

**SIGNATURE INFORMATION****Document:** 1218-0095--protocol-revision-01**Document No.:** U12-1208-02**Title** Post Marketing Surveillance on Long Term Drug Use of Trazenta Tablets  
in Patients with type 2 Diabetes Mellitus**SIGNATURES (ELECTRONICALLY OBTAINED)**

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**Document** 1218-0095--protocol-revision-01

**Document No.:** U12-1208-02

**Title** Post Marketing Surveillance on Long Term Drug Use of Trazenta Tablets  
in Patients with type 2 Diabetes Mellitus

**SIGNATURES (ELECTRONICALLY OBTAINED)**

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## POST MARKETING SURVEILLANCE STUDY PROTOCOL SYNOPSIS

<b>Name of company/Marketing Authorisation Holder:</b> Boehringer Ingelheim		<b>Tabulated Study Protocol</b>	
<b>Name of finished product:</b> Trazenta <sup>®</sup> Tablets			
<b>Name of active ingredient:</b> Linagliptin			
<b>Protocol date</b> 3 July 2012	<b>Trial number</b> 1218.95		<b>Revision date:</b> 4 April 2013
<b>Title of study:</b>	Post Marketing Surveillance study on Long term Drug Use of Trazenta <sup>®</sup> Tablets in Patients with type 2 Diabetes Mellitus		
<b>Co-ordinating Investigator:</b>	Not applicable		
<b>Study sites :</b>	400 <del>600</del>		
<b>Clinical phase:</b>	IV		
<b>Objectives:</b>	To investigate the safety and efficacy of long-term daily use of Trazenta <sup>®</sup> Tablets <b>as monotherapy</b> in patients with type 2 diabetes mellitus. To assess baseline characteristics of patients with type 2 diabetes mellitus starting Trazenta <sup>®</sup> Tablets or any other oral antidiabetic monotherapy (naïve or switched from prior therapy of different oral antidiabetic drug) .		
<b>Methodology:</b>	Non-interventional, prospective, observational		
<b>No. of patients:</b>	<b>Total entered:</b> 3,000 <del>6,000</del> <b>each treatment:</b> Trazenta <sup>®</sup> Tablets: 1,500 <del>3,000</del> Oral antidiabetic drugs except Trazenta <sup>®</sup> Tablets: 1,500 <del>3,000</del>		
<b>Diagnosis:</b>	Type 2 diabetes mellitus		
<b>Main criteria for inclusion:</b>	Trazenta <sup>®</sup> Tablets: Male and female patients with type 2 diabetes mellitus who have never been treated with Trazenta <sup>®</sup> Tablets/ linagliptin ( <b>monotherapy</b> ) before enrollment. Other oral antidiabetic drug: Male and female patients with type 2 diabetes mellitus starting any other oral antidiabetic monotherapy (naïve and switch) except Trazenta <sup>®</sup> Tablets.		
<b>Test product :</b>	Trazenta <sup>®</sup> Tablets		
<b>dose:</b>	5 mg		
<b>mode of admin. :</b>	Oral		
<b>Comparator product:</b>	Oral antidiabetic drugs except Trazenta <sup>®</sup> Tablets		

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<b>Name of active ingredient:</b> Linagliptin			
<b>Protocol date</b> 3 July 2012	<b>Trial number</b> 1218.95		<b>Revision date:</b> 4 April 2013
<b>dose:</b>	Refer each package insert of the prescribed oral antidiabetic drug		
<b>mode of admin. :</b>	Oral		
<b>Duration of treatment:</b>	Trazenta <sup>®</sup> Tablets: 156 weeks Other oral antidiabetic drug: Only baseline data and no observation period		
<b>Criteria for efficacy:</b>	Trazenta <sup>®</sup> Tablets: 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 Other oral antidiabetic drug: None		
<b>Criteria for safety:</b>	Trazenta <sup>®</sup> Tablets: Incidence of adverse drug reactions (ADRs) Incidence of serious adverse events (SAEs) [REDACTED] Other oral antidiabetic drug: None		
<b>Statistical methods:</b>	Descriptive		

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## FLOW CHART

Trazenta<sup>®</sup> Tablets:

Time	Observation period* <sup>1</sup>									
	Before first administration of Trazenta <sup>®</sup> 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 * <sup>2</sup>									
Item :										
• Patient demographics	X									
• Medical history/ Concomitant disease	X									
• Pretreatment drug	X									
• Administration of Trazenta <sup>®</sup> 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.

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\*2: Patients administered Trazenta<sup>®</sup> 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

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## FLOW CHART

Other oral antidiabetic drug:

Time	Observation point
	Before first administration of Oral antidiabetic drugs except Trazenta <sup>®</sup> Tablets
Patient enrolment	X <sup>*1</sup>
Item :	
• Patient demographics	X
• Medical history/ Concomitant disease	X
• Pretreatment drug	X
• Administration of Oral antidiabetic drugs except Trazenta <sup>®</sup> Tablets	
• Concomitant drug(s) and antidiabetic therapy	
• Blood pressure pulse rate and ECG	(X)
• HbA1c and fasting plasma glucose	X
• Laboratory tests	(X)
• Body weight	X

\*1: Patients administered Oral antidiabetic drugs except Trazenta<sup>®</sup> Tablets will be registered preferably within 14 days from the day of first administration.

eCRF (electronic case report form): After registration data should be entered into eCRF and transmitted using the EDC system.

(X): If applicable

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## 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 insulintropic 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
OAD	Oral Antidiabetic Drug
PCI	Percutaneous Coronary Intervention
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

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## 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  $\beta$ -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 polypeptide (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

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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  $\beta$ -cell apoptosis, increase  $\beta$ -cell mass, and preserve  $\beta$ -cell function and to show cardio-protective effects. The maintenance of  $\beta$ -cell function is of particular interest, due to the fact that loss of  $\beta$ -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 insulintropic peptides (GIP) both of which exert glucose-dependent insulintropic 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  $\beta$ -cells is increased and  $\beta$ -cell mass is diminished [R04-2630]. In an animal model, it has been demonstrated that DPP-4 inhibition preserves  $\beta$ -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.

## 1.2 DRUG PROFILE

The DPP-IV inhibitor compound linagliptin was discovered by Boehringer Ingelheim [BI] Pharma GmbH & Co. KG, Biberach, Germany.

It has been tested in phase I and phase II clinical trials of up to 12 weeks duration and has shown efficacy (reduced levels of fasting glucose, postprandial glucose and HbA1c) in type 2 diabetic patients at a daily dose of 5 mg.

Linagliptin has, until 16 February 2010, been tested in eight phase III trials (and several others are planned or ongoing) involving 5,239 patients (44.5% females, mean  $\pm$ SD age 58 $\pm$ 10 years, BMI 28.9 $\pm$ 5.0 kg/m<sup>2</sup>) with T2DM (HbA1c 8.1 $\pm$ 0.9%, fasting plasma glucose

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168±42 mg/dL, 52.4% diabetes duration > 5 years, 60.8% with metabolic syndrome, 10-year Framingham risk for coronary heart disease 10.0±8.3% [29.0% > 15%], 35.4% received statin treatment). Of the total number of recruited patients, 17.3% were treatment naïve and 45.5%, 37.0% and 0.2%, respectively, were previously treated with one, two and three or more oral antidiabetic drugs. 3,319 patients received treatment with linagliptin (5 mg: n=3159, 10 mg: n=160), 977 placebo and 943 active comparator (glimepiride or voglibose) and were followed for median periods of 175, 169 and 409 days respectively. Cumulative exposure (person years) was 2,060 for linagliptin and 1,372 for the total comparators.

In the phase III studies accounting for exposure up to 24 weeks, the overall incidence of adverse events (AEs) with linagliptin was comparable to placebo (linagliptin: 58.3%, placebo: 57.3%). In addition, the number of patients with AEs leading to discontinuation of trial drugs (linagliptin: 2.0%, placebo: 2.3%) and with investigator defined drug-related AEs (linagliptin: 11.0%, placebo: 8.3%) did not differ between linagliptin and placebo. AEs with the highest incidence in the linagliptin-treated patients were hypoglycaemia (linagliptin: 9.7%, placebo: 6.1%), nasopharyngitis (linagliptin: 5.5%, placebo: 5.3%), hyperglycaemia (linagliptin: 5.3%, placebo: 12.2%), upper respiratory tract infection (linagliptin: 4.1%, placebo: 6.0%), headache (linagliptin 3.3%, placebo: 3.4%), hypertension (linagliptin: 2.8%, placebo: 2.2%), urinary tract infection (linagliptin: 2.5%, placebo: 3.3%), dizziness (linagliptin: 2.2%, placebo: 1.9%), diarrhoea (linagliptin 2.2%, placebo: 2.2%) and back pain (linagliptin: 2.1%, placebo: 2.4%).

The increased incidence of hypoglycaemia observed in the phase III studies came from one study (1218.18 [\[U09-2458-02\]](#)), when linagliptin was added to a background treatment of metformin and sulfonylurea. There were no SAEs in the 1218.18 study related to hypoglycaemia.

The Phase III trial (1218.23 [\[U10-1466-01\]](#)) in Japan was a multi-centre, randomized, double-blind parallel group comparative study designed to investigate the efficacy, safety, and tolerability of linagliptin (5 mg or 10 mg once daily) compared with placebo for 12 weeks and voglibose for 26 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control. In addition, one-year safety of linagliptin was evaluated in an 26-week open label extension of this 26-week randomized trial. A total of 700 patients were enrolled and 561 patients were entered into the trial at 47 trial sites in Japan. At the start of randomized study medication, 80 patients were randomly assigned to receive placebos, 159 patients to receive linagliptin at 5 mg, 160 patients to receive linagliptin at 10 mg, and 162 patients to receive voglibose (0.2 mg, tid). Linagliptin showed clinically significant reduction in HbA1c from baseline to Week 12, in comparison to placebo, and from baseline to Week 26, in comparison to voglibose. Superiority of linagliptin over placebo and voglibose in HbA1c reduction was shown and treatment with linagliptin was well tolerated, and assessment of safety did not reveal any trends of clinical relevance for up to 52 weeks of treatment. The incidence of hypoglycaemic events during treatment with linagliptin was considerably low. The safety data figures were consistent with the reported safety profile of other DPP-4 inhibitors, and no new safety concerns were reported.

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Trough plasma concentrations of linagliptin were stable over 26 weeks after once daily administration of linagliptin, indicating that the pharmacokinetics profile of linagliptin does not change after multiple administrations over a long period. The trough concentration of linagliptin increased less than dose-proportionally when the dose was increased from 5 mg to 10 mg. In this trial, linagliptin was more efficacious than both placebo and voglibose, was well tolerated, and no new safety concerns arose. The 5 mg and 10 mg doses of linagliptin showed comparable efficacy over 52 weeks.

The 5 mg dose of linagliptin once daily was found to be the safe and efficacious dose in a number of phase III studies and hence appears to be the appropriate dose. Trazenta<sup>®</sup> Tablet 5mg was approved on 1<sup>st</sup> July 2011 by the Japanese Ministry of Health, Labour and Welfare (MHLW).

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## 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 Law (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<sup>®</sup> 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<sup>®</sup> 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 Law (J-PAL). It means surveillance for long use or special patient population (elderly, renal/hepatic dysfunction etc.).

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

The assessment of baseline characteristics of patients with type 2 diabetes mellitus starting any other oral antidiabetic monotherapy (naïve or switched from prior therapy of different oral antidiabetic drug) except Trazenta<sup>®</sup> Tablets is included in the surveillance.

There is only limited information available about clinical characteristics of patients using different oral antidiabetic drug (OAD) in Japan. In this study patient characteristics will be assessed at baseline for the different OADs in order to assess potential differences.

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## 2.2 STUDY OBJECTIVES

Study objectives are to investigate the safety and efficacy of long-term daily use of Trazenta<sup>®</sup> Tablets **as monotherapy** in patients with type 2 diabetes mellitus and to assess baseline characteristics of patients with type 2 diabetes mellitus starting Trazenta<sup>®</sup> Tablets or any other oral antidiabetic monotherapy (naïve or switched from prior therapy of different oral antidiabetic drug) .

## 2.3 BENEFIT - RISK ASSESSMENT

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

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### 3. DESCRIPTION OF DESIGN AND STUDY POPULATION

#### 3.1 OVERALL DESIGN AND PLAN

Trazenta<sup>®</sup> Tablets:

This PMS is a prospective study using a continuous investigation system. Patients with type 2 diabetes mellitus **who are treated as monotherapy** 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 **1,500**~~3,000~~. Patients with type 2 diabetes mellitus who have never received Trazenta<sup>®</sup> Tablets (**monotherapy**) will be enrolled in the surveillance. It is exclusively at the physician's discretion whether to initiate linagliptin on patients.

Patients administered Trazenta<sup>®</sup> 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<sup>®</sup> (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.

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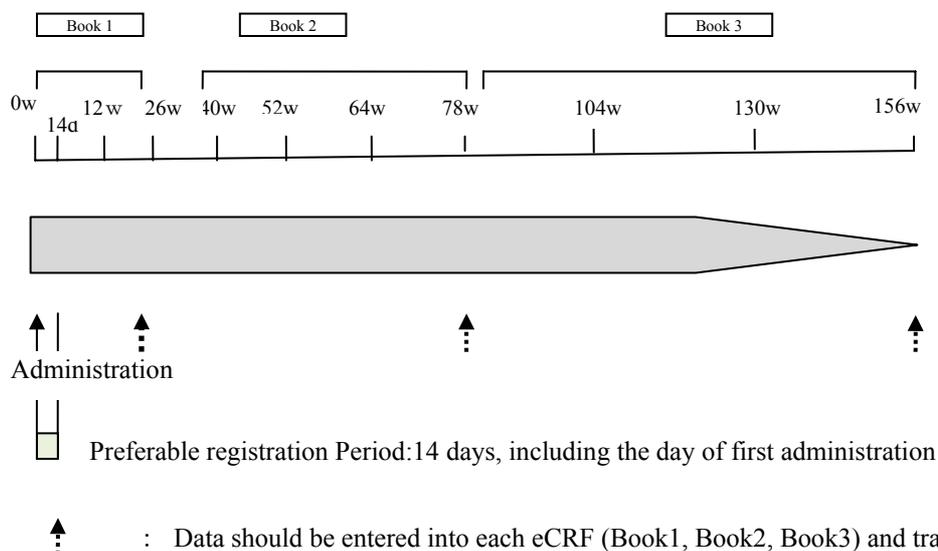


Figure 3.1: 1 Overall design of PMS

Other oral antidiabetic drug:

Patients with type 2 diabetes mellitus are included in the surveillance. No specific criteria (e.g., demographics, baseline characteristics, concomitant drugs in use) are defined for patient enrolment.

After the enrolment of each patient for whom Trazenta<sup>®</sup> Tablets are prescribed, the patient immediately following and initiating any other oral antidiabetic drug should be enrolled.

Planned number of patients to be entered is 1,500~~3,000~~. Patients with type 2 diabetes mellitus starting any other oral antidiabetic monotherapy (naïve or switched from prior therapy of different oral antidiabetic drug) except Trazenta<sup>®</sup> Tablets will be enrolled in the surveillance.

Patients administered Oral antidiabetic drugs except Trazenta<sup>®</sup> Tablets will be registered preferably within 14 days from the day of first administration.

After registration data should be entered into eCRF and transmitted using the EDC system.

The baseline data is collected and there is no observation period.

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### 3.1.1 Administrative structure of the study

#### Sponsor

[REDACTED]

Representative [REDACTED]

Nippon Boehringer Ingelheim Co., Ltd.

[REDACTED]

#### Co-sponsor

Representative [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### Trial statistician

[REDACTED]

Medical Data Services Department,

Nippon Boehringer Ingelheim Co., Ltd.

#### Data management

[REDACTED]

Medical Data Services Department,

Nippon Boehringer Ingelheim Co., Ltd.

#### Contract research organizations

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### 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

Trazenta<sup>®</sup> Tablets:

Planned number of patients to be entered is **1,500** ~~3,000~~.

Patients with renal dysfunction should be entered as listed below:

eGFR <60 mL/min/1.73m<sup>2</sup>: **70** ~~140~~ patients (including **20** ~~40~~ patients with ≥15 mL/min/1.73m<sup>2</sup> and <30 mL/min/1.73m<sup>2</sup> and **15** ~~30~~ patients with <15 mL/min/1.73m<sup>2</sup>)

**50** ~~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 phosphatase) 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<sup>®</sup> 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 enrolls 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<sup>®</sup> Tablets is started. However, patients who are registered over 15 days after starting administration of Trazenta<sup>®</sup> Tablets are also used for safety and efficacy analysis.

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Other oral antidiabetic drug:

Planned number of patients to be entered is **1,500** ~~3,000~~.

After the enrolment of each patient for whom Trazenta<sup>®</sup> Tablets are prescribed, the patient immediately following and initiating any other oral antidiabetic drug should be enrolled. The total number of Trazenta<sup>®</sup> Tablets patients and comparators are the same at each site.

### 3.3.1 Main diagnosis for study entry

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

### 3.3.2 Inclusion criteria

Trazenta<sup>®</sup> Tablets: Patients with type 2 diabetes mellitus who have never been treated with Trazenta<sup>®</sup> Tablets / linagliptin (**monotherapy**) before enrollment will be included.

Other oral antidiabetic drug: Patients with type 2 diabetes mellitus starting any other oral antidiabetic monotherapy (naïve or switched from prior therapy of different oral antidiabetic drug) except Trazenta<sup>®</sup> Tablets.

### 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).

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## **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<sup>®</sup> Tablet or other oral antidiabetic drug.

#### **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**

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

Other oral antidiabetic drug: Refer to the package insert of the prescribed oral antidiabetic drug

#### **4.1.4 Drug assignment and administration of doses for each patient**

Trazenta<sup>®</sup> Tablets: The investigators indicate doses of 5mg and timing based on package insert.

Other oral antidiabetic drug: The investigators indicate doses and timing based on the package insert of the prescribed oral antidiabetic drug.

### **4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT**

#### **4.2.1 Rescue medication, emergency procedures, and additional treatment**

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

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#### 4.2.2.2 Restrictions on diet and life style

There are no restrictions on diet and life style.

### 4.3 TREATMENT COMPLIANCE

Trazenta<sup>®</sup> Tablets: The investigators advise patients to take the prescribed product correctly and verbally confirm compliance to treatment medications at every patient visit.

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## 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.

[REDACTED]

- [REDACTED]

- [REDACTED]

  - [REDACTED]

  - [REDACTED]

- [REDACTED]

  - [REDACTED]

- [REDACTED]

- [REDACTED]

- [REDACTED]

#### 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.

$$\text{Estimated NGSP (\%)} = \text{measured value} + 0.4$$

[REDACTED]

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## 5.2 SAFETY

### 5.2.1 Endpoints of safety

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

- [REDACTED]

### 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

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#### 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 <sup>®</sup> Tablets administered and the AE.
Probably Yes:	It seems there is a reasonable causal relationship between Trazenta <sup>®</sup> 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 <sup>®</sup> 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<sup>®</sup> Tablets. The investigator will determine the relationship of Trazenta<sup>®</sup> 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<sup>®</sup> Tablets, or whether or not Trazenta<sup>®</sup> 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.

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### Pregnancy

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

[REDACTED]

[REDACTED]

#### **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.

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## 6. INVESTIGATIONAL PLAN

### 6.1 VISIT SCHEDULE

Trazenta<sup>®</sup> Tablets:

The investigators will enrol patients who are prescribed Trazenta<sup>®</sup> Tablets. The observation time points will be as follows: before administration of Trazenta<sup>®</sup> 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.

Other oral antidiabetic drug:

After the enrolment of each patient for whom Trazenta<sup>®</sup> Tablets are prescribed, the patient immediately following and initiating any other oral antidiabetic drug should be enrolled. Only patient demographic and baseline characteristics will be collected at enrolment. No further assessment is needed.

### 6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

#### 6.2.1 Screening and run-in period

Trazenta<sup>®</sup> Tablets:

##### 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<sup>®</sup> 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)

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Haematology

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

Blood chemistry

- AST (aspartate transaminase, SGOT)
- ALT (alanine transaminase, SGPT)
- $\gamma$ -GTP (gamma-glutamyl-transferase)
- Total bilirubin (T-BIL)
- Alkaline phosphatase (ALP)
- Lactic dehydrogenase (LDH)
- CK (creatine kinase)
- Total cholesterol (T-CHO)
- HDL cholesterol (HDL)
- LDL cholesterol (LDL)
- Triglycerides (TG)
- Blood urea nitrogen (BUN)
- Amylase (AMY)
- Lipase (LIP)
- Creatinine (CRE)
- Uric acid (UA)
- Sodium (Na)
- Potassium (K)
- Chlorine (Cl)

Urinalysis

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

eGFR

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

For female,  $\times 0.739$

Other oral antidiabetic drug:

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 oral antidiabetic drugs except Trazenta<sup>®</sup> 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

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- status, name of other oral antidiabetic drug, start date of administration, total daily dose
- Concomitant drugs and antidiabetic therapy
- Measurement of vital signs (blood pressure and pulse rate and ECG) (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)
- $\gamma$ -GTP (gamma-glutamyl-transferase)
- Total bilirubin (T-BIL)
- Alkaline phosphatase (ALP)
- Lactic dehydrogenase (LDH)
- CK (creatine kinase)
- Total cholesterol (T-CHO)
- HDL cholesterol (HDL)
- LDL cholesterol (LDL)
- Triglycerides (TG)
- Blood urea nitrogen (BUN)
- Amylase (AMY)
- Lipase (LIP)
- Creatinine (CRE)
- Uric acid (UA)
- Sodium (Na)
- Potassium (K)
- Chlorine(Cl)

#### Urinalysis

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

### 6.2.2 Treatment period

Trazenta<sup>®</sup> Tablets:

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

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### 6.2.3 End of trial and follow-up period

Trazenta<sup>®</sup> Tablets:

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

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## 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<sup>®</sup> Tablets **as monotherapy** 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<sup>®</sup> Tablets.

The safety evaluation will be performed on the “safety set” that will include all patients who have received treatment of Trazenta<sup>®</sup> 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.

Descriptive statistics for the baseline data will be calculated for the patients who are treated with Trazenta<sup>®</sup> Tablets as well as other oral antidiabetic monotherapy.

#### 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.

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

### 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<sup>®</sup> 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<sup>®</sup> 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 0.20-1% (or 0.310-16%) or greater in at least one patient with a probability of 95% (or 99%) or greater, at least 1,500 3,000 patients need to be entered and have at least one observation after treatment.

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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.

Other oral antidiabetic drug:

Descriptive statistics for all baseline characteristics will be analyzed.

As this will be exploratory and descriptive and no statistical tests will be performed the same number of patients for both groups is appropriate.

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## **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

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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<sup>®</sup> Tablets, or whether or not Trazenta<sup>®</sup> 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.

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#### **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<sup>®</sup> Tablets. The investigator will determine the relationship of Trazenta<sup>®</sup> 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 TRIAL**

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

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## 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, Ehse 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 [REDACTED] and [REDACTED] 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 [REDACTED] A double-blind phase III study to evaluate the efficacy of BI 1356 5 mg and 10 mg vs. placebo for 12 weeks and vs. voglibose 0.6 mg for 26 weeks in patients with type 2 diabetes mellitus and insufficient glycaemic control, followed by an extension study to 52 weeks to evaluate long-term safety
- U11-1807-01 [REDACTED] Special surveillance on cerebrovascular and cardiovascular events under long-term use of Micardis Tablets
- U11-3170-01 [REDACTED] A phase III, randomised, double-blind, placebo-controlled, parallel group, safety and efficacy study of BI 1356 (5 mg), compared to placebo as add on to pre-existing antidiabetic therapy (insulin or any combination with insulin; sulphonylurea or glinides as monotherapy; pioglitazone or any other antidiabetics, excluding only DPP-4 inhibitors other than BI 1356) over 52 weeks in type 2 diabetic patients with severe chronic renal impairment

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## 10. APPENDICES

Not applicable.

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## 11 SUMMARY OF PMS STUDY PROTOCOL MODIFICATIONS

### Summary of Modifications Sheet (SOMS)

<b>Number of Protocol modification</b>		1
<b>Date of Protocol modification</b>		4 April 2013
<b>BI Trial number</b>		1218.95
<b>BI Product(s)</b>		BI 1356
<b>Title of protocol</b>		Post Marketing Surveillance on Long Term Drug Use of Trazenta® Tablets in Patients with type 2 Diabetes Mellitus
<b>To be implemented only after approval of the IRB/IEC/Competent Authorities</b>		<input checked="" type="checkbox"/>
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		<input type="checkbox"/>
<b>Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only</b>		<input type="checkbox"/>
<b>Section to be changed</b>		Study sites
<b>Description of change</b>		The total number of study sites has been changed from 600 to 400.
<b>Rationale for change</b>		Since the total number of entered sites has been increased.
<b>Section to be changed</b>		Objectives
<b>Description of change</b>		To investigate the safety and efficacy of long-term daily use of Trazenta® Tablets in patients with type 2 diabetes mellitus.  has been changed to say:  To investigate the safety and efficacy of long-term daily use of Trazenta® Tablets as <b>monotherapy</b> in patients with type 2 diabetes mellitus.
<b>Rationale for change</b>		To fulfil the requirements of PMDA that

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<b>Number of Protocol modification</b>		1
		should perform separate surveillance without control group for the add-on therapy.
<b>Section to be changed</b>		No. of patients:
<b>Description of change</b>		Total entered: 6,000 each treatment: Trazenta <sup>®</sup> Tablets: 3,000 Oral antidiabetic drugs except Trazenta <sup>®</sup> Tablets: 3,000  has been changed to say:  Total entered: <b>3,000</b> each treatment: Trazenta <sup>®</sup> Tablets: <b>1,500</b> Oral antidiabetic drugs except Trazenta <sup>®</sup> Tablets: <b>1,500</b>
<b>Rationale for change</b>		To fulfil the requirements of PMDA that should perform separate surveillance without control group for the add-on therapy. Originally total entered (3,000) included patients with mono therapy and add-on therapy and it was reduced as only mono therapy patients to be enrolled.
<b>Section to be changed</b>		2.2 STUDY OBJECTIVES
<b>Description of change</b>		Study objectives are to investigate the safety and efficacy of long-term daily use of Trazenta <sup>®</sup> Tablets in patients with type 2 diabetes mellitus and.....  has been changed to say:  Study objectives are to investigate the safety and efficacy of long-term daily use of Trazenta <sup>®</sup> Tablets <b>as monotherapy</b> in patients with type 2 diabetes mellitus and.....
<b>Rationale for change</b>		To fulfil the requirements of PMDA that should perform separate surveillance without control group for the add-on therapy.
<b>Section to be changed</b>		3.1 OVERALL DESIGN AND PLAN
<b>Description of change</b>		This PMS is a prospective study using a continuous investigation system. Patients with

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<b>Number of Protocol modification</b>		1
		<p>type 2 diabetes mellitus are included in the surveillance.</p> <p>.....</p> <p>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 have never received Trazenta<sup>®</sup> Tablets will be enrolled in the surveillance.</p> <p>.....</p> <p>Planned number of patients to be entered is 3,000.</p> <p>has been changed to say:</p> <p>This PMS is a prospective study using a continuous investigation system. Patients with type 2 diabetes mellitus <b>who are treated as monotherapy</b> are included in the surveillance.</p> <p>.....</p> <p>Planned number of patients to be entered and have at least one observation after treatment is <b>1,500</b>. Patients with type 2 diabetes mellitus who have never received Trazenta<sup>®</sup> Tablets (<b>monotherapy</b>) will be enrolled in the surveillance.</p> <p>.....</p> <p>Planned number of patients to be entered is <b>1,500</b>.</p>
<b>Rationale for change</b>		<p>To fulfil the requirements of PMDA that should perform separate surveillance without control group for the add-on therapy. Originally total entered (3,000) included patients with mono therapy and add-on therapy and it was reduced as only mono therapy patients to be enrolled.</p>
<b>Section to be changed</b>		3.3 SELECTION OF POPULATION
<b>Description of change</b>		<p>Trazenta<sup>®</sup> Tablets:</p> <p>Planned number of patients to be entered is 3,000.</p> <p>Patients with renal dysfunction should be entered as listed below:</p> <p>eGFR &lt;60 mL/min/1.73m<sup>2</sup>: 140 patients</p>

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<b>Number of Protocol modification</b>		1
		<p>(including 40 patients with <math>\geq 15</math> mL/min/1.73m<sup>2</sup> and &lt;30 mL/min/1.73m<sup>2</sup> and 30 patients with &lt;15 mL/min/1.73m<sup>2</sup>)          100 patients with hepatic dysfunction should be also entered.</p> <p>.....</p> <p>Other oral antidiabetic drug:          Planned number of patients to be entered is 3,000.</p> <p>has been changed to say:</p> <p>Trazenta<sup>®</sup> Tablets:          Planned number of patients to be entered is <b>1,500</b>.          Patients with renal dysfunction should be entered as listed below:          eGFR &lt;60 mL/min/1.73m<sup>2</sup>: <b>70</b> patients (including <b>20</b> patients with <math>\geq 15</math> mL/min/1.73m<sup>2</sup> and &lt;30 mL/min/1.73m<sup>2</sup> and <b>15</b> patients with &lt;15 mL/min/1.73m<sup>2</sup>)  <b>50</b> patients with hepatic dysfunction should be also entered.</p> <p>.....</p> <p>Other oral antidiabetic drug:          Planned number of patients to be entered is <b>1,500</b>.</p>
<b>Rationale for change</b>		<p>To fulfil the requirements of PMDA that should perform separate surveillance without control group for the add-on therapy. Originally total entered (3,000) included patients with mono therapy and add-on therapy and it was reduced as only mono therapy patients to be enrolled.</p>
<b>Section to be changed</b>		3.3.1 Inclusion criteria
<b>Description of change</b>		<p>Trazenta<sup>®</sup> Tablets: Patients with type 2 diabetes mellitus who have never been treated with Trazenta<sup>®</sup> Tablets / linagliptin before enrollment will be included.</p> <p>has been changed to say:</p>

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<b>Number of Protocol modification</b>		1
		Trazenta <sup>®</sup> Tablets: Patients with type 2 diabetes mellitus who have never been treated with Trazenta <sup>®</sup> Tablets / linagliptin ( <b>monotherapy</b> ) before enrollment will be included.
<b>Rationale for change</b>		To fulfil the requirements of PMDA that should perform separate surveillance without control group for the add-on therapy.
<b>Section to be changed</b>		7.1 STATISTICAL DESIGN - MODEL
<b>Description of change</b>		<p>This is a non-interventional, observational study to investigate the safety and efficacy of long-term use of Trazenta<sup>®</sup> Tablets in patients with type 2 diabetes mellitus.</p> <p>has been changed to say:</p> <p>This is a non-interventional, observational study to investigate the safety and efficacy of long-term use of Trazenta<sup>®</sup> Tablets <b>as monotherapy</b> in patients with type 2 diabetes mellitus.</p>
<b>Rationale for change</b>		To fulfil the requirements of PMDA that should perform separate surveillance without control group for the add-on therapy.
<b>Section to be changed</b>		7.6 DETERMINATION OF SAMPLE SIZE
<b>Description of change</b>		<p>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.</p> <p>.....</p> 

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<b>Number of Protocol modification</b>		1
<b>Rationale for change</b>		

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