

## Non-interventional Study Protocol

<b>Document Number:</b> c02153926-02	
<b>BI Study Number:</b>	1245.94
<b>BI Investigational Product(s):</b>	Empagliflozin, BI 10773
<b>Title:</b>	Post Marketing Surveillance in Japan on Long Term Drug Use of JARDIANCE <sup>®</sup> Tablets in Patients with type 2 Diabetes Mellitus
<b>Clinical Phase:</b>	IV
<b>Trial Clinical Monitor:</b>	<div style="background-color: black; width: 100px; height: 15px; margin-bottom: 5px;"></div> Phone: <div style="background-color: black; width: 150px; height: 15px; display: inline-block;"></div> Fax: <div style="background-color: black; width: 150px; height: 15px; display: inline-block;"></div> <div style="background-color: black; width: 450px; height: 45px; margin-top: 10px;"></div>
<b>Co-ordinating Investigator:</b>	Not applicable
<b>Status:</b>	Final Protocol
<b>Version and Date:</b>	<b>Version: 1</b> <b>Date: 10 APR 2015</b>
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1245.94

Observational plan

c02153926-02

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## NON-INTERVENTIONAL STUDY PROTOCOL SYNOPSIS

<b>Name of company/Marketing Authorisation Holder:</b> Boehringer Ingelheim		<b>Tabulated Study Protocol</b>	
<b>Name of finished product:</b> JARDIANCE® Tablets			
<b>Name of active ingredient:</b> Empagliflozin			
<b>Protocol date:</b> 10 APR 2015	<b>Trial number:</b> 1245.94		<b>Revision date:</b>
<b>Title of study:</b>		Post Marketing Surveillance in Japan on Long Term Drug Use of JARDIANCE® Tablets in Patients with type 2 Diabetes Mellitus	
<b>Co-ordinating Investigator :</b>		Not applicable	
<b>Study site(s) :</b>		1,300 in Japan	
<b>Clinical phase:</b>		IV	
<b>Objectives:</b>		To investigate the safety and efficacy of long-term daily use of JARDIANCE® Tablets in Japanese patients with type 2 diabetes mellitus.	
<b>Methodology:</b>		Non-interventional, prospective, observational	
<b>No. of patients:</b>			
<b>Total entered:</b>		3,000 patients with the assessment of 3-year completed administration	
<b>each treatment:</b>			
<b>Diagnosis:</b>		Type 2 diabetes mellitus	
<b>Main criteria for inclusion:</b>		Male and female Japanese patients with type 2 diabetes mellitus who have never been treated with JARDIANCE® Tablets before the enrolment.	
<b>Test product(s) :</b>		JARDIANCE® Tablets	
<b>dose:</b>		10 mg, 25 mg	
<b>mode of admin. :</b>		Oral	
<b>Comparator product(s):</b>		Not applicable	
<b>dose:</b>		Not applicable	
<b>mode of admin. :</b>		Not applicable	
<b>Duration of treatment:</b>		156 weeks	

**1245.94**

**Observational plan**

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<b>Name of company/Marketing Authorisation Holder:</b> Boehringer Ingelheim		<b>Tabulated Study Protocol</b>	
<b>Name of finished product:</b> JARDIANCE® Tablets			
<b>Name of active ingredient:</b> Empagliflozin			
<b>Protocol date:</b> 10 APR 2015	<b>Trial number:</b> 1245.94		<b>Revision date:</b>
<b>Criteria for efficacy:</b>	Primary efficacy endpoint: None Secondary efficacy endpoint: Change from baseline in HbA1c and FPG to the last- observation on treatment.		
<b>Criteria for safety:</b>	Primary safety endpoint: Incidence of adverse drug reactions (ADRs)		
<b>Statistical methods:</b>	Descriptive statistics will be summarised for safety and efficacy. A mixed model repeated measures analysis will be performed for HbA1c over time.		

## FLOW CHART

	Screening	Treatment	End of Trial
Observation period*	Before first administration of JARDIANCE® Tablets	12, 26, 40, 52, 64, 78, 104, 130 W	156 W <sup>5</sup>
Registration	X <sup>1</sup>		
Demographics	X		
Administration of JARDIANCE® Tablets		X	X
Medical History/ Concomitant disease	X		
Waist circumference	X		
Blood pressure pulse rate and ECG	X	X	X
HbA1c and fasting plasma glucose	X	X	X
Laboratory tests	X	X	X
Physical examination (Body weight, height)	X	X <sup>2</sup>	X <sup>2</sup>
12-lead ECG	X	X	X
Pregnancy status <sup>3</sup>	X	X	X
Concomitant drug(s) and antidiabetic therapy <sup>4</sup>	X	X	X
Adverse events ██████████		X	X

W: Weeks

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

1: Patients administered JARDIANCE® Tablets will be registered preferably within 14 days from the day of first administration.

2: Body weight only

3: Only for female patients

4: From 1 month before first administration of JARDIANCE® Tablets

5: Time point for 156 weeks should be more than 1092 days.

Electronic case report form (eCRF): At 12 weeks, 52 weeks, 104 weeks, 156 weeks or discontinuation and each time when an adverse event has occurred, data in corresponding observation period should be entered into eCRF and transmitted using the EDC system.

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## ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMY	Amylase
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
BICMQ	Boehringer Ingelheim customised MedDRA query
BMI	Body-mass index
BUN	Blood Urea Nitrogen
CK	Creatine Kinase
CRF	Case Report Form
DEDP	Drug Exposure During Pregnancy
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular filtration Rate
FPG	Fasting plasma glucose
$\gamma$ -GTP	Gamma-glutamyl-transferase
GPSP	Good Post-marketing Study Practice
GVP	Good Vigilance Practice
HDL	High Density Lipoprotein cholesterol
IRB	Institutional Review Board
J-PAL	Japanese Pharmaceutical Affairs Law
LDH	Lactic dehydrogenase
LDL	Low Density Lipoprotein cholesterol
LIP	Lipase
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MMRM	Mixed model repeated measures
NGSP	National Glycohemoglobin Standardization Program
NYHA	New York Heart Association
MR	Medical Representative
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
REML	Restricted maximum likelihood
SAE	Serious Adverse Event
SGLT-2	Sodium-dependent glucose co-transporter-2
SMQ	Standardised MedDRA Queries
SOP	Standard Operating Procedure
T-BIL	Total Bilirubin
T-CHO	Total Cholesterol
TG	Triglycerides
UA	Uric Acid



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ULN

Upper Limit of Normal range

## **1. INTRODUCTION**

### **1.1 MEDICAL BACKGROUND**

The estimated worldwide prevalence of diabetes in 2011 was 366 million with an increase of 50% expected within the next 20 years. Most of these patients have type 2 diabetes mellitus, which is characterised by insulin resistance and impaired insulin secretion. Diabetes is associated with microvascular complications and elevated cardiovascular risk. Treatment of type 2 diabetes usually involves lifestyle interventions such as diet and exercise, as well as the administration of oral or injectable antidiabetic drugs. Although initially effective, currently available oral antidiabetic agents often fail to maintain long-term glycaemic control or are associated with side effects that may limit their use. Hence, there is a need for new therapeutic options for patients with type 2 diabetes to provide sustained improvements in glycaemic control and to contribute to reducing cardiovascular risk factors such as overweight and hypertension.

The kidney has a role in the regulation of blood glucose levels and can therefore serve as a target for new antidiabetic drugs. The sodium-dependent glucose co-transporter-2 (SGLT-2) is mainly expressed in the renal proximal tubules and accounts for approximately 90% of renal glucose reabsorption. Inhibition of SGLT-2 decreases the renal reabsorption of glucose, thereby promoting glucose excretion in the urine with a resulting reduction in blood glucose levels. Due to their insulin-independent mechanism of action, SGLT-2 inhibitors have a low risk of hypoglycaemia. Further benefits of SGLT-2 inhibition may include weight reduction due to the calorie loss associated with increased glucose excretion and a decrease in blood pressure that is possibly due to a mild diuretic effect.

### **1.2 DRUG PROFILE**

Empagliflozin (internal code: BI 10773) is a novel, orally administered, potent, and selective SGLT-2 inhibitor developed by Boehringer Ingelheim. Empagliflozin is proposed to be registered for treatment of type 2 diabetes mellitus in conjunction with diet and exercise, as monotherapy or as add on other oral antidiabetic treatments or insulin. Empagliflozin tablets are to be administered once daily, with or without food. The recommended therapeutic dose is 10 mg. If treatment efficacy is insufficient, the daily dose can be increased to 25 mg once daily while the patient's condition is being carefully monitored.

## **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 re-examination. Re-examination period is defined by J-PAL. New integrant is 8 years for re-examination. Eight years after approval of a new substance, 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 JARDIANCE<sup>®</sup> Tablets (except that for this change a re-examination 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 JARDIANCE<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 J-PAL. It means surveillance for long-term use or special patient population (elderly, renal/hepatic dysfunction etc.).

SGLT-2 inhibitor is a drug class with a new mode of action, and does not comprise sufficient Japanese safety data within the class. It's not that there is a particular safety issue concerning JARDIANCE<sup>®</sup>; however, further surveillance is needed to monitor possible increase in the incidence of malignant tumor which is potentially associated with drugs of the same class, as well as the effect on kidneys attributable to its mode of action by which a long-term use stimulates the urinary excretion of glucose, and also the effect on hepatic function and bone metabolism.

This long-term drug use surveillance is planned to collect and investigate primarily safety data.

### **2.2 STUDY OBJECTIVES**

Study objectives are to investigate the safety and efficacy of long-term daily use of JARDIANCE<sup>®</sup> Tablets in patients with type 2 diabetes mellitus.

### **2.3 BENEFIT-RISK ASSESSMENT**

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

### 3. DESCRIPTION OF DESIGN AND STUDY POPULATION

#### 3.1 OVERALL DESIGN AND PLAN

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

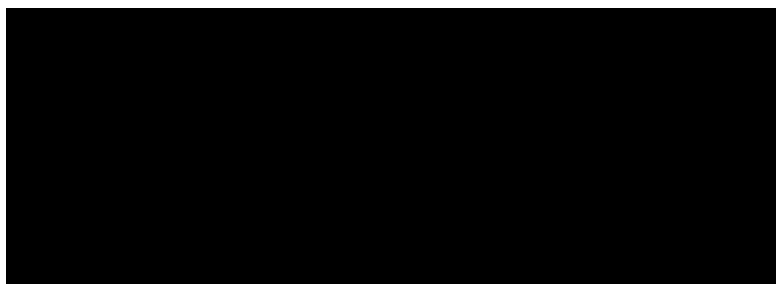
Patients administered JARDIANCE® Tablets will be registered preferably within 14 days from the day of first administration. Patients will be observed for up to 156 weeks (approximately 36 months) after start of the treatment with JARDIANCE® Tablets or at premature discontinuation and dropout. Observations are made at the following time points: before first administration of JARDIANCE® Tablets (screening, this visit is defined as baseline) and 12, 26, 40, 52, 64, 78, 104, 130 and 156 weeks after the start of treatment, or at discontinuation.

There are 4 separate eCRFs for 0-12 (Book 1), 13- 52 (Book 2), 53- 104 (Book 3) and 105-156 weeks (Book 4).

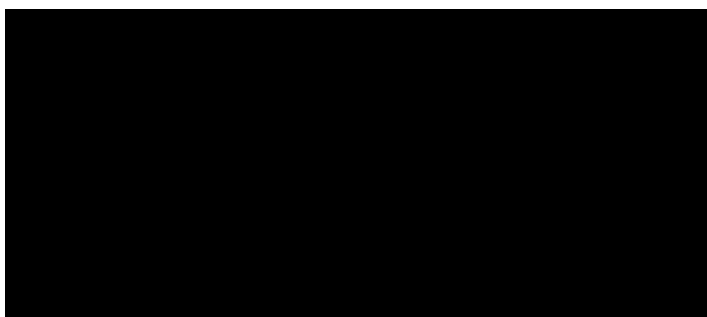
At 12, 52, 104 and 156 weeks after the start of treatment or at discontinuation, data are to be transmitted immediately after entered into eCRF. In case of occurrence of any adverse events, data in corresponding observation period should be immediately entered into eCRF and transmitted.

##### 3.1.1 Administrative structure of the study

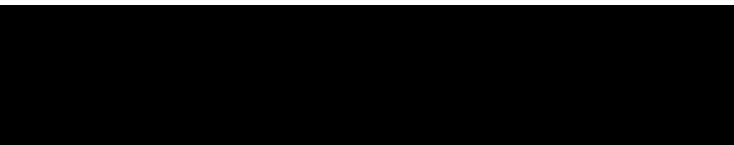
###### Sponsor



###### Co-sponsor

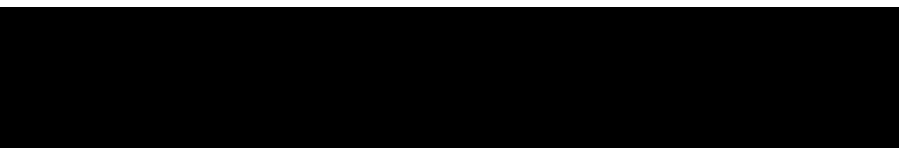


Contract research organizations



Task: Registration centre and data management

Medical advisor



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

**3.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)**

This is a non-interventional, observational study based on newly collected data under routine medical practice. There is no control group.

**3.3 SELECTION OF POPULATION**

Total number of entered patients is 3,000 patients with the assessment of 3-year completed administration.

No limitations are set up on background factors of patients and their concomitant drugs in use of actual medical practice.

Estimated number of enrolled patients with renal dysfunction ( $45 \text{ mL/min/1.73m}^2 \leq \text{eGFR} < 60 \text{ mL/min/1.73m}^2$ ) is 100.

Grades for renal dysfunction are as follows.

Normal:  $\text{eGFR} \geq 90 \text{ mL/min/1.73m}^2$   
Mild:  $\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$  and  $< 90 \text{ mL/min/1.73m}^2$   
Moderate:  $\text{eGFR} \geq 30 \text{ mL/min/1.73m}^2$  and  $< 60 \text{ mL/min/1.73m}^2$   
Severe:  $\text{eGFR} < 30 \text{ mL/min/1.73m}^2$

Estimated number of enrolled elderly patients ( $\geq 75$  years) is 100.

Estimated number of enrolled patients with hepatic dysfunction is 100.

Patients with hepatic dysfunction: Investigator judgment is moderate or severe.

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).

Sites throughout entire country will be equally listed according the size of the hospitals or general clinics at which JARDIANCE<sup>®</sup> Tablets are available for prescription.

Expected number of patients per site is 5-30 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 JARDIANCE<sup>®</sup> Tablets is started. However, patients who are registered over 15 days after starting administration of JARDIANCE<sup>®</sup> Tablets are also used for safety and efficacy analysis.

The registered patients: The patient registration date are entered into eCRF and transmitted using the EDC system.

The entered patients: The patient are registered and observational data after taking JARDIANCE<sup>®</sup> Tablets are entered into eCRF and transmitted using the EDC system.

Investigators will confirm the continuous registration at the site at the end of the enrolment period with the signed form.

### **3.3.1 Main diagnosis for study entry**

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

### **3.3.2 Inclusion criteria**

Patients with type 2 diabetes mellitus who have never been treated with JARDIANCE<sup>®</sup> Tablets / Empagliflozin before enrollment will be included.

### **3.3.3 Exclusion criteria**

None

### **3.3.4 Removal of patients from therapy or assessments**

#### **3.3.4.1 Removal from individual patients**

Patients may voluntarily discontinue the treatment under study 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 PMS overall or at a particular PMS 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 PMS site will be reimbursed for reasonable expenses incurred as a result of PMS termination (except in case of the third reason).



## **4. TREATMENTS**

### **4.1 PRESCRIBED TREATMENTS TO BE OBSERVED**

#### **4.1.1 Identity of test product(s) and comparator product(s)**

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 JARDIANCE<sup>®</sup> Tablets.

#### **4.1.2 Method of assigning patients to treatment groups**

There is no randomisation, since this is an observational surveillance study.

#### **4.1.3 Selection of doses in the study**

The usual dose is 10 mg of a JARDIANCE<sup>®</sup> Tablet administered orally once daily. If treatment efficacy is insufficient, the daily dose can be increased to 25 mg once daily while the patient's condition is being carefully monitored.

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

The investigators indicate doses and timing based on the package insert.

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

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

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

#### **4.2.2 Restrictions**

##### **4.2.2.1 Restrictions regarding concomitant treatment**

All the restrictions listed in the package insert are applied.

##### **4.2.2.2 Restrictions on diet and life style**

All the restrictions listed in the package insert are applied.

### **4.3 TREATMENT COMPLIANCE**

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

## 5. VARIABLES AND THEIR ASSESSMENT

### 5.1 EFFICACY

#### 5.1.1 Endpoint(s) of efficacy

There is no primary endpoint for efficacy as the primary objective of a PMS is evaluating safety (See Section 5.2).

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

#### 5.1.2 Assessment of efficacy

##### *HbA1c:*

The blood samples can be taken at any time and will be measured at the sites by using National Glycohemoglobin Standardization Program (NGSP).

##### *Fasting plasma glucose (FPG):*

Fasting is defined as before breakfast and more than 10-hr past from previous JARDIANCE<sup>®</sup> Tablets administration. The blood samples should be taken before breakfast and before JARDIANCE<sup>®</sup> Tablets administration. The blood samples will be taken and measured at the sites. Plasma glucose will be reported in mg/dL.

### 5.2 SAFETY

#### 5.2.1 Endpoint(s) of safety

Primary endpoint of this study is the number of patient with adverse drug reactions (ADRs)

The other safety endpoint is the number of patient with serious adverse events (SAEs) [REDACTED]

## 5.2.2 Management and reporting of adverse events/adverse reactions

### 5.2.2.1 Definitions of adverse events

#### Adverse event

An adverse event (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 adverse event can therefore be any unfavorable 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 drug reaction

An adverse drug 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 adverse event 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 serious adverse event 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 judgment 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.

#### Adverse Event of Special Interest (AESI)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

### **5.3 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING**

#### **5.3.1 Adverse event and serious adverse event collection**

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 authorisation. 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 (e)CRF from first intake of JARDIANCE® Tablets at baseline visit and within 7 days (inclusive) after the last intake:

- all ADRs (serious and non-serious) as soon as possible,
- all AEs with fatal outcome in patients exposed to JARDIANCE® Tablets as soon as possible,

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 adverse event. An adverse reaction, in contrast to an adverse event, is characterised 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.

Possibility high:	There is a reasonable causal relationship between JARDIANCE <sup>®</sup> Tablets administered and the AE.
Possibility low:	It is probably/possibly that there is a reasonable causal relationship between JARDIANCE <sup>®</sup> Tablets administered and the AE.
Unknown:	Cannot be judged because information is insufficient or contradictory.
Unrelated:	There is no reasonable causal relationship between JARDIANCE <sup>®</sup> Tablets administered and the AE.

ADRs are defined that causal relationship is "Possibility high " or "Possibility low" or "Unknown".

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 patient has been enrolled into the PMS, after having taken JARDIANCE<sup>®</sup> Tablets, the investigator must report any drug exposure during pregnancy which occurred in a female patient or in a partner to a male patient 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.

Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator to the Sponsor's unique entry point from first intake of JARDIANCE<sup>®</sup> Tablets at baseline visit and within 7 days (inclusive) after last intake:

Type of Report	Timeline
All <b>SA</b> DRs associated with the JARDIANCE <sup>®</sup> Tablets	As soon as possible
All <b>A</b> Es with <b>fatal outcome</b> in patients exposed to JARDIANCE <sup>®</sup> Tablets	As soon as possible
All <b>non-serious</b> ADRs associated with the JARDIANCE <sup>®</sup> Tablets	As soon as possible
All <b>pregnancy monitoring</b> forms	As soon as possible

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete the appropriate (e)CRF.



### 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 adverse events related to any BI drug other than the JARDIANCE<sup>®</sup> Tablets 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.

#### **5.3.2 Reporting to health authorities**

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

#### **5.3.3 Assessment of safety laboratory parameters**

The laboratory tests will be performed when required by investigator.

Safety laboratory assessment will be performed according to local practice and if available the following parameters will be recorded in the eCRFs:

<b>Haematology</b>	Erythrocyte count (RBC), haemoglobin (Hb), haematocrit (Hct), Leukocyte counts (WBC) and platelet count.
<b>Blood chemistry</b>	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 ( $\gamma$ -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, iPTH, ketone and creatine kinase (CK).
<b>Urinalysis</b>	Glucose, protein, urobilinogen, sediment, albumin, ketone and creatinine.

Enzymatic method:

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

For female,  $\times 0.739$

Jaffe rate assay:

$$\text{eGFR (mL/min/1.73 m}^2) = 175 \times \text{Creatinine (mg/dL)}^{-1.154} \times \text{Age}^{-0.203}$$

For female,  $\times 0.742$

### 5.3.4 Electrocardiogram

If a resting 12-lead 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 eCRF.

### 5.3.5 Assessment of other safety parameters

#### Vital signs

Vital signs (usually blood pressure and pulse after 2 minutes supine rest) will be recorded at the screening visit and at the closest time points specified in the Flow Chart.



## **5.4 OTHER**

### **5.4.1 Other parameter**

#### **Demographics and history**

Demographics (gender, date of birth, indication, pregnancy status, height, body weight, waist circumference, hypersensitivity factor, alcohol habit, pre-treatment drug, diagnosed date of type 2 diabetes mellitus, smoking history, start date of administration)

Medical history (malignant tumor, cardiovascular/cerebrovascular disease (severity for cardiac failure for patients with past history of cardiac failure (NYHA classification)), urinary tract infection, genital infection, hypertension, osteoporosis, dyslipidaemia, goat/hyperuricaemia, others)

Concomitant disease (malignant tumor, cardiovascular/cerebrovascular disease (severity for cardiac failure for patients with past history of cardiac failure (NYHA classification)), urinary tract infection, genital infection, osteoporosis, others), presence or absence of diabetic concomitant diagnosis (neuropathy/nephropathy/retinopathy), degree of renal/hepatic functions at baseline, history of antidiabetic treatment (drug therapy, diet therapy)

### **5.4.2 Other assessment**

#### **Concomitant drugs and antidiabetic therapies**

Concomitant drugs and antidiabetic therapies present during PMS will be recorded in the CRF.

## **5.5 APPROPRIATENESS OF MEASUREMENTS**

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

## **6. INVESTIGATIONAL PLAN**

### **6.1 VISIT SCHEDULE**

#### **Screening and run-in period(s)**

##### 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 JARDIANCE<sup>®</sup> Tablets.

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

#### **Treatment period(s)**

Patients will receive continuous daily treatment until the criteria for stopping medication are met according to the package insert.

During the treatment phase visits will be performed as planned if applicable and assessments will be documented within the nearest PMS visit.

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

The visit at 156 weeks after starting JARDIANCE<sup>®</sup> Tablets treatment or the last visit before discontinuation will be the end of the PMS.

**6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS**

**6.2.1 Screening and run-in period(s)**

<b>Screening Visit</b>	
Screening Visit is before the first administration of JARDIANCE® Tablets	
Demographics	Gender, birth date, indication, pregnancy status, height, body weight, BMI (derived from weight and height), waist circumference, smoking history, duration of type 2 diabetes mellitus, grade of hepatic dysfunction and hypersensitivity factor.
Medical history / Concomitant disease	Document medical history and concomitant disease
Pre-treatment drug	Document start and stop date of each pre-treatment drug
Vital signs	Blood pressure and pulse rate.
ECG	Resting 12-lead ECG will be performed if applicable.
Laboratory tests	Haematology, Biochemistry, Urinalysis (see section 5.3.3 for minimum assessments).
Concomitant drugs and antidiabetic therapies	Document indication, start and stop date of each concomitant drugs and antidiabetic therapies.
Administration	Document dose and start date.

**6.2.2 Treatment period(s)**

<b>Treatment period(s)</b> 12, 26, 40, 52, 64, 78, 104 and 130 weeks after the start of treatment When stop the treatment, please complete the EOT visit instead.	
Vital signs	Blood pressure and pulse rate.
Body weight	Document body weight
Pregnancy status	Document when pregnancy is discovered.
ECG	Resting 12-lead ECG will be performed if applicable.
Laboratory tests	Haematology, Biochemistry, Urinalysis (see section 5.3.3 for minimum assessments).
Concomitant drugs and antidiabetic therapies	Document indication, start and stop date of each concomitant drugs and antidiabetic therapies.
Administration	Document dose, start and stop date and reason of termination.
Adverse events ██████████	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit. ██████████ ██████████ ██████████

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

<b>End of trial</b> EOT Complete this visit at 156 weeks after the start of treatment or at discontinuation.	
Vital signs	Blood pressure and pulse rate.
Body weight	Document body weight
Pregnancy status	Document when pregnancy is discovered.
ECG	Resting 12-lead ECG will be performed if applicable.
Laboratory tests	Haematology, Biochemistry, Urinalysis (see section 5.3.3 for minimum assessments).
Concomitant drugs and antidiabetic therapies	Document indication, start and stop date of each concomitant drugs and antidiabetic therapies.
Administration	Document dose, start and stop date and reason of termination.
Adverse events ██████████	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit. ██████████ ██████████ ██████████

## 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

### 7.1 STATISTICAL DESIGN - MODEL

This is a non-interventional, prospective and observational study to investigate the safety and efficacy of long-term use of JARDIANCE<sup>®</sup> Tablets in patients with type 2 diabetes mellitus.

### 7.2 NULL AND ALTERNATIVE HYPOTHESES

The analyses in this PMS are descriptive and exploratory by nature. No formal hypotheses tests will be made.

### 7.3 PLANNED ANALYSES

The safety evaluation will be performed on the “safety set” that will include all patients who have received treatment of JARDIANCE<sup>®</sup> Tablet at least one time except those who are found to have no observation after enrolment, invalid registration, or invalid contract with the site. 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.

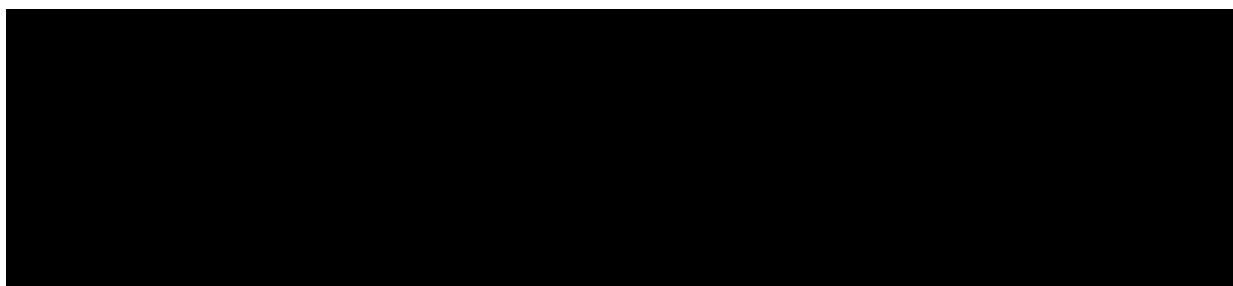
#### 7.3.1 Primary analyses

In this PMS, the primary endpoint is the number of patient with ADRs. The details are given in Section [7.3.3](#)

#### 7.3.2 Secondary analyses

For change from baseline in HbA1c and FPG, descriptive statistics will be calculated with 95% confidence interval for the mean change from baseline.

A mixed model repeated measures analysis using all the available longitudinal observations during the observation period after the first administration of JARDIANCE<sup>®</sup> Tablets will be performed. Within-patient variability from all time points is assumed to have a particular variance-covariance structure, which is “compound symmetry.” Least square means will be computed at every time point and their respective standard error and 95% confidence interval estimate account for the estimated covariance parameters.



### **7.3.3 Safety analyses**

The analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between first drug intakes until 7 days after last treatment administration will be considered ‘treatment-emergent’. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

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 JARDIANCE<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 JARDIANCE<sup>®</sup> Tablets either as “Possibility high”, “Possibility low” or “Unknown”.

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

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

### **7.3.4 Interim analyses**

Interim analyses will be performed periodically for the purpose of creating safety update reports to the local authority as well as for publications.

## **7.4 HANDLING OF MISSING DATA**

The REML based MMRM analysis will handle missing data for continuous efficacy endpoints for patients who discontinue the study treatment prematurely or whom corresponding assessments / measurements are not documented / available.

## **7.5 RANDOMISATION**

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

## **7.6 DETERMINATION OF SAMPLE SIZE**

According to the request from the Japanese authority, this PMS will target to include 3,000 patients who complete a 3-year JARDIANCE<sup>®</sup> observation period. There is no target number of enrolment. For the 3,000 completer patients, an ADR with a true incidence of at least 0.10% (or 0.16%) will occur in at least one patient with a probability of 95% (or 99%).

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

Elderly patients ( $\geq 75$  years)

Elderly patients were observed in 14.6% of the patients with type 2 diabetes mellitus based on the National Health and Nutrition Examination Survey (2007) [R13-5199]; it is estimated that approximately 400 ~ 500 elderly patients will be included in the 3,000 completer patients.

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

#### Renal dysfunction

The patients with renal dysfunction (eGFR 45~60 mL/min/1.73m<sup>2</sup>) were observed in 14.8% of the patients with type 2 diabetes mellitus in based on the historical cohort study with type 2 diabetes [R13-5102]; it is estimated that approximately 400 ~ 500 patients with renal dysfunction will be included in the 3,000 completer patients.

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

#### Hepatic dysfunction

Based on the result that hepatic function disorder was observed in 13.7% of the patients in the surveillance on the long-term use of Amaryl<sup>®</sup> Tablets, an agent for type 2 diabetes [R11-4205], it is estimated that approximately 350 ~ 450 patients with hepatic dysfunction will be included in the 3,000 completer patients.

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

If the number of completer patients with 3-year JARDIANCE<sup>®</sup> observation period or specific diseases is less than expected by monitoring received CRF data, registration period or total number of enrolled patients may be extended.

## **8. INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS**

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

The rights of the investigator and of the sponsor with regard to publication of the results of this PMS are described in the 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**

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

#### **8.3.1 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 investigator's 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 trial; also current medical records must be available.

For eCRFs, all of the following data must be derived from source documents.

- Patient identification (gender, date of birth)
- Patient participation in the PMS (substance, patient number)
- Dates of Patient's visits, including dispensing of medication
- Medical history (including indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date, end date, treatment for AEs)
- Serious adverse events (onset date, and end date)
- Laboratory results

### **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 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 on request by the regulatory authorities.

## **8.5 COMPLETION OF STUDY**

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

## **9. REFERENCES**

### **9.1 PUBLISHED REFERENCES**

- R13-5199 National Health and Nutrition Examination Survey (2007)
- R13-5102 Wada T, et al: Clinical and Experimental Nephrology, Published online: 2014 Aug; 18(4):613-20.
- 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**

## **10. APPENDICES**

Not applicable.

**11. SUMMARY OF NON-INTERVENTIONAL STUDY  
PROTOCOL MODIFICATIONS**

Summary of Modifications Sheet (SOMS)

<b>Number of Protocol modification</b>		
<b>Date of Protocol modification</b>		
<b>BI Trial number</b>		
<b>BI Product(s)</b>		
<b>Title of protocol</b>		
<b>To be implemented only after approval of the IRB/IEC/Competent Authorities</b>		<input 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>		
<b>Description of change</b>		
<b>Rationale for change</b>		