®
- Age categories 1: ≤50 years, 51 to 64 years, 65 to 74 years, ≥75 years
- Age categories 2: <65 years, ≥65 years
- Height [cm]
- Body weight [kg]
- Body weight categories: ≤50 kg, >50 to 70 kg, >70 to 90 kg, >90 kg
- Body mass index (BMI) [kg/m^2]
  BMI [kg/m^2] = weight [kg] / (height [m])^2
- BMI categories 1: <25 kg/m^2, 25 to <30 kg/m^2, ≥30 kg/m^2
- BMI categories 2: <25 kg/m^2, ≥25 kg/m^2
- BMI categories 3: <30 kg/m^2, ≥30 kg/m^2
- Waist circumference [cm]
- Renal dysfunction : estimated glomerular filtration rate (eGFR) [mL/min/1.73m^2]
- eGFR categories 1: ≥90 mL/min/1.73m^2(Normal), 60 to <90 mL/min/1.73m^2(Mild), 30 to <60 mL/min/1.73m^2(Moderate), 15 to <30 mL/min/1.73m^2(Severe), <15 mL/min/1.73m^2 (Endstage)

- eGFR categories 2: ≥60 mL/min/1.73m^2, <60 mL/min/1.73m^2
- Hepatic dysfunction categories 1: (>ULN [35 U/L] of AST, >ULN of ALT [35 U/L], >ULN of total bilirubin [17 umol/L], or >ULN of ALP [120 U/L]), or other

  In case > ULN of AST and CK increase (>400 U/L), patients do not include in hepatic dysfunction.

  Conversion factors:
  For total bilirubin: 17.102787754404 x [mg/dL] = [umol/L]
  For AST, ALT, ALP: [IU/L] = [U/L]
- Hepatic dysfunction categories 2: ≤ 1*ULN, >1*ULN to ≤ 2*ULN, >2*ULN to ≤ 3*ULN, >3*ULN
  Note: worst value of AST, ALT, total bilirubin, or ALP will be used for the categorization
- Hepatic dysfunction categories 3: (Yes, No, Unknown)
  - Hepatic disorders (Narrow) (SMQ 20000005)
  - Biliary disorders (Narrow) (SMQ 20000118)
    Note: Presence at baseline is yes
- Patient status: (In patient, Out patient)
- Indication (Type II diabetes mellitus, Other)
- Smoking status (Never, Ex-smoker, Smoker, Unknown)
- Duration of diabetes (≤1 years, >1 to 5 years, >5 years, Unknown)
  [First administration of Trazenta® (or other oral antidiabetic drug) – first diagnosis of type 2 diabetes mellitus + 1 (if negative value due to the missing and imputation, then 1)] / 365.25
- Hypersensitivity factor (Yes, No, Unknown)
- Concomitant diagnosis (Yes, No, Unknown)
- Cardiovascular (SMQ) history (Yes, No, Unknown)
  - Ischemic heart disease (SMQ: 20000043)
  - Cardiac failure (SMQ: 20000004)
  - Cerebrovascular disorders (SMQ: 20000060)
  - Torsade de pointes/QT prolongation (SMQ: 20000001)
    Note: regardless of presence at baseline
- Baseline HbA1c [%] (based on NGSP)
- Baseline HbA1c categories: <7.0%, 7 to <8%, 8 to <9%, ≥9%
- Baseline FPG [mg/dL]
- Baseline FPG categories: <126 mg/dL, 126 to <140 mg/dL, 140 to <200 mg/dL, ≥200 mg/dL
- Number of prior antidiabetic medication (class) (none, one, two or more)
- Number of back ground antidiabetic medication (class) at baseline(none, one, two or more)
- Prior antidiabetic medication 1 (Yes, No, Unknown)
- Prior antidiabetic medication 2: (only, combination with other DM medication, none)
  - Sulfonylurea (only, combination with other DM medication, none)
  - Biguanide (only, combination with other DM medication, none)
  - Thiazolidinedione (only, combination with other DM medication, none)

  - Alpha-glucosidase inhibitor (only, combination with other DM medication, none)
  - DPP-IV inhibitor (except Linagliptin) (only, combination with other DM medication, none)
  - Glinide (only, combination with other DM medication, none)
  - SGLT2 inhibitor (only, combination with other DM medication, none)
  - Insulin (only, combination with other DM medication, none)
  - GLP-1 receptor agonist(only, combination with other DM medication, none)
- Back ground antidiabetic medication at baseline:
  - Sulfonylurea (only, combination with other DM medication, none)
  - Biguanide (only, combination with other DM medication, none)
  - Thiazolidinedione (only, combination with other DM medication, none)
  - Alpha-glucosidase inhibitor (only, combination with other DM medication, none)
  - DPP-IV inhibitor (except Linagliptin) (only, combination with other DM medication, none)
  - Glinide (only, combination with other DM medication, none)
  - SGLT2 inhibitor (only, combination with other DM medication, none)
  - Insulin (only, combination with other DM medication, none)
  - Insulin use at baseline (Yes, No, Unknown)
  - GLP-1 receptor agonist(only, combination with other DM medication, none)

Table 5.4 Categories for antidiabetic medication based on Nihon-iyakuhinshu

Class	Medication name	Code
Sulfonylurea		First 4 numbers = 3961
Biguanide		First 4 numbers = 3962
Thiazolidinedione	PIOGLITAZONE HYDROCHLORIDE	First 7 numbers = 3969007
Alpha-glucosidase inhibitor	ACARBOSE	First 7 numbers = 3969003
	VOGLIBOSE	First 7 numbers = 3969004
	MIGLITOL	First 7 numbers = 3969009
DPP-IV inhibitor	SITAGLIPTIN PHOSPHATE HYDRATE	First 7 numbers = 3969010
	VILDAGLIPTIN	First 7 numbers = 3969011
	ALOGLIPTIN BENZOATE	First 7 numbers = 3969012
	LINAGLIPTIN	First 7 numbers = 3969014
	TENELIGLIPTIN HYDROBROMIDE HYDRATE	First 7 numbers = 3969015
	ANAGLIPTIN	First 7 numbers = 3969016
	SAXAGLIPTIN HYDRATE	First 7 numbers = 3969017
	TRELAGLIPTIN SUCCINATE	First 7 numbers = 3969024
	OMARIGLIPTIN	First 7 numbers = 3969025
Glinide	NATEGLINIDE	First 7 numbers = 3969006
	MITIGLINIDE CALCIUM HYDRATE	First 7 numbers = 3969008
	REPAGLINIDE	First 7 numbers = 3969013
SGLT2 inhibitor	IPRAGLIFLOZIN	First 7 numbers = 3969018
	DAPAGLIFLOZIN	First 7 numbers = 3969019
	LUSEOGLIFLOZIN	First 7 numbers = 3969020
	TOFOGLIFLOZIN	First 7 numbers = 3969021
	CANAGLIFLOZIN	First 7 numbers = 3969022
	EMPAGLIFLOZIN	First 7 numbers = 3969023
GLP-1 receptor agonist	LIRAGLUTIDE	First 7 numbers = 2499410
	EXENATIDE	First 7 numbers = 2499411
	LIXISENATIDE	First 7 numbers = 2499415
	DULAGLUTIDE	First 7 numbers = 2499416
Insulin		First 4 numbers = 2492
Other		First 3 numbers = 396 but not above Or any combination

Treatment exposure

Duration of Trazenta® treatment [days] = Treatment end date – Treatment start date + 1

If a patient interrupts the Trazenta®, such duration will not be included in the treatment exposure.

- First dose of Trazenta®:(5mg, Other)

Pregnancy status

Pregnancy status reported at any time during the observation period: (Yes, No, Unknown)

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 For safety analyses, data up to 7 days after last treatment intake will be considered as on treatment for AE.

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important protocol violations (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	Excluded from
A		**Entrance criteria not met**		
	A1.1	No type 2 diabetes		Efficacy
	A1.2	Patient received Trazenta® treatment before registration		All
	A1.5	Patient not treated as add-on therapy at baseline	1) No antidiabetic medication until start of TRZ, and start only TRZ 2) Used antidiabetic medication but stopped before start of TRZ. And start only TRZ. 3) Used antidiabetic medication but stopped at start of TRZ. And start only TRZ.	All
	A1.6	Patient start TRZ with one more OAD, but no antidiabetic medication before starting TRZ.	No antidiabetic medication until start of TRZ, but start antidiabetic medication with TRZ	Efficacy
B		**Informed consent**		
C		**Trial medication and randomization**		
C1		**Incorrect study medication taken**		
	C1.1	No treatment with Trazenta®		All
E		**Missing data**		

Table 6.2: 1(cont.): Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
	E1	No baseline value	No available baseline value of HbA1c for efficacy analysis	Efficacy
G		**Trial specific**		
G	**G1**	**Invalid registration**		
	G1.1	No patient visit after entry	Patient made no visit after the entry	All
	G1.2	Multiple registration	Patient who were already registered this trial with another patient ID In this case, all data for the later patient ID will not be used.	All
	G1.3	Registration rule not followed		All
	G1.4	Patient started Trazenta® treatment without registration period		All
	G1.5	Not continuous investigation		All

6.3 SUBJECT 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 had no invalid registration, who were dispensed Trazenta® and were documented to have taken at least one dose of Trazenta®.

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

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

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of Missing and Incomplete AE Dates"). (2)

No imputation will be performed in efficacy and safety analyses.

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

YEAR	MONTH	DAY	YMD	DT
"Unknown" (tick-box)			UNKNOWN	.
<2007	Null	Null	2007	2007/07/01
yyyy	Null or "Unknown"	Null	yyyy	yyyy/07/01
yyyy	*Mm*	Null or "Unknown"	yyyymm	yyyy/mm/15
yyyy	*Mm*	"First ten days of the month"	yyyymm "First ten days of the month"	yyyy/mm/01
yyyy	*Mm*	"Second ten days of the month"	yyyymm "Second ten days of the month"	yyyy/mm/11
yyyy	*Mm*	"Third ten days of the month"	yyyymm "Third ten days of the month"	yyyy/mm/21

If the date of data which is collected as after treatment of Trazenta® in the CRF is before start of Trazenta®, these data are regarded as erroneous and will be set to missing.

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 Trazenta® including the first administration date.

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, 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
Week 12	84	2	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 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 two decimal places. The category missing will be displayed only if there are actually missing values.

Analyses will be performed for overall patients as one treatment group. In addition, same analyses by background medication groups as defined in Table 5.4 will be performed all analyses.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics for the demographic and other baseline characteristics described in Section 5.4 are planned by treatment (background medication and total).

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 summarised by treatment (background medication and total), system organ class (SOC) and preferred term (PT).

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

7.3 TREATMENT COMPLIANCE

It is not planned the analysis for the treatment compliance.

7.4 PRIMARY ENDPOINT(S)

The incidence of adverse drug reactions (ADRs) will be evaluated descriptively as specified in Section 7.8.1.

7.5 SECONDARY ENDPOINT(S)

7.5.1 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 at the last observation, descriptive statistics will be calculated by treatment (background medication and total). A 95% confidence interval for the mean change from baseline will also be calculated by treatment (background medication and total).

7.7 EXTENT OF EXPOSURE

Only descriptive statistics by treatment (background medication and total) are planned for this section of the report. The followings are the categories of exposure-ranges (in weeks):

>0 to 12 weeks, >12 to 26 weeks, >26 to 40 weeks, >40 to 52 weeks, >52 to 64 weeks, >64 to 78 weeks, >78 to 104 weeks,>104 to 130 weeks,>130 to 156 weeks, >156 weeks

7.8 SAFETY ANALYSIS

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 case report form, 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 the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' (1).

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.

Two overall summaries of AEs will be presented. One will be also made for patients including those who were not treated add-on therapy at baseline (i.e. all patients with Trazenta® treatment). Another one will include patients only with add-on therapy at baseline (i.e. safety set). The frequency of patients with AEs,ADRs, and serious AEs will be also summarised by primary SOC and PT in each patient set.

The frequency of patients with ADRs and with serious AEs will be summarised by treatment (background medication and total), primary SOC and PT. AEs will also be reported by intensity.

To compare risks of overall ADR in different patient subgroups, frequency tabulation stratified by different patient subgroups will be provided with odds ratios and exact 95% confidence intervals whenever specified (see Section 6.4). Logistic regression will be used for odds ratio.

In addition, summaries for the time to onset of first episode for the ADRs will be tabulated, by duration (>0 to 12 weeks, >12 to 26 weeks, >26 to 40 weeks, >40 to 52 weeks, >52 to 64 weeks, >64 to 78 weeks, >78 to 104 weeks,>104 to 130 weeks,>130 to 156 weeks, >156 weeks, unknown), primary SOC, and PT.

An ADR is defined as an AE for which either the investigator or the sponsor (or both) assess the causal relationship to Trazenta® either as “Related,” “Probably related,” or “Cannot be denied”. The SOCs will be sorted according to the standard sort order specified by European medicines agency, PTs will be sorted by frequency (within SOC).

7.8.2 Laboratory data

Table and figure of eGFR (measurement value and change from baseline) by week will be created. Use age at baseline for calculation

7.8.3 Vital signs

Table and figure of blood pressure and weight (measurement value and change from baseline) by week will be created.

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 *001-MCG-156: "*Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON.

2 *001-MCG-156_RD-01:* "Handling of Missing and Incomplete AE Dates", current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**12-Oct-18**		None	This is the final TSAP without any modification