Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c20025178-02**
BI Study Number:	1275.0026
BI Investigational Product(s):	Empagliflozin + linagliptin
Title:	Post Marketing Surveillance in Japan on Long Term Drug Use of TRADIANCE® Combination Tablets AP and BP in Patients with type 2 Diabetes Mellitus
Brief lay title	A long-term study on the side effects of TRADIANCE® in Japanese patients with type 2 diabetes
Protocol version identifier:	Version 2.0
Date of last version of protocol:	8 December 2017
PASS:	Yes
EU PAS register number:	EUPAS26442
Active substance:	Empagliflozin + linagliptin
Medicinal product:	TRADIANCE® Combination Tablets AP, BP
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	Study objective is to investigate the safety of long-term daily use of TRADIANCE® Combination Tablets AP and BP in Japanese patients with type 2 Diabetes Mellitus under real-world use.
Country(-ies) of study:	Japan
Author:	[redacted] (Trial Clinical Monitor, [redacted]
Marketing authorisation holder(s):	[redacted]

MAH contact person:	[redacted]
EU-QPPV:	[redacted]
Signature of EU-QPPV:	e-signature is on BIRDS
Date:	20 November 2018

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CRF	Case Report Form
eCRF	Electronic Case Report Form
DPP-4	Dipeptidyl-peptidase IV
ECG	Electrocardiogram
EDC	Electronic Data Capture
EU-QPPV	European Union – Qualified Person for Pharmacovigilance
GPSP	Good Post- marketing Study Practice
J-PMD Act	Japanese pharmaceuticals and Medical Devices Act
J-RMP	Japan Risk Management Plan
MedDRA	Medical Dictionary for Drug Regulatory Activities
MHLW	Ministry of health, Labour and Welfare
[redacted]	
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
T2DM	Type 2 Diabetes mellitus

3. RESPONSIBLE PARTIES

[redacted]

Contact details and the list of all investigators will be kept in a stand-alone document. This document will be managed in the Post Marketing Surveillance (PMS) tracking system which manage the contracts with site and investigators name.

Co-sponsor

[redacted]

Medical advisor

[redacted]

Task:

1. Providing medical advice and comments on the study results
2. Providing medical advice on risk minimisation
3. Reviewing the contents of publication for the study results

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: TRADIANCE® Combination Tablets AP, BP			
Name of active ingredient: Empagliflozin, Linagliptin			
Protocol date: 8 December 2017	**Study number:** 1275.0026	**Version/Revision:** Version 2.0	**Version/Revision date:** 20 November 2018
Title of study:	Post Marketing Surveillance in Japan on Long Term Drug Use of TRADIANCE® Combination Tablets AP and BP in Patients with type 2 Diabetes Mellitus		
Rationale and background:	In Japan, post-approval execution of Post Marketing Surveillance is requested by the Japanese Pharmaceuticals and Medical Devices Act (J-PMD Act) in order to accumulate safety and efficacy data for re-examination. Re-examination period is defined by J-PMD Act. Four years after approval of combination drugs, results of PMS need to be submitted as a part of re-examination 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 re-examination period.		
Research question and objectives:	Study objective is to investigate the safety of long-term daily use of TRADIANCE® Combination Tablets AP and BP in Japanese patients with type 2 Diabetes Mellitus under real-world use.		
Study design:	Cohort study Non-interventional, single arm study based on newly collected data Patients will be observed for up to 52 weeks after start of the treatment with TRADIANCE® Combination Tablets AP or BP or until discontinuation of administration.		
Population:	Inclusion criteria - Japanese patients with type 2 Diabetes mellitus who are prescribed with TRADIANCE® Combination Tablets AP or BP - Patients who have never been treated with TRADIANCE® Combination Tablets AP or BP before enrolment Exclusion criteria None		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: TRADIANCE® Combination Tablets AP, BP			
Name of active ingredient: Empagliflozin, Linagliptin			
Protocol date: 8 December 2017	**Study number:** 1275.0026	**Version/Revision:** Version 2.0	**Version/Revision date:** 20 November 2018
Variables:	Outcomes: <u>Primary outcome:</u> Incidences of adverse drug reactions (ADRs) <u>Secondary outcomes:</u> None [redacted]		
Data sources:	Patients' data will be collected by electronic Case Report Form on Electronic Data Capture system		
Study size:	1000 (safety set)		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: TRADIANCE® Combination Tablets AP, BP			
Name of active ingredient: Empagliflozin, Linagliptin			
Protocol date: 8 December 2017	**Study number:** 1275.0026	**Version/Revision:** Version 2.0	**Version/Revision date:** 20 November 2018
Data analysis:	Descriptive statistics will be summarised for safety and efficacy. A mixed model repeated measures analysis will be performed for HbA1c and FPG over time.		
Milestones:	Planned start of data collection: 15 JAN 2019 Planned end of data collection: 30 APR 2021 Study Report planned to be archived in 1Q 2022		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	20 November 2018	Title page, abstract, 8, 9.1, 9.3.2, 9.7.2, 11.2	Delete objective "investigate effectiveness". Change outcomes: - "secondary outcome" was transferred to "other outcomes". - delete identified and potential risks and added "priority survey items" for safety outcomes.	Results of discussion with PMDA
		Abstract, 6, 9.2.2.2	Milestone update	Change initiation date
		Title page, 3, abstract, 6, 9.6	Update person in charge, Co-sponsor, medical advisor, CRO, timelines	Administrative updates
		9.8	Delete local SOP	Administrative updates
		Annex 2	Delete "Compliance"	Results of discussion with PMDA The compliance is included in the "Administration status of TRADIANCE® Combination Tablets AP or BP".

6. MILESTONES

Milestone	Planned Date
Start of data collection	15 January 2019
End of data collection	30 April 2021
Registration in the EU PAS register	7 November 2018
Final report of study results:	1Q 2022

7. RATIONALE AND BACKGROUND

Treatment Guide for Diabetes 2014-2015 (R14-4302) in Japan recommends to achieve the glycaemic goal of HbA1c to <7.0% in preventing the onset of microangiopathy and inhibiting its progress, while it states that suitable current treatment aims should be established according to age and complications on a case-by-case basis. If good control cannot be achieved with one type of oral antidiabetic agent, combination therapy with another drug having a different mode of action should be recommended.

TRADIANCE® Combination Tablets are the fixed dose combination of two oral antidiabetic agents for the treatment of type 2 Diabetes mellitus (T2DM). Empagliflozin is an inhibitor of the sodium-glucose co-transporter 2 (SGLT-2) and linagliptin is an inhibitor of the enzyme dipeptidyl-peptidase IV (DPP-4) both of which decrease blood glucose concentrations in patients with T2DM.
Empagliflozin received its first worldwide marketing approval in Australia on 17 Apr 2014. To this day, marketing approval has been received in many countries including European countries and US. In Japan, empagliflozin has received marketing approval on 26 Dec 2014.
Linagliptin received its first worldwide marketing approval, from the US Food and Drug Administration (FDA) on 02 May 2011. To this day, marketing approval has been received in many countries including European countries. In Japan, linagliptin has received marketing approval on 01 Jul 2011.
TRADIANCE® Combination Tablets received its first worldwide marketing approval, from the US Food and Drug Administration (FDA) on 30 Jan 2015.

Based on the complementary mechanisms of action of SGLT-2 inhibitors and DPP-4 inhibitors TRADIANCE® Combination Tablets have the potential to show additional efficacy, in terms of optimised glucose control, than its individual components in patients with T2DM. In addition, with use of a fixed dose combination formulation, the required number of tablets will be decreased, which is expected to improve adherence of the patient to the recommended treatment, compared to treatment combining single agents.

In Japan, post-approval execution of Post Marketing Surveillance (PMS) is requested by the Japanese Pharmaceuticals and Medical Devices Act (J-PMD Act) in order to accumulate safety and efficacy data for re-examination. Re-examination period is defined by J-PMD Act. Four years after approval of combination drugs, results of PMS need to be submitted as a part of re-examination 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 re-examination 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 re-examination period of TRADIANCE® Combination Tablets AP and BP (except that for this change a re-examination period is newly designated by MHLW) and [redacted] 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 TRADIANCE® Combination Tablets AP and BP) 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 J-PMD Act. It means surveillance for long-term use or special patient population (elderly, renal/hepatic dysfunction etc.).

8. RESEARCH QUESTION AND OBJECTIVES

Study objective is to investigate the safety of TRADIANCE® Combination Tablets AP and BP in patients with T2DM used in routine care. The primary outcome of this study is the incidence of any adverse drug reactions (ADRs) (see section 9.3.2).

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional study based on newly collect data of patients under routine care to confirm safety of TRADIANCE® Combination Tablets AP and BP in real-world setting in Japanese patients with T2DM.

The study will consist of a baseline visit and further visits in a 52-week follow-up for patients who have initiated TRADIANCE® Combination Tablets AP or BP treatment.

9.2 SETTING

9.2.1 Study sites

Sites throughout entire country will be equally listed according the size of the hospitals or general clinics at which TRADIANCE® Combination Tablets AP or BP are available for prescription.

Planned number of site: Approximately 200 Sites

A medical representative will explain the objective and design of this study to investigators at each study site and conclude a written contract with the head of the study site (e.g., hospital director).

9.2.2 Study population

As this is a non-interventional study, no specific treatment is mandated or withheld from the patients. No limitations are set up on background factors and their concomitant drugs in use of actual medical practice.

9.2.2.1 Inclusion/ exclusion criteria

Inclusion criteria
- Japanese patients with T2DM who are prescribed with TRADIANCE® Combination Tablets AP or BP
- Patients who have never been treated with TRADIANCE® Combination Tablets AP or BP before enrolment

Exclusion criteria
None

9.2.2.2 Registration period

From January 2019 to January 2020

9.2.2.3 Patient registration method

The registration method will be a continuous investigation system. Patients who begin treatment with TRADIANCE® Combination Tablets AP or BP after the conclusion of the contract will be registered by entering necessary information in the Electronic Data Capture (EDC) system within 14 days whenever possible from the day of treatment initiation (inclusive).

Patient registration will be stopped when the overall target number of patients for the study is reached. After the end of the registration period, investigators use a signed form to confirm that patients have been registered continuously at the site. A log of all patients included in the study will be maintained at the site.

9.2.3 Discontinuation of the study by the sponsor

[redacted] reserves the right to discontinue the PMS overall or 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 or any other administrative reasons.
3. Violation of Good Post- marketing Study Practice (GPSP), the Non-interventional Study protocol, or the contract by study site or investigator, disturbing the appropriate conduct of the PMS.

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

9.3 VARIABLES

9.3.1 Exposures

Exposure to TRADIANCE® Combination Tablets AP or BP is estimated as time from the day TRADIANCE® Combination Tablets AP or BP is initiated until the day the drug is last administrated on a patient-level (or the final contact with the patient during the regular observation period).

Patients newly initiating TRADIANCE® Combination Tablets AP or BP will be followed up to 52 weeks.

9.3.2 Outcomes

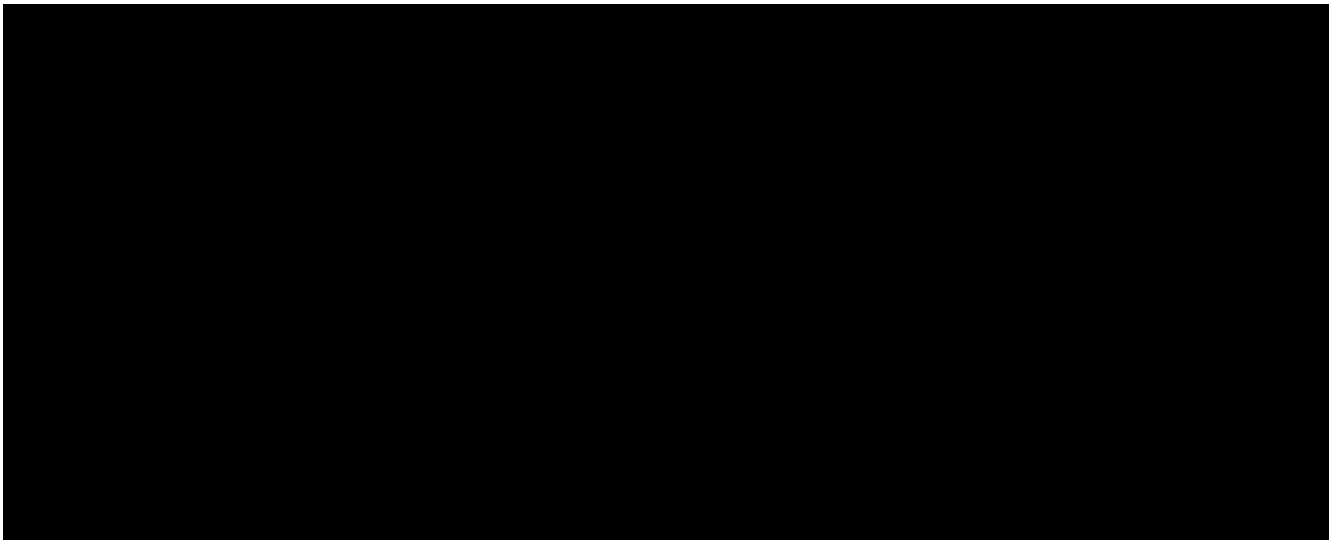
9.3.2.1 Primary outcome

The primary endpoint of this study is the incidence of adverse drug reactions (ADRs). ADRs definition and reposrting is described in section 11.

There is no primary outcome for effectiveness as the primary objective of a PMS is evaluating safety.

9.3.2.2 Secondary outcomes

None



9.3.3 Covariates

The following variables based on physician's report will be considered important baseline characteristics and potential risk factors for the outcomes of interest.

Demographics:

Gender, date of birth, indication, pregnancy status, height, body weight, Body Mass Index (derived), waist circumference, hypersensitivity factor (pick up from medical history and concomitant disease data), diagnosed date of T2DM, alcohol habit, smoking history, degree of renal/hepatic functions at baseline

Medical history / Concomitant disease:

Malignant tumor, cardiovascular/cerebrovascular disease, heart failure (severity for cardiac failure for patients with cardiac failure (NYHA classification)), urinary tract infection, genital infection, hypertension, osteoporosis, dyslipidaemia, intestinal obstruction, gout/hyperuricaemia, others, presence or absence of diabetic concomitant diagnosis (neuropathy/nephropathy/retinopathy)

Previous / Concomitant drugs and therapies:
Antidiabetics (in the 3 months before newly starting TRADIANCE):
Dose, daily frequency, start and end date
Concomitant drugs:
Dose, daily frequency, start and end date, reason for use, route of administration
Exercise and diet therapies:
Start and end date, compliance

Administration of TRADIANCE® Combination Tablets AP or BP:
Dose, daily frequency, start and end date, primary reason of discontinuation, compliance

Compliance:
All previous antidiabetics drugs compliance, TRADIANCE® Combination Tablets AP or BP compliance

Electrocardiogram:
If a resting 12-lead electrocardiogram (ECG) will be performed by investigator's order during the PMS and the investigator should review the ECG data and record the results (abnormal Yes or No) in the Electronic Case Report Form (eCRF).

Blood pressure and pulse rate (if applicable):
Systolic / diastolic blood pressure, pulse rate

Physical examination:
Body weight

Laboratory tests (blood biochemistry and urinalysis) (if applicable):

Haematology:	Erythrocyte count (RBC), haemoglobin (Hb), haematocrit (Hct), leukocyte counts (WBC) , platelet count
Blood chemistry:	HbA1c , fasting plasma glucose, sodium (Na), potassium (K), chlorine (Cl), magnesium (Mg), calcium (Ca), phosphorus (P), creatinine (CRE), aspartate transaminase (AST, SGOT), alanine transaminase (ALT, SGPT), alkaline phosphatase (ALP), gamma-glutamyl-transferase (γ-GTP), albumin , lactic dehydrogenase (LDH), total bilirubin (T-BIL), blood urea nitrogen (BUN), total cholesterol (T-CHO), HDL cholesterol (HDL), LDL cholesterol (LDL), Triglycerides (TG), Amylase (AMY), Lipase (LIP), uric acid (UA), 25-OH vitamin D, intact parathyroid hormone (iPTH), ketone, creatine kinase (CK)
Urinalysis:	Glucose, protein, urobilinogen, sediment, albumin, ketone, creatinine.

Body Mass Index (BMI):
BMI (kg/m^2) = weight(kg) / height^2 (m^2)

Grades for renal dysfunction are as follows.
Normal: eGFR ≥90 mL/min/1.73m^2
Mild: eGFR ≥60 mL/min/1.73m^2 and <90 mL/min/1.73m^2
Moderate: eGFR ≥30 mL/min/1.73m^2 and <60 mL/min/1.73m^2
Severe: eGFR <30 mL/min/1.73m^2

Investigator should judge the grade for hepatic dysfunction by using lab data category as described below and symptoms/concomitant diagnoses.
Normal: Normal AST/ALT
Mild: AST/ALT >ULN and <3x ULN
Moderate: AST/ALT≥3xULN and <5x ULN + total Bil<= 2xULN
Severe: AST/ALT≥5 xULN, or AST/ALT≥3xULN and <5x ULN + total Bil> 2xULN

ULN is taken from the corporate standard reference range (001-MCG-157_RD-01: Standard Ranges).

Enzymatic method:
$eGFR\ (mL/min/1.73\ m^2) = 194 \times Creatinine\ (mg/dL)^{-1.094} \times Age^{-0.287}$
For female, ×0.739
Jaffe rate assay:
$eGFR\ (mL/min/1.73\ m^2) = 175 \times Creatinine\ (mg/dL)^{-1.154} \times Age^{-0.203}$
For female, ×0.742

See ANNEX 2 for more details.

9.4 DATA SOURCES

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via the EDC system.

In EDC system, two casebooks will be set:
Book 1 includes baseline, 4 weeks, 12 weeks and 26 weeks.
Book 2 includes 40 weeks and 52 weeks.

The data are to be transmitted immediately after being entered into EDC at 26 weeks (Book 1) and 52 weeks (Book 2) after the start of treatment or at discontinuation.
For any adverse events, the data should be immediately entered into EDC and transmitted.

9.5 STUDY SIZE

1000 patients will be included in the study.

Hypoglycaemic Adverse Event (AE) is an important factor for evaluating risk-benefit balance of diabetes treatment and collected with high sensitivity and specificity in routine care. It is used as reference event for the sample size evaluation in PMS studies in Japan.
The proportion of Japanese patients with hypoglycaemic AE was 1.1% in Emapgliflozin + Linagliptin group in the 52 weeks data of 1275.19 trial (c14725107). If the true proportion of patients with hypoglycaemic AE is assumed to be 2-fold (i.e., 2.2%), the given sample size of 1000 gives more than 80% power to show that the proportion of patients with hypoglycaemic AE is not equal to 1.1% by using one sample chi-square test with a 0.05 two-sided significance level.

9.6 DATA MANAGEMENT

Patients' data will be gathered by EDC system provided by external vendor below.

	Contract 1	Contract 2
Company Name	[redacted]	[redacted]
Outsourced work	EDC system setting Patient registration Clinical Data Management	Document management of contract with site.

9.7 DATA ANALYSIS

This is a non-interventional study to collect data on patients under routine medical practice on safety, effectiveness and appropriate use of TRADIANCE® Combination Tablets AP and BP treatment. Analyses are descriptive in nature, including confidence intervals. Subgroup analyses will be performed if sample size allows.

Per local regulation, any patient who meets one of the following criteria is treated as ineligible for all analyses:

- No safety observation was documented after registration.
- No required registration procedure was followed.
- No valid site contract was available.

9.7.1 Analyses of Safety

The safety analysis will include all patients who registered in the study and receiving the TRADIANCE® Combination Tablets AP or BP treatment at least one time except those who are found to have no observation after enrolment, invalid registration, or invalid contract with the site (see section 9.7). In general, safety analyses will be descriptive,based on BI standards, and focus on AEs related to the TRADIANCE® Combination Tablets AP or BP treatment.

AEs will be coded using the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) and will be based on the concept of treatment emergent AEs. To this end, all AEs occurring between the initiation of TRADIANCE® Combination Tablets AP or BP prescribed at baseline visit and 7 days (inclusive) after the last administration will be considered 'treatment emergent'. An AE is considered to be an ADR if either the physician/investigator who has reported the AE or the sponsor assesses its causal relationship as 'related'.

The frequency of ADRs will be tabulated by system organ class and preferred term according to the current MedDRA version. The frequency of SAEs will also be tabulated likewise. The incidence of ADRs stratified based on patient demographics will also be investigated.

No imputation is planned for missing AE data except for missing onset dates which will be handled according to BI standard.

[redacted]

9.7.3 Interim analyses

Several interim analyses will be performed for the purpose of submission of periodic safety reports to PMDA (Pharmaceuticals and Medical Devices Agency) in project (status update of using TRADIANCE® Combination Tablets AP and BP not only with this study but all usage, every 6 month in two years after approval and every 12 months afterward. The submission date is depending on the time from the approval).

Final results will be submitted in the re-examination dossier to PMDA by 25 March 2023.

9.8 QUALITY CONTROL

All processes are conducted according to GPSP Standard Operating Procedures (SOP) (102-MLS-90-119). Appropriate records and documents are stored based on the GPSP SOPs and these processes are checked by internal self-check.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The general scientific objective of this non-interventional study is to obtain an estimate of the occurrence of ADRs in the population under study. Due to the absence of a comparator arm, there are issues that may impose limitations in particular on the validity of the assessment based on the study data such as selection bias, loss to follow up, channelling bias and information and recall bias. Thus, comparisons and causal conclusions cannot be made. To provide context to the results of this study, effort will be made to compare data to data from similar population available from other studies.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

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

9.10.2 Study records

CRFs for individual patients will be provided by the sponsor via EDC system.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the study site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For eCRFs all data must be derived from source documents.

9.10.2.2 Direct access to source data and documents

Direct access to source data and documents for PMS study is not allowed in Japan.

9.10.3 Completion of study

Completion of the PMS will be notified to PMDA when the re-examination document is applied to in accordance with J-PMD Act and GPSP.

10. PROTECTION OF HUMAN SUBJECTS

There is no regulation or requirement for ensuring the well-being and rights of participants in a non-interventional observational study.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the patient's treating physician.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

The review by Institutional Review Board is not mandatory for conducting PMS in Japanese GPSP. 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 a regulatory or legal requirement in accordance with GPSP.

10.2 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.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions (see 001-MCS-05-501-RD-01 for collection requirements) and of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted.

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A SAE is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

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

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the eCRF. When any adverse events occur, the data should be immediately entered into eCRF and transmitted. :

- all ADRs (serious and non-serious),
- all AEs with fatal outcome,

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).

- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

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

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken TRADIANCE® Combination Tablets AP or BP, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the Non-interventional Study AE form is to be completed and forwarded as well as soon as possible.

Priority survey items:

Fluid volume decreased events and Hypoglycaemia (important identified risks), safety of administration to patients with renal impairment or elderly patients (important missing information) stated in the Japan Risk Management Plan

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all AEs related to any BI drug other than TRADIANCE® Combination Tablets AP and BP, according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to the local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The progress reports and final reports will be submitted to PMDA in Japan Periodic safety report. And also the final report for this PMS is included in re-examination documents.
This study is planned for the publication based on the final report.

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

In addition, further interim analysis might be performed for the scientific presentations and publications for the purposes of promoting appropriate use of TRADIANCE® Combination Tablets AP and BP.

13. REFERENCES

13.1 PUBLISHED REFERENCES

R14-4302 The Japan Diabetes Society. Treatment Guide for Diabetes 2014-2015. Tokyo: Bunkodo; 2014.

13.2 UNPUBLISHED REFERENCES

001_MCG_157 RD_01 Standard Ranges, current version, IDEA for CON.

c14725107 [redacted] A phase III, randomised, double-blind, parallel group, 52-week study to evaluate efficacy and safety of once daily empagliflozin and linagliptin fixed dose combination compared with linagliptin plus placebo in Japanese type 2 diabetes mellitus patients with insufficient glycaemic control after 16 weeks treatment with once daily linagliptin 5 mg. BI Trial No. 1275.19. 28 June 2017.

102-MLS-90-119 Standard Operating Procedure for Good Post-marketing Study Practice, current version, IDEA for CON.

001-MCS-05-501-RD-01 Individual Case Safety Report (ICSR) collection, processing and reporting by Source, current version, IDEA for CON.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
None	None		

ANNEX 2. FLOW CHART OF VARIABLES

Time point / Item	Observation period [*1]				
	Before first administration of TRADIANCE® Combination Tablets AP or BP	Week 12	Week26	Week 40	Week 52 or at discontinuation
Registration	X[*2]				
Demographics	X				
Physical examination (Body weight, height)	X	X[*3]	X[*3]	X[*3]	X[*3]
HbA1c and fasting plasma glucose	X	X	X	X	X
Concomitant disease/ medical history	X				
Waist circumference	X				
Prior Antidiabetic drugs	X[*4]				
Administration status of TRADIANCE® Combination Tablets AP or BP		X (Record throughout the observation period)			
Concomitant drug and Concomitant therapy	X[*]	X (Record throughout the observation period)			
Blood pressure, pulse rate and ECG	(X)	(X)	(X)	(X)	(X)
Pregnancy status[*5]	X (confirm throughout the observation period)			X (confirm throughout the observation period)	
Laboratory tests	(X)	(X)	(X)	(X)	(X)
Adverse events		X (Examine throughout the observation period)			

*1: Time points during the observation period are approximate. Collected data should be reported as of the closest available visit.
*2: Patients administered TRADIANCE® Combination Tablets AP or BP will be registered within 14 days from whenever the day of first administration is possible.
*3: Body weight only
*4: From 3 month before first administration of TRADIANCE® Combination Tablets AP or BP
*5: Only for female patients
(X): If applicable

eCRF (electronic case report form): At 26 weeks, 52 weeks, and each time an adverse event has occurred, data in corresponding observation period should be entered into the eCRF and transmitted using the EDC system.

APPROVAL / SIGNATURE PAGE

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Title: Post Marketing Surveillance in Japan on Long Term Drug Use of TRADIANCE Combination Tablets AP and BP in Patients with type 2 Diabetes Mellitus

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	23 Nov 2018 08:10 CET
Approval-EU Qualified Person Pharmacovigilance		23 Nov 2018 08:37 CET
Approval-Team Member Medical Affairs		23 Nov 2018 09:26 CET
Approval-Therapeutic Area [redacted]		23 Nov 2018 09:51 CET
Approval-[redacted] Pharmacovigilance		23 Nov 2018 11:10 CET
Approval-Team Member Drug Safety		23 Nov 2018 11:15 CET
Author-Trial Statistician		26 Nov 2018 05:47 CET
Approval-Safety		27 Nov 2018 18:16 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical [redacted]	[redacted]	30 Nov 2018 03:27 CET