Non-Interventional Study Protocol

Doc. No.: U13-3721-01

BI Study No.:	1288.22
BI Investigational Product(s):	Linagliptin, Metformin
Title:	A regulatory requirement non interventional study to monitor the **s**afety and **e**ffectiveness of Trajenta Duo® (Linagliptin/Metformin HCl, 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg, b.i.d) in Korean patients with type 2 diabetes mellitus (SELINA Duo study)
Clinical Phase:	IV
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]
Principal Investigator:	Not Applicable
Status:	Final protocol
Version and Date:	**Version: 1.3** **Date: 22 Feb 2017**

NON-INTERVENTIONAL STUDY PROTOCOL SYNOPSIS

Name of company/Marketing Authorisation Holder: Boehringer Ingelheim Korea		**Tabulated Study Protocol**	
Name of finished product: Trajenta Duo®.			
Name of active ingredient: Linagliptin/Metformin FDC			
Protocol date: 25 January 2013	**Trial number:** 1288.22/U13-3721-01		**Revision date:** 22 Feb 2017

Title of study:	A regulatory requirement non interventional study to monitor the safety and effectiveness of Trajenta Duo®. (Linagliptin/Metformin HCl, 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg, b.i.d) in Korean patients with type 2 diabetes mellitus (SELINA Duo study)
Principal Investigator:	Not Applicable
Study site(s) :	Multi-centre study
Clinical phase:	IV
Objectives:	To monitor the safety profile and effectiveness of linagliptin, metformin fixed dose combination in Korean patients with type 2 diabetes mellitus in a routine clinical practice setting
Methodology:	observational, non-interventional, open-label, multi-centre national study
No. of patients:	
Total entered:	600 approximately
each treatment:	Single arm (N=600 approximately)
Diagnosis:	Patients diagnosed with type 2 diabetes mellitus
Main criteria for inclusion:	1) No previous exposure to Trajenta®, Trajenta Duo® 2) Patients who have been started on Trajenta Duo® in accordance with the approved label in Korea 3) No current participation in clinical trials 4) No contraindications to linagliptin or metformin in accordance with local prescribing information 5) Patients who have signed on the data release consent form
Test product(s) :	Linagliptin/Metformin FDC
dose:	2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg, b.i.d
mode of admin. :	Oral administration
Comparator product(s):	Not applicable

Name of company/Marketing Authorisation Holder: Boehringer Ingelheim Korea		**Tabulated Study Protocol**	
Name of finished product: Trajenta Duo®.			
Name of active ingredient: Linagliptin/Metformin FDC			
Protocol date: 25 January 2013	**Trial number:** 1288.22/U13-3721-01		**Revision date:** 22 Feb 2017
dose: **mode of admin. :**			

Duration of treatment:	1) Treatment duration for short-term surveillance: 12±2 weeks, long-term surveillance: 24±2 weeks. 2) Study duration: 5 years. (MFDS set Trajenta Duo® re-examination period from 15 Nov 2012 to 13 September 2017. Interim report planned biannually for the initial two years and annually thereafter by Dec 2017.)
Criteria for effectiveness:	1. Main endpoint 1) Change from baseline in HbA1c after 24 weeks of treatment. 2. Other endpoint 1) Occurrence of treat to target effectiveness response that is an HbA1c under treatment of < 6.5% after 24 weeks of treatment. 2) Occurrence of relative effectiveness response (HbA_{1c} lowering by at least 0.5% after 24 weeks) 3) Change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment
Criteria for safety:	All reported adverse events including hypoglycemic events in patients who take at least one dose of Trajenta Duo® will be noted. Endpoints pertaining to safety will be presented as incidence rates of adverse events
Statistical methods:	Descriptive statistics

FLOW CHART

Data points	**Baseline**	**Follow-up 1**	**Follow-up 2**
Visit Number	1	2	3
Week/s	0	12±2	24±2
Diagnosis	X		
Inclusion / exclusion criteria	X		
Demographics	X		
Diabetes mellitus complications	X		
Other medical history	X		
Anti-hyperglycemic agents	X	X	X
Concomitant medications	X	X	X
Trajenta Duo® administration status	X	X	X
Renal function	X [A]		
Effectiveness endpoints		X	X
Changes in lab tests		X [A]	X [A]
Adverse events		X	X
Study completion		X	X

[A]: If applicable.

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ABBREVIATIONS

AE	Adverse Event
ACR	Albumin Creatinine Ratio
ADR	Adverse Drug Reaction
CA	Competency Authority
CEU	Case Entry Unit
CML	Clinical Monitor Local
CRF	Case Report Form
CRO	Contract Research Organization
CSO	Clinical Safety Officer
DPP-4	Dipeptidyl-peptidase 4
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EDC	Electronic Data Capture
FU	Follow up
FPG	Fasting Plasma Glucose
GIP	Glucose dependent Insulinotropic Peptide
GLP-1	Glucagon-Like Peptide-1
HbA_{1c}	Glucosylated Hemoglobin
MFDS	Ministry of Food and Drug Safety
KIMS	Korea Index of Medical Specialties
KPAC	Korean Pharmaceutical Affairs Code
KPMA	Korea Pharmaceutical Manufacturers Association
KRPIA	Korean Research-based Pharmaceutical Industry Association
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Drug Regulatory Activities
NCE	New Chemical Entity
NIS	Non Interventional study
SAE	Serious Adverse Event
T2DM	Type 2 Diabetes Mellitus
TSAP	Trial Statistical Analysis Plan

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Type 2 diabetes mellitus (T2DM) accounts for 90% to 95% of all cases of diabetes and is an increasingly prevalent disease with an estimated 347 million affected people worldwide. Its incidence is expected to double during the next 20 years[1]. About 3.2 million Korean people (10.1%) aged over 30 years or older had diabetes in 2010. Based on fasting glucose, 19.9% of adults had prediabetes (impaired fasting glucose). Accordingly 3 out of 10 people in Korea are diabetes or at high risk of future diabetes in 2010. Diabetes will affect 6.0 million people in Korea by 2050, which will be twice higher than that of 2010.The growth rate would be 183% for the next 40 years.[2]. Complications induced by hyperglycaemia are currently the most frequent cause of adult-onset loss of vision, renal failure, and non-traumatic lower extremity amputations in the industrialized world. T2DM is also associated with macrovascular complications with a 2- to 4-fold increase in cardiovascular disease risk. The high frequency of complications leads to a significant reduction of life expectancy [R09-4241].

Although several antidiabetic compounds have been developed to improve glucose control and attenuate the metabolic derangements that accompany uncontrolled T2DM, none of these compounds has been able to maintain long-term glycaemic control.

The improved understanding of the incretin effect has contributed to the development of a new class of antidiabetic agents. The incretin effect results from glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP), two intestinal peptides that are released in the presence of glucose or nutrients in the gut. GLP-1 stimulates insulin secretion, thereby augmenting glucose-stimulated insulin release. However, there is little risk of hypoglycaemia due to GLP-1 because GLP-1 activity decreases when glucose concentrations fall below 55 milligrams per deciLiter (mg/dL). Normally, GLP-1 is almost instantaneously inactivated by the enzyme DPP-4 that is widely expressed in many tissues including kidney, liver, intestine, lymphocytes and vascular endothelial cells. Therefore, inhibiting DPP-4 would prolong the activity of GLP-1 for stimulating insulin secretion.

Linagliptin is a potent inhibitor of DPP-4 activity and prolongs the half-life of GLP-1. This has been shown in vitro, in various animal models, and in clinical trials. Linagliptin is an orally available compound with a low risk for hypoglycaemic episodes [U04-1767-11].

1.2 DRUG PROFILE

1.2.1 Linagliptin

Treatment with 5 mg linagliptin, once daily, has been shown to result in clinically meaningful and statistically significant reductions in HbA1c, FPG and PPG. There was a consistent pattern in the improvement in HbA1c when linagliptin was used in patients with different background therapies. In phase III trials in monotherapy (including a trial in patients intolerant of metformin), combination with metformin, combination with sulfonylurea, combination with metformin and sulfonylurea, and initial combination with pioglitazone,

linagliptin 5 mg led to a significant reduction of HbA1c (placebo corrected HbA1c changes from baseline were in the range of -0.47% to -0.87%).[U04-1767-11]

The efficacy and safety of linagliptin in combination with metformin in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double blind placebo controlled study of 24 weeks duration. Linagliptin added to metformin provided significant improvements in HbA1c, (-0.64 % change compared to placebo), from a mean baseline HbA1c of 8 %. Linagliptin also showed significant improvements in fasting plasma glucose (FPG) by -21.1 mg/dl and 2-hour post-prandial glucose (PPG) by -67.1 mg/dl compared to placebo, as well as a greater portion of patients achieving a target HbA1c of < 7.0% (28.3% on linagliptin vs. 11.4% on placebo). The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo. Body weight did not differ significantly between the groups.

The efficacy and safety of linagliptin 2.5 mg twice daily versus 5 mg once daily in combination with metformin in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double blind placebo controlled study of 12 weeks duration. Linagliptin 5 mg once daily and 2.5 mg twice daily provided comparable (CI: -0.07; 0.19) significant HbA1c reductions of -0.80% (from baseline 7.98%), and -0.74% (from baseline 7.96%) compared to placebo. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo.

For further details, please see refer to the local prescribing information of Trajenta Duo®.

1.2.2 Metformin

Metformin is an oral antihyperglycaemic agent that reduces plasma glucose levels by decreasing intestinal glucose absorption and hepatic glucose production and enhancing the glucose uptake and utilization of peripheral tissue. Thus metformin renders a reduction of basal and postprandial plasma glucose in patients with type 2 diabetes. Unlike sulfonylureas (e.g. glyburide) metformin does not increase insulin secretion and is not associated with hypoglycaemia in either patients with type 2 diabetes or healthy volunteers [R10-5537].
Gastrointestinal absorption of metformin is incomplete with an absolute bioavailability of 50-60 % under fasting conditions. The intake of food decreases the extent of absorption. A 40% lower Cmax and a 25% lower area under the curve were reported following a single dose administration of 850 mg metformin with food. Studies using single oral doses of 500 – 1500 mg metformin indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination [R10-5341].
In contrast to sulfonylureas metformin is negligibly bound to plasma proteins. The drug partitions into erythrocytes, which might represent a deep compartment of distribution. Intravenous studies in healthy volunteers demonstrate that metformin is excreted unchanged in the urine and neither undergoes hepatic metabolism nor biliary excretion. Following oral administration approximately 90% of the absorbed drug is eliminated via the renal route with a plasma-elimination half-life of about 6.2 hours [R10-5341].
Metformin is available as tablets for oral administration in the strength of 500, 850 and 1000 mg [R10-5341]. The maximum recommended daily dose is 3000 mg in adults [R10-5537].

In a double-blind, placebo-controlled US clinical trial involving obese patients with type 2 diabetes whose hyperglycemia was not adequately controlled with diet alone, treatment with metformin (up to 2550 mg/day) for 29 weeks resulted in significant mean net reductions in FPG, PPG and HbA1c of 59 mg/dl, 83 mg/dl, and 1.8 %, respectively, compared to the placebo group [R10-5341].
Metformin was well tolerated by healthy male volunteers given alone (3 x 850 mg daily) and in combination with linagliptin (1 x 10 mg daily) for 3 days. Drug related adverse events, which occurred in both treatment periods with the same frequency (12.5%), refer only to the gastrointestinal tract and represent well-known side-effects of metformin – abdominal pain, diarrhoea, nausea. The combined administration of both drugs did not increase the incidence of adverse events compared to single drug treatment. Hypoglycaemic events did not occur in any treatment period [U06-3414].

1.2.3 Trajenta Duo®

Trajenta Duo® contains the active substances linagliptin which is a potent, synthetic, nonpeptide competitive, rapidly acting and reversible inhibitor of dipeptidyl-peptidase-4 (DPP4) and the biguanide metformin hydrochloride The ATC code is A10BD11. Linagliptin inhibits proteolytic processing of the incretins GLP-1 and GIP by DPP-4, resulting in increased glucose-dependent insulin secretion, suppression of glucagon secretion, delay of gastric emptying and induction of satiety. Metformin suppresses hepatic gluconeogenesis.

Trajenta Duo® tablets are supplied as immediate release film-coated tablets containing 2.5 mg linagliptin and either 500 mg, 850 mg or 1000 mg metformin hydrochloride for twice daily adminstration. Theinactive ingredients of the tablet core are arginine, copovidone, magnesium stearate, maize
starch, colloidal anhydrous silica. The film-coatings contain hypromellose, titanium dioxide, talc, propylene glycol, iron oxide red and/or iron oxide yellow.
Further information is provided in the local prescribing information of Trajenta Duo®.

2. RATIONALE, OBJECTIVES, AND BENEFIT-RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE STUDY

According to the local regulations, when a new chemical entity (NCE) is registered, a regulatory non interventional study (rNIS) of an extended period (4 or 6 years) should be conducted. Such rNIS can provide supplementary data to monitor the safety of NCEs in a real-life situation. Data collected in randomised clinical trials with strict inclusion/exclusion criteria and rigorous monitoring schemes have limitations.

This is a prospective, non-interventional, open-label, multi-centre study. It will provide additional safety information of Trajenta Duo®in Korean patients with type 2 diabetes mellitus in routine clinical settings.

2.2 STUDY OBJECTIVES

2.2.1 Primary objective

The primary objective of this study is to monitor the safety profile of Trajenta Duo® in Korean patients with type 2 diabetes mellitus (T2DM) in a routine clinical setting.

2.2.2 Secondary objective

The secondary objective of the study is to monitor the effectiveness of Trajenta Duo® by evaluating the change from baseline to endpoint in the glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG) of Korean T2DM patients.

2.3 BENEFIT-RISK ASSESSMENT

Patients will be managed according to the local practice guidelines. The choice of treatment will be solely at the discretion of the participating physician. Trajenta Duo® will be administered according to the approved label in Korea. Hence there are no additional risks to patients by participating in this rNIS.

3. DESCRIPTION OF DESIGN AND STUDY POPULATION

3.1 OVERALL DESIGN AND PLAN

This rNIS is a prospective, non-interventional, open-label, multi-centre study. As per regulation, the re-examination period extends from 15 Nov 2012 until 13 Sep 2017. However, active enrollment is to be initiated in 2013 after finalizing the re-imbursement agreement with the authority. Before initiation of the study, any newly reported adverse events collected from other sources such as spontaneous cases, literature cases etc will be closely monitored. The last patient follow up is expected in 2016.

3.1.1 Administrative structure of the study

This study will be managed by a project manager of Boehringer Ingelheim Korea. Data management and statistics will be outsourced to a qualified contract research organization (CRO).

3.2 DISCUSSION OF STUDY DESIGN

This is a single arm study with linagliptin/metformin.

Loss to follow up

All efforts will be made to minimize loss to follow up, particularly in the tracking of lost patients. To the extent possible, occurrence of adverse event, at minimum, for patients lost to follow up will be obtained. This allows assessing the impact of informative censoring due to treatment discontinuation. Also, patients lost to follow up will be characterized compared to the remaining patients and reason and time point of loss to follow up will be evaluated.

Channeling bias

Channeling bias can occur due to preferential prescribing in relation to different risks for the events of interest: e.g., if linagliptin/metformin would be more often prescribed to higher risk patients compared to other treatments, higher incidences of outcome events were then expected in the linagliptin/metformin group.

Confounding

As in any observational study, confounding may affect the estimation of associated between drug exposure and outcome of interest and statistical techniques. However, as only major confounders for selected research questions can be captured, residual (unmeasured) confounding may remain.

3.3 SELECTION OF POPULATION

A total of 600 patients will be enrolled at approximately 15 sites by as many as 20 or more NIS physicians. To minimize the selection bias at the site level, the goal is to have participating centers reflect a balance between general hospitals and clinics for surveillance. The treating physicians will mainly be internists who treat diabetes mellitus as an endocrine or cardiovascular disease, etc., in clinics or general hospitals which have internal medicine or family medicine department. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.

3.3.1 Main diagnosis for study entry

Patients diagnosed with T2DM will be included.

3.3.2 Inclusion criteria

- Patients who have been started on Trajenta Duo® in accordance with the approved label in Korea
- Patients who have signed on the data release consent form

3.3.3 Exclusion criteria

- Patients with previous exposure to Trajenta®, Trajenta Duo®
- Current participation in clinical trials
- Patients for whom metformin or linagliptin is contraindicationed according local label of Trajenta Duo®

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients (therapy or assessments)

This section is not applicable.

3.3.4.2 Discontinuation of the study by the sponsor

Boehringer Ingelheim Korea reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Emergence of any effectiveness/safety information that could significantly affect continuation of the study
2. Violation of applicable local regulations, the NIS protocol, or the contract by a study site or participating physician, disturbing the appropriate conduct of the study.

4. TREATMENTS

4.1 PRESCRIBED TREATMENTS TO BE OBSERVED

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

Trajenta Duo® will be prescribed according to the local label and at the discretion of the treating physician. Since this is a non-interventional study, the drug will not be supplied by the sponsor. Furthermore, the sponsor will not cover the expenses related to other medications taken by the patient, interventions, procedures, or diagnostic tests.

4.1.2 Method of assigning patients to treatment groups

The choice of treatment is fully at the discretion of the physician and the patient. There is no treatment assignment by a third party.

4.1.3 Selection of doses in the study

Linagliptin/Metformin will be administered 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg twice a day which is within the authorized label in Korea.

4.1.4 Drug assignment and administration of doses for each patient

The physicians indicate doses and timing.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

The protocol will allow additional drugs considered necessary for the patient's welfare to be prescribed at the discretion of the treating physician. It is required, however, to record the details of all concomitant medication administered to the patient during the course of treatment in eCRF. This includes concomitant therapies started one month prior to Trajenta Duo® initiation until the patient completes the final follow-up visit.

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

Please refer to the current local label.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Please refer to the current local label.

4.2.2.2 Restrictions on diet and life style

Please refer to the current local label.

5. VARIABLES AND THEIR ASSESSMENT

5.1 SAFETY

5.1.1 Endpoint(s) of safety

All reported adverse events including hypoglycemic events in patients who take at least one dose of Trajenta Duo® will be noted.

Hypoglycemic events include the overall hypoglycemic events, symptomatic hypoglycemia, confirmed hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia.

Endpoints pertaining to safety will be presented as incidence rates of adverse events and will include:

- adverse events
- unexpected adverse events
- serious adverse events
- drug-related adverse events
- adverse events leading to discontinuation
- adverse events by intensity, outcome of the event, causality

5.1.2 Assessment of adverse events

5.1.2.1 Definitions of adverse events

Adverse event

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

Adverse event of special interest

Irrespective of whether an AE is serious or non-serious, some events are defined as ‘special interest of adverse events’ and have additional reporting requirements (See Section 8.4.1). ‘Special interest of adverse events’ refers to the list in the Investigator’s Study File or in electronic CRF web page for the latest version(Attachment 5).

Serious adverse event

A serious adverse event (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 judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Always serious adverse events

BI has defined a list of adverse events that are considered as "always serious" (Attachment 4) by fulfilling the criterion "medically important event" by definition and are therefore judged as serious. If a non-serious AE meets this definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion. The list of these adverse events can be found via the eCRF system.

Adverse drug reaction

Adverse drug reaction (ADR) refers to any harmful, unintended reaction to the pharmaceutical product of any dose at which a causal relationship with the pharmaceutical product cannot be ruled out.

Non serious adverse drug reaction

Non serious adverse drug reaction is defined as any ADR which does not meet the SAE criteria.

Intensity of adverse event

The intensity of the AE should be defined based on the following three categories and according to medical and scientific judgment:

Mild:	Transient symptoms which are subjective or objective but no interference with the patient's daily activities. No change in dosage is needed to continue the treatment.
Moderate:	Marked symptoms with moderate interference with the patient's daily activities. Reduced dosage or unplanned treatment is necessary for the relief of adverse events.
Severe:	Considerable and unacceptable interference with the patient's daily activities. Discontinuation of the study drug is required because of significant adverse events.

To ensure that no confusion or misunderstanding of the difference between the terms 'serious' and 'severe' which are not synonymous, it should be noted that SAE does not necessarily correspond to serious or not serious AE to severe ones. All SAEs will be reported regardless of the intensity as mentioned above.

Causal relationship of adverse event

Medical judgment will be used to determine the causal relationship, after 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 will be recorded in the eCRF.

Related

a. Certain: An event occurring in a plausible time relationship to drug administration and that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

b. Probable/Likely: An event with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

c. Possible: An event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

d. Conditional/Unclassified: Case of requiring more data or reviewing the additional data for the appropriate assessment

e. Unassessable/Unclassifiable: Case that it cannot be judged and complemented or confirmed due to the insufficient or contradictory information

Unrelated

d. Unlikely: An event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Worsening of the 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, 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 NIS physician.

5.1.2.2 Adverse event and serious adverse event reporting

All adverse events occurring from the start of Trajenta Duo® treatment up to 7 days after last follow-up visit need to be collected, documented and reported to the sponsor using the AE

reporting form of eCRF (Attachment 1). All SAEs must be reported with details of non-serious AEs occurring at the same time, within 24 hours of occurrence via telephone/fax to the Clinical Safety Officer (CSO) of BI Korea using the SAE report form (Attachment2). If any new or further information to these events is available, a follow-up SAE report has to be sent to BI. All SAEs and non-serious AEs must include a causal relationship assessment from the physician.

All other Adverse Events must be reported using eCRFs within 2 weeks to the Sponsor.

Contact details:

Clinical Safety Officer

Tel: [redacted]

Fax: [redacted]

Address: [redacted]

[redacted]

Pregnancy

Rarely, patients taking part in regulatory non interventional studies can get pregnant. Once a patient enrolled into the study and exposed to Trajenta Duo® becomes pregnant, the NIS physician will stop the drug and report immediately to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day, whichever is shorter) to CSO. Furthermore, the details of all the drugs to which the patient exposed at the time of pregnancy will be recorded. The outcome of the pregnancy associated with the drug exposure will be assessed. In the absence of an (S)AE, only the Pregnancy Monitoring Form (Attachment 3) for NIS, not the SAE form is to be completed.

5.1.3 Assessment of safety laboratory parameters

This section is not applicable.

5.1.4 Electrocardiogram

This section is not applicable.

5.1.5 Assessment of other safety parameters

This section is not applicable.

5.2 EFFECTIVENESS

5.2.1 Endpoint(s) of effectiveness

The main effectiveness endpoint in this study is the change from baseline in HbA_{1c} after 24 weeks of treatment.

The other effectiveness endpoints are the following:

- Occurrence of treat to target effectiveness response, that is an HbA_{1c} under treatment of < 6.5% after 24 weeks of treatment.
- Occurrence of relative effectiveness response (HbA_{1c} lowering by at least 0.5% after 24 weeks)
- Change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment

5.2.2 Assessment of effectiveness

HbA_{1c}:

HbA_{1c} should be collected within 1 month prior to baseline and after 12weeks and 24 weeks of treatment.

Fasting plasma glucose (FPG):

FPG should be collected within 1 month prior to baseline and after 12weeks and 24 weeks of treatment.

5.3 OTHER

This section is not applicable.

5.4 APPROPRIATENESS OF MEASUREMENTS

This section is not applicable.

6. SURVEILLANCE PLAN

6.1 VISIT SCHEDULE

The flow chart at the front of the protocol summarizes the data to be collected at each visit(recommended visit schedule - Visit 2 : 12±2weeks/ Visit 3 : 24±2weeks). The procedures are further described below.

6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

This section is not applicable as this is a non-interventional study.

6.2.2 Treatment period(s)

As per regulations, enrolled patients will be followed up for 12 or 24 weeks treatment period. There will be a visit window of ±2 weeks. To minimize the selection bias at the site level, the goal is to have participating centers reflect a balance between general hospitals and clinics for surveillances.

6.2.2.1 Visit 1 – Baseline Visit

Upon patient enrollment, the following will be recorded on the patient's eCRF.

- Visit date
- Diagnosis: date of the diagnosis of T2DM, family history
- Inclusion / exclusion criteria
- Demographic data: year of birth(age), gender, pregnancy, previous allergy, height, weight, waist circumference, smoking status, alcohol consumption
- Diabetes mellitus related complication
- Other medical history: history of concomitant disease within 6 months
- Renal Function: record Serum creatinine, eGFR, urin ACR if blood test result is available (collected within the latest 6-month period)
- Effectiveness endpoints : HbA_{1c}, FPG (Lab data should be collected within 1month prior to baseline)
- Concomitant anti-hyperglycemic agent: record any anti-hyperglycemic agents have been taken prior to the baseline visit
- Concomitant medications: record all medications have been taken at least once since one month prior to the baseline visit
- Dose of Trajenta Duo® given

At Visit 1, the patient will be requested to contact the treating physician in the event of any adverse events noted after initiating Trajenta Duo® treatment.

6.2.2.2 Visit 2 (12±2 weeks from Visit 1)

After 12±2 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the eCRF:

- Visit date
- Any change of Trajenta Duo® given
- Any changes in laboratory tests if there is any lab result which was clinically significant compared to data before Trajenta Duo® therapy (This data is collected on the basis of medical need, i.e. independent of the NIS)
- Effectiveness endpoints : HbA_{1c}, FPG
- Concomitant anti-hyperglycemic agent including new medications taken since last visit: any change in the concomitant medications (dose and dosing intervals)
- Concomitant medications including new medications taken since last visit: any change in the concomitant medications (dose and dosing intervals)
- Any adverse events noted
- Study completion status

6.2.2.3 Visit 3 (24±2 weeks from Visit 1)

After 24±2 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the eCRF:

- Visit date
- Any change of Trajenta Duo® given
- Any changes in laboratory tests if there is any lab result which was clinically significant compared to data before Trajenta Duo® therapy (This data is collected on the basis of medical need, i.e. independent of the NIS)
- Effectiveness endpoints : HbA_{1c}, FPG
- Concomitant anti-hyperglycemic agent including new medications taken since last visit: any change in the concomitant medications (dose and dosing intervals)
- Concomitant medications including new medications taken since last visit: any change in the concomitant medications (dose and dosing intervals)
- Any adverse events noted
- Study completion status
- NIS physician's electronic signature for data integrity

6.2.3 End of trial and follow-up period

Patients with adverse events noted at the final follow-up visit or upon premature discontinuation of Trajenta Duo® will be monitored further until the resolution of those adverse events. Alternatively, those patients will be followed up until the NIS physician and sponsor agree that no further follow-up is necessary.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Details are provided in the statistical Trial Statistical Analysis Plan (TSAP).

7.1 STATISTICAL DESIGN - MODEL

In this non-interventional study, all statistical analyses will be descriptive statistics(N, mean, median, standard deviation, minimum and maximum, etc.). Demographic data and baseline characteristics will be described in each ratio including the confidence intervals. All analysis will be accomplished after dividing according to condition of the anti-diabetic agents use(patients who have no experience treated with DPP-4/patients who have experiences treated with DPP-4). In addition, data on special patients(children/patients with hepatic or renal disorder/elderly patients, etc.) will be analyzed separately.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No hypotheses are tested. (See Section 7.1)

7.3 PLANNED ANALYSES

7.3.1 Safety analyses

Demographic(year of birth(age), gender, etc.) and baseline characteristics will be summarized descriptively for the entire cohort of eligible patients.

Adverse events (AEs) will be coded according to the latest version of Medical Dictionary for Drug Regulatory Affairs (MedDRA) coding system. Concomitant therapies will be coded according to the latest version of KIMS (Korea Index of Medical Specialties) coding system. The trial database will not be locked until coding is complete.

Safety analyses will be based on all patients treated, i.e. all patients who received at least one dose of Trajenta Duo®. However, if data for patients who have been treated with Trajenta Duo® beyond the scope of approved label are collected, separate safety analyses will be performed. Safety analyses will be performed based on demographics and baseline characteristics.
Adverse events, unexpected adverse events, serious adverse events and each adverse drug reactions is classified into the system organ class(SOC), symptoms(preferred term) and presented the incidence and precision(95% confidence intervals).
Patients lost to follow up will be characterized compared to the remaining patients and reason and time point of loss to follow up will be evaluated.

① Occurrence of adverse events after Trajenta Duo® administration: Contingency table for frequency and incidence of adverse events is presented according to occurrence situation of adverse events by sign/symptoms, action taken for Trajenta Duo®, intensity,

relationship, outcome and category and test for the differences of AE frequency is analyzed using Chi-square test(or Fisher's exact test).

② Contingency table is presented based on nominal variables as demographic characteristics(gender, age(children and elderly, weight, etc.) and medical history(family history for diabetes mellitus, diabetic complication, hepatic/renal disorder, etc.) so on and test for the differences of AE frequency is analyzed using Chi-square test(or Fisher's exact test).

③ Logistic regression as a multivariate analysis is performed and presented odd ratio in order to find the factor affecting occurrence of adverse events by demographic characteristics(gender, age(children and elderly, weight, etc.) and medical history(family history for diabetes mellitus, diabetic complication, hepatic/renal disorder, etc.) so on.

7.3.2 Effectiveness analyses

A descriptive analysis of endpoints is planned and for patients treated with Trajenta Duo®, the change of HbA1c from baseline and last follow-up visit(12/24weeks) is analyzed using paired t-test(or Wilcoxon signed rank test).
The occurrence of treat to target effectiveness response, that is an HbA1c under treatment of < 6.5% after 24weeks and relative effectiveness response (HbA1c lowering by at least 0.5%) after 24 weeks is summarized with frequency distribution for patients' number and percentage and presented 95% confidence intervals.
The change of FPG from baseline and last follow-up visit(12/24weeks) is analyzed using paired t-test(or Wilcoxon signed rank test).

In order to investigate the factor affecting effectiveness, the following analysis is performed with the case of HbA1c under treatment of < 6.5% after 24 weeks is considered as effectiveness and the other cases are considered as ineffectiveness.

① Contingency table is presented based on nominal variables as demographic characteristics(gender, age(children and elderly, weight, etc.) and medical history(family history for diabetes mellitus, diabetic complication, hepatic/renal disorder, etc.) so on and the test for the differences of frequency for effectiveness/ineffectiveness is analyzed using Chi-square test(or Fisher's exact test).

② Logistic regression as a multivariate analysis is performed and presented odd ratio in order to find the factor affecting effectiveness by demographic characteristics(gender, age(children and elderly, weight, etc.) and medical history(family history for diabetes mellitus, diabetic complication, hepatic/renal disorder, etc.) so on.

7.3.3 Interim analyses

In accordance with local regulation for rNIS, interim analyses are planned biannually for the initial two years and annually thereafter.

7.4 HANDLING OF MISSING DATA

As this is non-interventional study, there are no required investigations and diagnostic procedures (e.g. lab, ultrasound).
Maximum attempt will be made to ensure the completeness of data collection. All available data will be used in the data analysis. There will be no imputation of data to fill the missing values.

7.5. RANDOMISATION

This section is not applicable as this is a non-interventional study.

7.6 DETERMINATION OF SAMPLE SIZE

Sample size of 600 patients is based on the requirement of the local regulatory authority (Ministry of Food and Drug Safety, MFDS). As per regulation, long-term surveillance is necessary for the indication. Since T2DM is chronic disease, it might be restrictive to collect safety and effectiveness data in short-term (12±2weeks) period, all patients will be enrolled for longer-term (24±2weeks) surveillance.

8. DATA PROTECTION, STUDY RECORDS

The International Conference on Harmonization/Harmonized Tripartite Guideline for Good Clinical Practice (ICH/GCP) does not often apply to NIS as most elements are relevant for controlled clinical trials. However, in this NIS, all attempts will be made to adhere, as close as possible, to the standards of ICH/GCP.

The protocol of this regulatory requisite NIS will be submitted to the Korea Food and Drug Administration (MFDS) for notification. It is not a local requirement in Korea to obtain Institutional Review Board (IRB) approval for the conduct of regulatory requisite NIS. However, the protocol of this NIS will be submitted to IRBs whenever required or requested by these institutions. This study will be conducted in accordance with the Standards for Re-examination of New Medicines notified by MFDS, Korean Pharmaceutical Affairs Code (KPAC), Enforcement Regulation of KPAC and other applicable local laws and industry code (including but not limited to the Regulations on Fair Competition in the Trade of Medicines of KPMA and KRPIA).

Boehringer Ingelheim Korea will submit periodic reports during re-examination period, and the final report to MFDS upon study completion. The periodic report for the final year will be substituted with the final report. When required, the interim reports and the final report will be submitted to the IRBs as well.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB/IEC and the competent authority (CA) according to the local regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written data release consent form shall be obtained from each patient (or the patient's legally accepted representative). Each signature must be personally dated by each signatory and the data release consent and any additional patient-information form retained by the NIS physician as part of the study records. A signed copy of the data release consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim Korea in accordance with the local data protection law. The level of disclosure shall also be explained to the patient.

The patient shall be informed that his/her medical records may be examined by authorised monitors (MPMs) or Clinical Quality Assurance auditors appointed by sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the participating physician's study-related files and correspondence, and the data release agreement documentation of this study.

8.3 RECORDS

All of the clinical data will be captured via a web-based EDC (Electronic Data Capture) System. The site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained. The treating physician will approve the data using an electronic signature.
Patients will not be identified on the eCRF by name. Appropriate coded identification (i.e., patient number) will be used. The treating physician will make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in this study in case follow-up is required. Likewise, any supporting documentation will be redacted of any patient identifying information, and the patient ID number clearly written on the documents.

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 will be filed at the treating physician's site.

It is necessary that the data entered in the eCRFs that are transcribed from the source documents are consistent with the source documents or the discrepancies need to be explained. The treating physician may need to request previous medical records, transfer records, and current medical records.

8.3.2 Direct access to source data and documents

The NIS physician / site will permit study-related monitoring, audits and regulatory inspection, providing direct access to all related source data/documents. All source documents including eCRFs will be made available for review by sponsor's Medical Project Manager (MPM) or designees and inspection by health authorities (e.g., MFDS). The MPM and auditor may review all eCRFs, and written data release agreements. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage of records

The NIS physician and the site are jointly responsible for maintaining essential study documents for 3 years after completion of the study (defined as termination date of re-examination period) by the Pharmaceutical Affairs Law and shall take measures to prevent accidental or premature destruction of these documents.

8.4 PROCEDURES FOR REPORTING ADVERSE EVENTS

8.4.1 Time windows

All AEs, serious and non-serious, occurring during the course of the rNIS will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRF. 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 rNIS, 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 Trajenta Duo® tablets, or whether or not Trajenta Duo® tablets has been administered, must be reported immediately via eCRF and SAE/Special interest of AE Report Form.

For special interest of AE, even though they might be non-serious, require expedited reporting (within 24 hours or the next business day whichever is shorter) to the sponsor via eCRF and SAE/Special interest of AE Report Form.

8.4.2 Documentation of adverse events and patient narratives

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to the local regulatory requirements.

For each AE, the investigator will provide the onset, end, intensity, outcome, seriousness and action taken with Trajenta Duo® tablets. The investigator will determine the relationship of Trajenta Duo® tablets to all AEs as defined in the 'Adverse Event Reporting' section of the physician binder.

8.5 STATEMENT OF CONFIDENTIALITY

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

Treatment data will be made available to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated from the study will be made available for inspection on request by the participating physicians, the sponsor and/or its representatives and/or designees, by the IRBs/IECs and the regulatory authorities.

8.6 PUBLICATION POLICY

Boehringer Ingelheim, to the best of their ability will support the process of free exchange of relevant scientific information. Any publication of the result of this NIS study must be consistent with the Boehringer Ingelheim publication policy.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R09-4241 Haffner SM, Letho S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. N. Engl. J. Med. 1998; 339 (4): 229-234.

R10-5341 Glucophage (metformin hydrochloride tablets), Glucophage XR (metformin hydrochloride extended-release tablets) (Bristol-Myers Squibb), Rx only (NDA 20-357/S-030, NDA 21-202/S-015, revised January 2009)

R10-5537 Glucophage 500 and 850 mg film coated tablets (Merck Serono) (summary of product characteristics, last updated on the eMC: 17/08/2010) http://emc.medicines.org.uk/medicine/1043/SPC/Glucophage 500 mg and 850 mg film coated tablets

9.2 UNPUBLISHED REFERENCES

U04-1767-11 [redacted], Linagliptin Investigator's Brochure. Version 11. 28 Nov 2012.

U06-3414 [redacted]. Bioavailability of both BI 1356 and metformin after co-administration compared to the bioavailability of multiple oral doses of BI 1356 10 mg daily alone and metformin 850 mg three times a day alone in healthy male volunteers (an open-label, randomized, crossover study). 1218.4. 7 July 2006.

1 (WHO Fact sheet; no 312) Nov 2012 http://www.who.int/mediacentre/factsheets/fs312/en/index.html

2 Korean Diabetes Association. http://www.diabetes.or.kr/temp/Diabetes_Fact_sheet2012.pdf

3. Trajenta Duo® Prescription information for Korea

10. APPENDICES

10.1 ELECTRONIC CASE REPORT FORM

See the Attachment 1.

10.2 SAE/ SPECIAL INTEREST OF AE REPORT FORM

See the Attachment 2.

10.3 PREGNANCY MONITORING FORM

See the Attachment 3.

10.4 LIST OF ALWAYS SERIOUS ADVERSE EVENTS

See the Attachment 4. Please refer to “List of Always Serious Adverse Event” in site file or in electronic CRF web page for the latest version.

10.5 LIST OF SPECIAL INTEREST OF ADVERSE EVENTS

See the Attachment 5. Please refer to “List of special interest of adverse events’” in site file or in electronic CRF web page for the latest version.

11. SUMMARY OF NIS PROTOCOL MODIFICATIONS

Summary of Modifications Sheet (SOMS)

Number of Protocol modification		3
Date of Protocol modification		22 Feb2017
BI Trial number		1288.22
BI Product(s)		Trajenta DUO
Title of protocol		A regulatory requirement non interventional study to monitor the **s**afety and **e**ffectiveness of Trajenta Duo® (Linagliptin/Metformin HCl, 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg, b.i.d) in Korean patients with type 2 diabetes mellitus (SELINA Duo study)
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Refer to amendment table
Description of change		
Rationale for change		