SIGNATURE INFORMATION

Document: 1218-0147--protocol

Document No.: U13-1769-01

Title Post Marketing Surveillance on Long Term Drug Use of Trazenta Tablets as add-on therapy in Patients with type 2 Diabetes Mellitus

SIGNATURES (ELECTRONICALLY OBTAINED)

Meaning of Signature:	Signed by:	Date signed: (GMT)
Author-Trial Clinical Monitor		6/7/2013 09:45:21
Author-Trial Statistician		6/7/2013 09:48:13
Approval-Team Member Medicine		6/7/2013 10:33:16
Approval-Other		6/10/2013 00:34:01
Approval-Other		6/11/2013 10:02:55
Approval-Therapeutic Area		6/17/2013 14:10:00
Approval-Medical		6/19/2013 05:49:25

SIGNATURE INFORMATION (continued)

Document 1218-0147--protocol

Document No.: U13-1769-01

Title Post Marketing Surveillance on Long Term Drug Use of Trazenta Tablets as add-on therapy in Patients with type 2 Diabetes Mellitus

SIGNATURES (ELECTRONICALLY OBTAINED)
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Boehringer Ingelheim

Non-interventional Study Protocol

	Document Number: U13-1769-01
BI Study Number:	1218.147
BI Investiational Product(s):	Linagliptin, BI 1356
Title:	Post Marketing Surveillance on Long Term Drug Use of Trazenta® Tablets as add-on therapy in Patients with type 2 Diabetes Mellitus
Clinical Phase:	IV
Trial Clinical Monitor:	Phone: Fax:
Co-ordinating Investigator:	Not applicable
Status:	Final Protocol
Version and Date:	**Version: 1 . Date: 07 Jun 2013**
	Page 1 of 37

NON-INTERVENTIONAL STUDY PROTOCOL SYNOPSIS

Name of company/Marketing Authorisation Holder: Boehringer Ingelheim		**Tabulated Study Protocol**	
Name of finished product: Trazenta ® Tablets			
Name of active ingredient: Linagliptin, BI 1356			
Protocol date: 07 June 2013	**Trial number:** 1218.147		**Revision date:**

Title of study:	Post Marketing Surveillance study on Long term Drug Use of Trazenta® Tablets as add-on therapy in Patients with type 2 Diabetes Mellitus
Co-ordinating Investigator	Not applicable
Study site(s) :	600
Clinical phase:	IV
Objectives:	To investigate the safety and efficacy of long-term daily use of Trazenta® Tablets as add-on therapy in patients with type 2 diabetes mellitus.
Methodology:	Non-interventional, prospective, observational
No. of patients: **Total entered:** **each treatment:**	3,000 3,300 Linagliptin: 3,300
Diagnosis:	Type 2 diabetes mellitus
Main criteria for inclusion:	Male and female patients with type 2 diabetes mellitus who are treated with antidiabetic drugs and have never been treated with Trazenta ® Tablets/ linagliptin before enrollment
Test product(s) : **dose:** **mode of admin. :**	Trazenta ® Tablets 5 mg Oral
Duration of treatment:	156 weeks
Criteria for efficacy*:*	Primary endpoint: There is no primary efficacy endpoint in this study. Secondary endpoints: Change from the baseline in HbA1c to the last- observation on treatment.
Criteria for safety:	Incidence of adverse drug reactions (ADRs) Incidence of serious adverse events (SAEs)
Statistical methods:	Descriptive

FLOW CHART

Time	Observation period[*1]									
	Before first administration of Trazenta® Tablets	12W (3M)	26W (6M)	40W (9M)	52W (12M)	64W (15M)	78W (18M)	104W (24M)	130W (30M)	156W (36M) (or at discontinuation)
Patient enrolment	X *[2]									
Item :										
・Patient demographics	X									
・Medical history/ Concomitant disease	X									
・Pretreatment drug	X									
・Administration of Trazenta® Tablets		X (to be recorded throughout the observation period)								
・Compliance and fasting condition			X				X			X
・Concomitant drug(s) and antidiabetic therapy		X (to be recorded throughout the observation period)								
・Blood pressure pulse rate and ECG	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
・HbA1c and fasting plasma glucose	X	X	X	X	X	X	X	X	X	X
・Laboratory tests	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
・Body weight	X	X	X	X	X	X	X	X	X	X
・Adverse Event		X(to be recorded throughout the observation period)								
・Pregnancy status	X	X	X	X	X	X	X	X	X	X

W: Weeks

M: Approximate months

*1: Time points during the observation period are approximate. Collected data should be reported as of the closest available visit.

*2: Patients administered Trazenta® Tablets will be registered preferably within 14 days from the day of first administration.

eCRF (electronic case report form): At 26 weeks, 78 weeks, 156 weeks or discontinuation and each time an adverse event has occurred, data in corresponding observation period should be entered into eCRF and transmitted using the EDC system.

(X): If applicable

TABLE OF CONTENTS

ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse Event
BI	Boehringer Ingelheim
CABG	Coronary Artery Bypass Graft
CRF	Case Report Form
CTP	Clinical Trial Protocol
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
DPP-4	Dipeptidyl peptidase IV
EDC	Electronic Data Capture
eGFR	Estimated Glomerular filtration Rate
FPG	Fasting plasma glucose
GIP	Glucose-dependent insulinotropic peptides
GLP-1	Glucagon-like peptide 1
GPSP	Good Post-marketing Study Practice
GVP	Good Vigilance Practice
IRB	Institutional Review Board
JDS	Japan Diabetes Society
J-PAL	Japanese Pharmaceutical Affairs Law
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MPH	Master of Public Health
NBI	Nippon Boehringer Ingelheim
MR	Medical Representative
NGSP	National Glycohemoglobin Standardization Program
PCI	Percutaneous Coronary Intervention
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Type 2 diabetes mellitus accounts for 90-95% of diabetes and its prevalence tends to increase. Type 2 diabetes affects 180 million people worldwide and its incidence is estimated to double in the next 20 years. In Japan, there are about 7.4 million people "strongly suspected of having diabetes" and about 8.8 million people "for whom the possibility of diabetes may not be ruled out," making a total of about 16.2 million people, which indicates that one out of six adults are considered to have diabetes or the potential of developing diabetes (Ministry of Health, Labour and Welfare "Diabetes Surveillance" in 2002). The total number of patients with diabetes (estimated number of patients who are continuously receiving medical care) is 2,284,000 and ranks third (35.9%) in terms of the number of male outpatients amongst patients experiencing accidents and sickness. Diabetes causes 12,879 deaths (1.3% of the total) and ranks 10th amongst causes of death for males and ninth for females in Japan.

Multiple metabolic abnormalities have been described in Type 2 diabetes. It appears, however, that almost invariably a failure of the pancreatic ß-cells is involved. In most cases, insulin resistance cannot be compensated by an adequately increased insulin secretion, ultimately leading to increased fasting and postprandial glucose concentrations. Currently available antidiabetic agents are not sufficient to maintain long term glycaemic control. Loss of glycaemic control appears to be related to the progressive loss of beta cell function in patients with type 2 diabetes, resulting in secondary drug failure and the necessity to institute insulin therapy in many patients.

Traditional insulin secretagogues such as the sulphonylurea drugs increase insulin secretion in a non-glucose-dependent manner and carry an increased risk for hypoglycaemia. Additionally, it is unclear whether such a glucose independent stimulation of insulin secretion accelerates the loss of beta cell function.

An improved understanding of the interaction between gut-derived hormones and the endocrine pancreas has led to the incretin concept and, based on this concept, to the development of a new class of antidiabetic agents. The incretin effect is a phenomenon where the glucose-stimulated insulin secretion is augmented by intestinally derived peptides, which are released in the presence of glucose or nutrients in the gut. Glucagon-like peptide 1 (GLP-1) is an important member of the incretin hormone family together with glucose dependant insulinotropic polypepitide (GIP). It is important to note that the glucose-lowering actions of GLP-1 depend on the actual plasma glucose concentration and the GLP-1- dependent stimulation of insulin secretion ceases when glucose concentrations fall below 55 mg/dL. Therefore, elevation of GLP-1 levels bears little to no risk of hypoglycaemia.

Circulating GLP-1 is almost instantaneously rendered inactive by the enzyme dipeptidyl peptidase IV (DPP-4), which explains its short half-life of only 2-3 minutes. Postprandial GLP-1 secretion has been reported to be attenuated in type 2 diabetes, which may partially explain the increased postprandial glucose excursions. Therefore, a prolongation of the half-

life of active GLP-1 may be seen as a therapy which compensates for the reduced incretin effect in diabetes patients. In addition to its stimulatory effects on insulin secretion, GLP-1 has been shown to suppress glucagon secretion, to delay gastric emptying, to induce satiety, and, in animal models, to reduce β-cell apoptosis, increase β-cell mass, and preserve β-cell function and to show cardio-protective effects. The maintenance of ß-cell function is of particular interest, due to the fact that loss of ß-cell function has been identified as a major contributor to the deterioration of long term glycaemic control in type 2 diabetes.

DPP-4 is an enzyme that is widely expressed in many tissues including kidney, liver, intestine, lymphocytes and vascular endothelial cells. In addition, a significant level of DPP-4 activity is also observed in plasma, DPP-4 is believed to play an important role in the degradation of a number of peptides, thus regulating their half-life. However, physiological evidence for the role of DPP 4 in this process is only available for a few DPP-4 substrates, e.g. GLP-1 and glucose-dependent insulinotropic peptides (GIP) both of which exert glucose-dependent insulinotropic actions and thereby contribute to the maintenance of post-meal glycaemic control. Rodents with a targeted mutation in the DPP-4 gene (DPP-4 knock-out) rodents exhibit improved glycaemic control and are resistant to diet induced obesity, indicating a physiological role of this enzyme in glucose homeostasis and body weight regulation.

Linagliptin is a potent inhibitor of DPP-4 activity. This has been shown in vitro, in various animal models, and in clinical trials. Linagliptin inhibits the proteolysis of GLP-1 and prolongs its half-life. Linagliptin is orally available and has a low risk for hypoglycaemic episodes. Furthermore, it may carry the potential for weight stabilization or even loss rather than weight gain as compared to the majority of other available oral treatments for Type 2 diabetes.

An autopsy study has shown that in diabetic patients, the apoptotic rate of pancreatic ß-cells is increased and ß-cell mass is diminished [R04-2630]. In an animal model, it has been demonstrated that DPP-4 inhibition preserves ß-cell mass through increased proliferation and decreased apoptosis [R04-2631]. Therefore, DPP-4 inhibitors such as linagliptin may also carry the potential to halt the deterioration of glycaemic control over time, thus preventing secondary failure of oral antidiabetic therapy.

2. RATIONALE, OBJECTIVES, AND BENEFIT-RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE STUDY

In Japan, post-approval execution of post marketing surveillance (PMS) is requested by the Japanese Pharmaceutical Affairs Law (J-PAL) in order to accumulate safety and efficacy data for reexamination. Reexamination period is defined by Japanese Pharmaceutical Affairs Low (J-PAL). New integrant is 8 years for reexamination. Eight years after approval of a new substance, results of PMS need to be submitted as a part of reexamination dossier to the Japanese regulatory authority, the Ministry of Health, Labour and Welfare (MHLW).

Collected data from PMS will be included in the Japanese periodic safety reports and submitted to MHLW on designated dates until the end of reexamination period.

The protocol may be revised because of new information or knowledge obtained in the course of conducting PMS. When a change of the approved label such as in dosage and administration or indications is made during the reexamination period of Trazenta® Tablets (except that for this change a reexamination period is newly designated by MHLW) and NBI finds it necessary to revise this protocol, handling each matter should be discussed and the protocol may be revised. If any issue or concern arises (e.g. suggestion of a potential for clinically significant adverse reaction, remarkable increase in incidence of an adverse reaction, or any issue or concern on safety or efficacy assessment made prior to the approval of Trazenta® Tablets) in the course of PMS, implementation of additional special surveillance or post-marketing clinical trial should be discussed to identify or confirm a cause or estimated cause of such issue. Special surveillance is defined by Japanese Pharmaceutical Affairs Low (J-PAL). It means surveillance for long use or special patient population (elderly, renal/hepatic dysfunction etc.).

The surveillance requested by the PMDA covers long term use as add-on therapy in patients with type 2 diabetes mellitus, type 2 diabetes mellitus patients with renal/hepatic dysfunction as concomitant disease and elderly type 2 diabetes mellitus patients . The rationale of the sample size for this surveillance was agreed with the PMDA. To ensure achievement of the number of patients entered, NBI will monitor the numbers of patients with type 2 diabetes mellitus who are treated as add-on therapy, patients with renal or hepatic dysfunction and elderly patients at registration and collection of eCRFs for book 1.

2.2 STUDY OBJECTIVES

Study objectives are to investigate the safety and efficacy of long-term daily use of Trazenta® Tablets as add-on therapy in patients with type 2 diabetes mellitus.

2.3 BENEFIT-RISK ASSESSMENT

In this non-investigational PMS, marketed products will be used. ADRs as risk of Trazenta® Tablets are listed in package insert.

3. DESCRIPTION OF DESIGN AND STUDY POPULATION

3.1 OVERALL DESIGN AND PLAN

This PMS is a prospective study using a continuous investigation system. Patients with type 2 diabetes mellitus who are treated as add-on therapy are included in the surveillance. No specific criteria (e.g., demographics, baseline characteristics, concomitant drugs in use) are defined for patient enrolment.

Planned number of patients to be entered and have at least one observation after treatment is 3,000. Patients with type 2 diabetes mellitus who are treated with anti-diabetic drugs and have never received Trazenta® Tablets will be enrolled in the surveillance. It is exclusively at the physician's discretion whether to initiate linagliptin on patients.

Patients administered Trazenta® Tablets will be registered preferably within 14 days from the day of first administration. Each patient will be observed for 156 weeks (approximately 36 months) after start of the treatment with this product until the end of the PMS or at premature discontinuation and dropout from the PMS. Observations are made at the following time points: before first administration of Trazenta® (baseline) and 12, 26, 40, 52, 64, 78, 104, 130 and 156 weeks after the start of treatment, or at discontinuation.

There are 3 eCRFs for 0-26 (Book 1), 40- 78 (Book 2) and 104-156 weeks (Book 3) individually.

At 26, 78 and 156 weeks after the start of treatment or at discontinuation, data are to be transmitted immediately after entered into eCRF. In case of occurrence of any adverse events, data in corresponding observation period should be immediately entered into eCRF and transmitted.

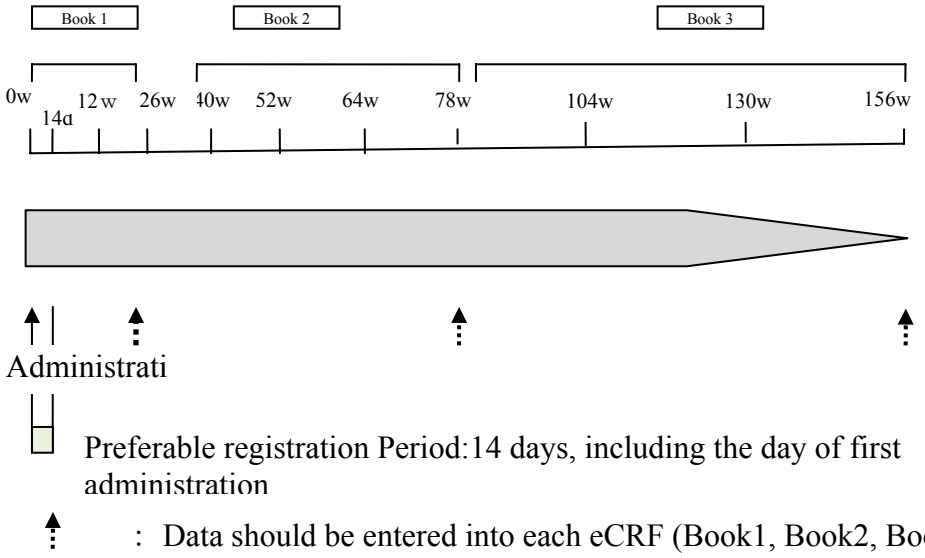

Figure 3.1: 1 Overall design of PMS

3.1.1 Administrative structure of the study

Sponsor

Representative

Co-sponsor

Representative

Trial statistician

Medical Data Services Department,

Nippon Boehringer Ingelheim Co., Ltd.

Data management

Medical Data Services Department,

Nippon Boehringer Ingelheim Co., Ltd.

Contract research organization

3.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

This is a non-interventional, observational prospective study based on newly collected data under routine medical practice.

3.3 SELECTION OF POPULATION

Planned number of patients to be entered is 3,000.

Patients with renal dysfunction should be entered as listed below:

eGFR <60 mL/min/1.73m^2: 140 patients (including 40 patients with ≥15 mL/min/1.73m^2 and <30 mL/min/1.73m^2 and 30 patients with <15 mL/min/1.73m^2)

100 elderly patients (≥75 years)

100 patients with hepatic dysfunction should be also entered.

Patients with hepatic dysfunction: >ULN (AST) x1 or >ULN (ALT) x1 or >ULN (Total bilirubin) x1 or >ULN (alkaline phospatase) x1

When both AST and CK increase, patients do not include in hepatic dysfunction.

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

Number of patients per site is 5-10 patients. Patients will be selected by using the continuous investigation system. The continuous investigation system is commonly used in Japanese PMS and accepted as a patient selection process by the PMDA.

Continuous investigation system is a method of registration that the investigator enrols the patients who will start administration of marketed product into the PMS continuously (without exception) until the requested number of patients is reached.

Preferably, investigators will register patients within 14 days including the day on which the administration of Trazenta® Tablets is started. However, patients who are registered over 15 days after starting administration of Trazenta® Tablets are also used for safety and efficacy analysis.

3.3.1 Main diagnosis for study entry

The PMS is performed in patients with type 2 diabetes mellitus.

3.3.2 Inclusion criteria

Patients with type 2 diabetes mellitus who are treated with anti-diabetic drugs and have never been treated with Trazenta® Tablets / linagliptin before enrollment will be included.

3.3.3 Exclusion criteria

None

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal from individual patients

Patients may voluntarily discontinue the treatment under surveillance for any reason. Patients may also discontinue the PMS if the investigator judges that the patient is no longer able to participate for any medical reason (pregnancy, surgery, adverse events, or other disease).

3.3.4.2 Discontinuation of the study by the sponsor

NBI reserves the right to discontinue the overall surveillance or a surveillance at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment overall goals or goals at a particular study site,
2. Emergence of any efficacy/safety information that could significantly affect continuation of the PMS,
3. Violation of Good Post-marketing Study Practice (GPSP) or the contract of a study site or investigator, thereby disturbing the appropriate conduct of the PMS.

The investigator / the study site will be reimbursed for reasonable expenses incurred as a result of study termination (except in case of the third reason).

4. TREATMENTS

4.1 PRESCRIBED TREATMENTS TO BE OBSERVED

4.1.1 Identity of test product and comparator product

In this non-interventional PMS, marketed products will be used. There will be no investigational products in this PMS. It is solely in the decision of the investigator to initiate Trazenta® Tablet.

4.1.2 Method of assigning patients to treatment groups

There will be no randomisation, since this is an observational surveillance.

4.1.3 Selection of doses in the study

The dose of linagliptine (5mg) used in this PMS is the dosage approved in Japan for Trazenta® Tablets.

4.1.4 Drug assignment and administration of doses for each patient

The investigators indicate doses of 5mg and timing based on package insert.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

There are no special emergency procedures to be followed stipulated by the protocol. It is solely the responsibility of the investigator to initiate such measures according to local clinical practice.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

None

4.2.2.2 Restrictions on diet and life style

There are no restrictions on diet and life style.

4.3 TREATMENT COMPLIANCE

The investigators advise patients to take the prescribed product correctly and verbally confirm compliance to treatment medications at every patient visit.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY

5.1.1 Endpoints of efficacy

There is no primary endpoint for efficacy as the primary objective of a PMS is evaluating safety.

The secondary endpoint for this PMS is the change from baseline in HbA1c at the last observation during the observation period.

5.1.2 Assessment of efficacy

HbA1c:

The blood samples can be taken at any time and will be measured at the sites by using National Glycohemoglobin Standardization Program (NGSP). Based on the value measured according to the method of the Japan Diabetes Society (JDS), an estimated NGSP value will be calculated by using the following expression.

Estimated NGSP（%）= measured value + 0.4

5.2 SAFETY

5.2.1 Endpoint(s) of safety

- Incidence of adverse drug reactions (ADRs)
- Incidence of serious adverse events (SAEs)

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An AE is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a PMS who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A SAE is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

An AE which possibly leads to disability will be reported as an SAE. Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate: Enough discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms (CRFs). The reason for the decision on causal relationship needs to be provided in the CRF.

Yes:	There is a reasonable causal relationship between Trazenta® Tablets administered and the AE.
Probably Yes:	It seems there is a reasonable causal relationship between Trazenta® Tablets administered and the AE.
Can't be denied:	Physician has no clear idea on causal relationship.
No:	There is no reasonable causal relationship between Trazenta® Tablets administered and the AE.

ADRs are defined that causal relationship is "Yes" or "Probable Yes" or "Can't be denied".

Worsening of underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

Changes in vital signs, Electrocardiogram (ECG), physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF , if they are judged clinically relevant by the investigator.

5.2.2.2 Adverse event and serious adverse event reporting

All AEs, serious and non-serious, occurring during the course of the PMS will be collected, documented and reported to the sponsor by the investigator on the appropriate CRFs. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the site materials (that include all necessary documents, the protocol, instructions for conducting PMS, the package insert etc.).

For each AE, the investigator will provide the onset, end, intensity, outcome, seriousness and action taken with Trazenta® Tablets. The investigator will determine the relationship of Trazenta® Tablets to all AEs as defined in the 'Adverse Event Reporting' section of the site materials.

The investigator has the responsibility to report AEs during the specified observational phase.

Any SAE, whether or not considered related to Trazenta® Tablets, or whether or not Trazenta® Tablets has been administered, must be reported immediately via EDC system or by a NBI MR. Further details regarding this reporting procedure are provided in the site materials.

Pregnancy

Once a female pregnancy patient has been enrolled into the PMS, after having taken Trazenta® Tablets the investigator must report immediately any drug exposure during pregnancy to the sponsor.

5.2.3 Assessment of safety laboratory parameters

The laboratory tests will be performed when required by investigator.

5.2.4 Electrocardiogram

The ECG will be performed when required by investigator.

5.2.5 Assessment of other safety parameters

Not applicable.

5.3 OTHER

5.3.1 Other endpoint

Not applicable.

5.3.2 Other assessment

Not applicable.

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this PMS are widely used measurements to monitor safety and efficacy aspects of treatment of type 2 diabetes mellitus.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The investigators will enrol patients who are prescribed Trazenta® Tablets. The observation time points will be as follows: before administration of Trazenta® Tablets (baseline), at 12 weeks, 26 weeks, 40 weeks, 52 weeks, 64 weeks, 78 weeks, 104 weeks, 130 weeks and 156 weeks after the start of administration, and at the time of discontinuation of administration.

6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in periods

Before administration

The investigator will enter the following data of the patient into eCRF for registration. Preferably, registration should be executed within 14 days from the day of first administration of Trazenta® Tablets.

- Name of site, department and Investigator
- Patient ID, date of birth, gender, treatment group, start date of administration, indication, serum creatinine

The observation items are followings:

- Gender, date of birth, indication, pregnancy status, patient status (inpatient/outpatient), height, body weight, waist circumference, hypersensitivity factor, concomitant disease and medical history, pre-treatment drug, duration of type 2 diabetes mellitus, smoking status, start date of administration
- Concomitant drugs and antidiabetic therapy
- Measurement of vital signs (blood pressure , pulse rate and ECG) as safety measurement (if applicable)
- HbA1c , Fasting plasma glucose
- Laboratory tests (blood, biochemistry and urinalysis) (if applicable)

  Haematology
  - Leukocyte counts (WBC)
  - Erythrocyte count (RBC)
  - Platelet count
  - Haemoglobin (Hb)
  - Haematocrit (Hct)

  Blood chemistry
  - AST (aspartate transaminase, SGOT)
  - ALT (alanine transaminase, SGPT)
  - γ-GTP (gamma-glutamyl-
  - HDL cholesterol (HDL)
  - LDL cholesterol (LDL)
  - Triglycerides (TG)
  - Blood urea nitrogen (BUN)
  - Amylase (AMY)

transferase)
- Total bilirubin (T-BIL)
- Alkaline phosphatase (ALP)
- Lactic dehydrogenase (LDH)
- CK (creatine kinase)
- Total cholesterol (T-CHO)
- Lipase（LIP）
- Creatinine (CRE)
- Uric acid (UA)
- Sodium (Na)
- Potassium (K)
- Chlorine(Cl)

Urinalysis
- Protein
- Glucose
- Urobilinogen
- Sediment
- Albumin
- Creatinine

eGFR

$$eGFR\ (mL/min/1.73\ m^2) = 194 \times Creatinine\ (mg/dL)^{-1.094} \times Age^{-0.287}$$

For female, ×0.739

6.2.2 Treatment periods

12 weeks, 26 weeks, 40 weeks, 52 weeks, 64weeks, 78 weeks, 104 weeks , 130 weeks, 156 weeks

The observation items are followings:

- Administration (compliance and fasting condition: 26, 78, 156 weeks)
- Concomitant drugs and antidiabetic therapy
- Adverse event
- Body weight
- Measurement of vital signs (blood pressure , pulse rate and ECG) (if applicable)
- HbA1c , Fasting plasma glucose
- Laboratory tests (blood biochemistry and urinalysis) (if applicable)

Pregnancy status

6.2.3 End of trial and follow-up period

The visit at 156 weeks after starting Trazenta® Tablets treatment or the last visit before discontinuation will be the end of the PMS. There is no follow-up period.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a non-interventional, observational study to investigate the safety and efficacy of long-term use of Trazenta® Tablets as add-on therapy in patients with type 2 diabetes mellitus.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The analyses in this PMS are descriptive and exploratory by nature. Any statistical tests will be performed to provide a framework from which to view the results. No formal statistical inference will be made.

7.3 PLANNED ANALYSES

The safety and efficacy analyses are applied only on Trazenta ® Tablets.

The safety evaluation will be performed on the "safety set" that will include all patients who have received treatment of Trazenta® Tablets except those who are found to have no observation after enrolment, invalid registration, or invalid contract. The efficacy evaluation will be performed on the "efficacy set", a subset of the safety set, which will include all patients in the "safety set" except those who have no available efficacy data and/or who do not suffer from type 2 diabetes mellitus from the safety set.

7.3.1 Primary analyses

In this PMS, the primary objective is safety. The details are given in Section 7.3.3.

7.3.2 Secondary analyses

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

7.3.3 Safety analyses

AEs will be coded using lowest level terms of the Medical Dictionary for Drug Regulatory Activities (MedDRA). AEs occurring in routine medical practice will be evaluated. The relationship of an AE to Trazenta® Tablets will be assessed by the investigator and the sponsor. An ADR is defined as an AE if either the investigator or the sponsor (or both) assess the causal relationship of Trazenta® Tablets either as "Yes", "Probably yes" or "Can't be denied".

The frequency of ADRs will be tabulated by system organ class and preferred term according to the current MedDRA version.

The incidence of ADRs stratified based on patient demographics will also be investigated.

7.3.4 Interim analyses

Not applicable.

7.4 HANDLING OF MISSING DATA

It is not planned to impute the missing data.

7.5 RANDOMISATION

No randomisation of patients to treatment is performed, since this is an observational study.

7.6 DETERMINATION OF SAMPLE SIZE

The sample size was determined based on the following: To detect an ADR with an incidence of 0.1% (or 0.16%) or greater in at least one patient with a probability of 95% (or 99%) or greater, at least 3,000 patients need to be entered and have at least one observation after treatment. According to the market survey for the patients with DPP-4 inhibitor, it is expected that 2010 patients with sulfonylurea, 1290 patients with biguanide, 840 patients with alpha glucosidase inhibitor, 510 patients with thiazolidinedione, and 90 patients with glinide will be entered, and the incidences of ADR in at least one patient with probability of 95% or greater are 0.15%, 0.24%, 0.36%, 0.59%, and 3.28% respectively.

In addition, according to the request from the Japanese authority, this PMS will target to include elderly patients, patients with renal dysfunction and hepatic dysfunction. The sample size for this patient subset was determined based on the following:

Elderly patients (>75 years)

In a PMS of Micardis®, an antihypertensive agent, for hypertensive patients (BI Trial No.: 502.511, Specified Drug Use Surveillance of Micardis [U11-1807-01]), 5,602 patients with diabetes mellitus were enrolled. Of the 5602 patients, 46.1% of the patients were <65 years, 33.1% of the patients were 65 to <75 years, and 20.8% of the patients were >=75 years.

Based on this assumption, more than 100 patients are highly likely to be collected in this PMS.

Renal dysfunction

In a PMS of Micardis® [U11-1807-01], 4,227 hypertention patients with diabetes mellitus and renal dysfunction were enrolled. According to their eGRF level, 52.4% of the patients were of mild renal dysfunction. 21.4% were moderate, 2.4% were severe, and 1.4% were end-stage, respectively. As this PMS plans to include a total of 3,000 patients, based on the above results of the Micardis® surveillance, it is estimated that numbers of patients included in this PMS and with mild, moderate, severe and end stage renal impairment will be about 1,572, 642, 72 and 42patients, respectively.

Based on this assumption, 140 patients with renal dysfunction including 30 end-stage patients are targeted to be included in this PMS.

Hepatic dysfunction

The rate of patients with hepatic dysfunction has not been analyzed in the previous clinical studies. However, based on the result that hepatic function disorder was observed in 13.7% of the patients in the surveillance on the long-term use of Amaryl ®Tablets, an agent for type 2 diabetes [R11-4205], it is estimated that number of patients (95% confidence interval) included in this PMS and with hepatic dysfunction will be 411 (374 - 448) patients.

Based on this assumption, 100 patients with hepatic dysfunction are highly likely to be collected in this PMS.

All patients within renal and hepatic dysfunction will be assessed.

If the number of patients is less than expected numbers, registration period or sample size will be extended.

8. INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS

The PMS will be carried out in routine clinical practice without any intervention involving the patients, and there is no restriction on daily clinical practice. Principles are specified in accordance with the Japanese GPSP regulations (Ministry of Health and Welfare Ordinance No.1711, December 12, 2004), Japanese Good Vigilance Practice (GVP) regulations (Ministry of Health and Welfare Ordinance No.1315, October 22, 2004) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the patient's treating physician.

The rights of the investigator and of the sponsor with regard to publication of the results of this PMS are described in the investigator contract. As a general rule, no PMS results should be published prior to finalisation of the Study Report.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

The review by IRB is not mandatory for conducting PMS in Japanese GPSP, due to the fact that required PMS by MHLW is an observational study using market products involved in normal therapeutic procedures without any interventional procedure.

The same applies for the implementation of changes introduced by amendments. The sponsor will enter into a contract with a representative, e.g. head of hospital, in accordance with GPSP.

Written informed consent prior to patient participation in the trial is not regulatory or legal requirements in accordance with GPSP.

8.2 DATA QUALITY ASSURANCE

This PMS is to be conducted in accordance with both the in-house PMS SOP and working instructions which are in compliance with GPSP.

8.3 RECORDS

eCRFs for individual patients will be provided by the sponsor via the Electronic Data Capture (EDC) System.

8.3.1 Source documents

Source documents provide evidence of the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that is transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. Depending on the PMS conducting under GPSP, the investigator may need to request previous medical records or transfer records, and current medical records must be made available. For eCRFs, all of the following data must be derived from source documents:

- Patient identification (gender, date of birth, hospitalization status)
- Patient participation in the PMS (substance, patient number)
- Dates of Patient's visits, including dispensing of the medication
- Medical history (including indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date, end date, treatment for AEs)
- Concomitant therapy (start date, changes, reasons for therapy)
- Laboratory results (in validated electronic format, if available)

8.3.2 Direct access to source data and documents

The investigator / institution will permit PMS-related regulatory inspection, providing direct access to all related source data / documents. All source documents, including progress notes and copies of laboratory and medical test results, must be available at all times for inspection by health authorities (e.g. PMDA). The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 PROCEDURES FOR REPORTING ADVERSE EVENTS

8.4.1 Time windows

All AEs, serious and non-serious, occurring during the course of the PMS will be collected, documented and reported to the sponsor by the investigator on the appropriate CRFs. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the site materials (that include all necessary documents, the protocol, instructions for conducting PMS, the package insert etc.).

The investigator has the responsibility to report AEs during the specified observational phase.

Any SAE, whether or not considered related to Trazenta® Tablets, or whether or not Trazenta® Tablets has been administered, must be reported immediately via EDC system or by a NBI MR. Further details regarding this reporting procedure are provided in the site materials.

8.4.2 Documentation of adverse events and patient narratives

Expedited reporting to health authorities of SAEs, e.g. suspected expected and suspected unexpected serious adverse reactions, will be done according to J-PAL requirements. To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular AE is expected.

For each AE, the investigator will provide the onset, end, intensity, outcome, seriousness and action taken with Trazenta® Tablets. The investigator will determine the relationship of Trazenta® Tablets to all AEs as defined in the 'Adverse Event Reporting' section of the site materials.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this PMS is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Data generated as a result of the PMS needs to be available for inspection on request by the regulatory authorities.

8.6 COMPLETION OF STUDY

Completion of the PMS will be notified to PMDA when the reexamination document is applied to in accordance with J-PAL and GPSP.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R04-2630 Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003;52:102-110.

R04-2631 Pospisilik JA, Martin J, Doty T, Ehses JA, Pamir N, Lynn FC, et al. Dipeptidyl peptidase IV inhibitor treatment stimulates beta-cell survival and islet neogenesis in streptozotocin-induced diabetic rats. Diabetes 2003;52:741-750.

R11-4205 Pharmacovigilance sanofi-aventis K.K.. Special Surveillance of Amaryl® Tablets (in Long-term Use) –Special Surveillance of Glimepiride (Amaryl® Tablets 1mg and 3mg Tablets)

9.2 UNPUBLISHED REFERENCES

U09-2458-02 and
A randomised, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg) administered orally once daily over 24 weeks in type 2 diabetic patients with insufficient glycaemic control despite a therapy of metformin in combination with a sulphonylurea

U10-1466-01 A double-blind phase III study to evaluate the efficacy of BI 1356 5 mgand 10 mg vs. placebo for 12 weeks and vs. voglibose 0.6 mg for 26weeks in patients with type 2 diabetes mellitus and insufficient glycaemic control, followed by an extension study to 52 weeks toevaluate long-term safety

U11-1807-01 Special surveillance on cerebrovascular and cardiovascular events under long-term use of Micardis Tablets

U11-3170-01 A phase III, randomised, double-blind, placebo-controlled, parallelgroup, safety and efficacy study of BI 1356 (5 mg), compared toplacebo as add on to pre-existing antidiabetic therapy (insulin or anycombination with insulin; sulphonylurea or glinides as monotherapy;pioglitazone or any other antidiabetics, excluding only DPP-4inhibitors other than BI 1356) over 52 weeks in type 2 diabetic patients with severe chronic renal impairment

U12-1296-01 An open label, randomised, parallel group safety and efficacy study of linagliptin (5 mg administered orally once daily) over 52 weeks in patients with type 2 diabetes mellitus and

insufficient glycaemic control despite background mono-therapy with ...
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10. APPENDICES

Not applicable.

11. SUMMARY OF NON-INTERVENTIONAL STUDY PROTOCOL MODIFICATIONS

Summary of Modifications Sheet (SOMS)

Number of Protocol modification		
Date of Protocol modification		
BI Trial number		
BI Product(s)		
Title of protocol		
To be implemented only after approval of the IRB/IEC/Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		
Description of change		
Rationale for change		