Non-Interventional Study Protocol

Doc. No.: c02597942-07

BI Study No.:	1200.235
BI Investigational Products:	afatinib dimaleate
Title:	A regulatory requirement post-marketing surveillance study to monitor the safety and efficacy of GIOTRIF®(afatinib dimaleate, 20mg, 30mg, 40mg, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutations or patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy
Clinical Phase:	IV
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Not Applicable
Status:	Revised Protocol
Version and Date:	Version : 7 Date : 18 May 2020

NON-INTERVENTIONAL STUDY PROTOCOL SYNOPSIS

Name of company/Marketing Authorisation Holder: Boehringer Ingelheim Korea		**Tabulated Study Protocol**	
Name of finished product: GIOTRIF®			
Name of active ingredient: afatinib dimaleate			
Protocol date: 07 May 2014	**Trial number:** 1200.235		**Revision date:** 18 May 2020

Title of study:	A regulatory requirement post-marketing surveillance study to monitor the safety and efficacy of GIOTRIF®(afatinib dimaleate, 20mg, 30mg, 40mg, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s) or patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy
Principal Investigator:	Not Applicable
Study site(s) :	Multi-centre study
Clinical phase:	IV
Objectives:	To monitor the safety profile and efficacy of GIOTRIF®(afatinib dimaleate, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s) or patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy in a routine clinical practice setting
Methodology:	Observational prospective, non-interventional, open-label, multi-centre national study
No. of patients:	
Total entered:	1,149 approximately
each treatment:	Single arm (N=1,149 approximately)
Diagnosis:	- Patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s) - Patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy

Name of company/Marketing Authorisation Holder: Boehringer Ingelheim Korea		**Tabulated Study Protocol**	
Name of finished product: GIOTRIF®			
Name of active ingredient: afatinib dimaleate			
Protocol date: 07 May 2014	**Trial number:** 1200.235		**Revision date:** 18 May 2020
Main criteria for inclusion:	Inclusion Criteria: 1) Patients who have been started on GIOTRIF® in accordance with the approved label in Korea 2) Age ≥ 19 years at enrolment 3) Patients who have signed on the patient consent form Exclusion Criteria: 1) Known hypersensitivity to afatinib or any of its excipients 2) Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption 3) Patients for whom GIOTRIF® is contraindicated according to the local label		
Test product(s) : **dose:** **mode of admin. :**	afatinib dimaleate 20 mg, 30 mg, 40 mg q.d Oral administration		
Comparator product(s): **dose:** **mode of admin. :**	Not applicable		
Duration of treatment:	Treatment duration for 1) short-term surveillance: 8±2 weeks 2) long-term surveillance: 24±2 weeks and 48±2 weeks Study duration: 6 years. (MFDS set GIOTRIF® re-examination period from 29 January 2014 to 28 January 2020. Interim report planned biannually for the initial two years and annually thereafter by April 2020.)		
Criteria for effectiveness:	Disease Assessment will be based on the assessment of cancer related symptoms and, if available, radiologic assessments as per standard of care at the site.		
Criteria for safety:	All reported adverse events in patients who take at least one dose of GIOTRIF® based on the current authorized label in Korea 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**	**Follow-up 3**	**Follow-up 4**
Visit Number	1	2	3	4	N/A
Week/s	0	8±2	24±2	48±2	End of PMS Period
Informed consent	X				
Inclusion / Exclusion	X				
Diagnosis	X				
EGFR positive	X				
Platinum-based chemotherapy	X				
Demographics	X				
Medical history	X				
Concomitant medications	X	X	X	X	
Physical examination	X	X	X	X	
GIOTRIF® Administration status	X	X	X	X	
Safety Laboratory Testing – Optional [1)]	X	X	X	X	
Effectiveness endpoints [2)]		X	X	X	
Adverse events		X	X	X	
Study completion		X	X	X	
Overall survival [3)]					X

1) Laboratory testing is optional at this study and may be performed at the discretion of investigator and in accordance to the current standard of care.

2) Disease Assessment will based on the assessment of cancer related symptoms and, if available, radiologic assessments as per standard of care at the site.

3) Collection of information on death. In the case of OS data of the survived subject at the end of the study (Visit 4) is not available, information should be collected by telephone, letter contact with the patient. In Korea public records may be utilized to assess the mortality status for patients lost to follow up or where mortality information is not readily available through 3 attempted contacts. A formal study visit is not required.

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT (SGPT)	Alanine Amino Transferase (Serum Glutamate Pyruvate Transaminase)
AST (SGOT)	Aspartate Amino Transferase (Serum Glutamic Oxaloacetic Transaminase)
BI	Boehringer -Ingelheim
BSC	Best Supportive Care
CA	Competent Authority
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
ECG	Electrocardiogram
eCRFs	electronic Case Report Forms
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EGFR TKI	Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ID	Identification
ILD	Interstitial lung disease
IRB	Institutional Review Board
ISF	Investigator Study File
KIMS	Korea Index of Medical Specialties
KPAC	Korean Pharmaceutical Affairs Code
KPMA	Korea Pharmaceutical Manufacturers Association
KRPIA	Korean Research based Pharmaceutical Industry Association
LPVM	Local PharmacoVigilance Manager
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MFDS	Ministry of Food and Drug Safety
MPM	Medical Project Manager
MTD	Maximum Tolerated Dose
NCE	New Chemical Entity
NIS	Non-Interventional Study
NSCLC	Non-Small-Cell Lung Cancer
OR	Objective Response
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
rNIS	regulatory Non Interventional Study

RP	Partial Response
SAEs	Serious Adverse Events
SD	Stable Disease
SUSARs	Suspected Unexpected Serious Adverse Reactions
TSAP	Trial Statistical Analysis Plan

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Non-Small Cell Lung Cancer (NSCLC) is the leading cause of cancer-related deaths in many countries, including Korea. The prognosis for advanced stage disease has improved modestly in the past 20 years. With an overall 5-year survival rate of only 15% the treatment of this disease clearly remains a major clinical challenge [R05-0876].

While systemic chemotherapy has demonstrated modest activity in advanced NSCLC, novel targeted therapies based on specific molecular and biological characteristics of lung cancer have emerged as a new treatment paradigm. Among the molecules most extensively studied are the Epidermal Growth Factor Receptors (EGFR) or the Subclass I of the superfamily of transmembrane tyrosine kinase receptors [R06-1301 , R06-1302].

Aberrant activation of EGFR frequently observed in a variety of malignant tumours can be induced by different molecular mechanisms including receptor overexpression, mutation, ligand-dependent receptor dimerization, and ligand-independent activation. Overexpression of EGFR has been detected in 40% to 80% of NSCLC patients [R06-1301 , R06-1393 , R06-1394]. However, recent clinical experiences with specific EGFR-Tyrosine Kinase Inhibitors (TKI) have demonstrated tumour regression in only 10% to 15% of unselected NSCLC patients [R05-0876 , R06-1301 , R06-1306].

In the randomized Phase III trials 1200.32 and 1200.34, afatinib demonstrated superiority over chemotherapy in patients with EGFR mutation positive stage IIIB/IV NSCLC who were chemotherapy-naive and EGFR TKI therapy- naïve. In both phase III trials, treatment with afatinib significantly improved PFS as well as secondary endpoints of objective response rate and time to deterioration of cancer-related symptoms including cough and dyspnea. With improvements, as demonstrated in trial 1200.32, in median PFS of 4.2 months (11.1 vs 6.9 months) in the overall population and 6.7 months (13.6 vs 6.9 months) in patients with common mutations. Afatinib offers a clinically relevant first-line treatment option for such patients [U12-1199-01 , U13-1625-01].

The thorough analysis of the large safety database of afatinib showed that treatment with afatinib effectively delays disease progression in patients with NSCLC harbouring EGFR mutations in any line of therapy. This clinically meaningful delay in progression is associated with improvements in regard to the global health status and lung cancer [U12-1482-01].

The adverse event profile of afatinib is determined by its EGFR tyrosine-kinase targeting mode of action, with the most common events being diarrhoea and the grouped terms ash/acne and stomatitis. The thorough analysis of the large safety database of afatinib showed that the most frequent adverse events of afatinib are predictable, related to its mode of action, and manageable by close monitoring, proactive treatment, and treatment interruption and dose reduction according to the well-defined dose reduction scheme [U12-1482-01].

1.2 DRUG PROFILE

For the latest information on the drug profile of afatinib, please refer to the current local prescribing information of GIOTRIF® (Attachment 5).

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 observational prospective, non-interventional, open-label, multi-centre national study. It will provide additional safety information of GIOTRIF®(afatinib dimaleate, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s) or in patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy in a routine clinical practice setting.

2.2 STUDY OBJECTIVES

2.2.1 Primary objective

To monitor the safety profile of GIOTRIF®(afatinib dimaleate, q.d) as first line treatment in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s) or in patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy in a routine clinical practice setting.

2.2.2 Secondary objective

To evaluate the tolerability and efficacy of GIOTRIF®(afatinib dimaleate, q.d) as first line treatment in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) or in patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy.

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. GIOTRIF® 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 observational prospective, non-interventional, open-label, multi-centre national study. As per regulation, the re-examination period extends from 29 Jan 2014 until 28 Jan 2020. However, active enrolment is to be initiated in Oct 2014 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 Jan 2020.

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).

3.1.2 Study method

This study will be carried out in the manner of successive survey that the investigator will be asked to successively write in the case report forms(CRFs) from the subject who was initially administered the drug following the study start date to the requested number of subjects without omission. Prior to initiation of the study, written contract shall be concluded, and this contract shall be concluded with the head of the site or the investigator with his/her consent.

3.2 DISCUSSION OF STUDY DESIGN

This is a single arm study with afatinib dimaleate.

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.

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 1,149 patients will be enrolled at approximately 50 sites by as many as 50 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 pulmonologist and oncologists. 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 locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR mutation(s) or patients diagnosed with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy will be included.

3.3.2 Inclusion criteria

- Patients who have been started on GIOTRIF® in accordance with the approved label in Korea
- Age ≥ 19 years at enrolment
- Patients who have signed on the patient consent form

3.3.3 Exclusion criteria

- Known hypersensitivity to afatinib or any of its excipients
- Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Patients for whom Afatinib is contraindicationed according local label of GIOTRIF®

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.

3.3.5 Subjects of special investigation

Any investigation for the elderly, pregnant women, and patients with renal impairment and hepatic impairment will not be separately conducted, and further investigation into cases collected from this study may be taken into account according to the outcome of retrospective analysis.

4. TREATMENTS

4.1 PRESCRIBED TREATMENTS TO BE OBSERVED

4.1.1 Identity of test products and comparator products

GIOTRIF® 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

The starting dose and the dose reduction schedule are based on the current authorized label in Korea.

4.1.4 Drug assignment and administration of doses for each patient

The physicians indicate doses and timing based on the current authorized label in Korea.

EGFR mutation status should be assessed when GIOTRIF® is administered as the 1st line treatment to patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

GIOTRIF® 40mg should be administered orally, once daily, at least 1 hour before a meal or at least 3 hours after a meal. GIOTRIF® should be taken without food and tablets should be swallowed whole with water.

GIOTRIF® should be interrupted when following adverse drug reactions occur;

- ADR ≥ NCI CTCAE[1] grade 3
- Diarrhoea ≥ grade 2 of not less than 2 days even during ongoing treatment of anti-diarrhoeal medicines
- Skin related adverse reaction ≥ grade 2 (prolonged (not less than 7 days) or intolerable)
- Renal impairment patient ≥ grade 2

[1] National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v 3.0

If adverse drug reaction is recovered to not more than Grade 1, GIOTRIF® should be re-administered with dose reduction by 10mg.

GIOTRIF® should be discontinued permanently for following cases;

- Severe bullous, blistering and exfoliative skin conditions

- Interstitial Lung Disease
- Severe hepatic impairment
- Prolonged ulcerative keratitis
- Left ventricular dysfunction
- Severe or intolerable adverse reaction at the regimen of 20mg once daily

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 GIOTRIF® initiation until the patient completes the final follow-up visit.

4.2.1 Rescue medication, emergency procedures, and additional treatments

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 Endpoints of safety

All reported adverse events in patients who take at least one dose of GIOTRIF® based on the current authorized label in Korea will be noted.

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 leading to dose reduction
- 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.

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.

The following hospitalizations are not considered to be serious adverse events (SAEs) because there is no “adverse event” (i.e., there is no untoward medical occurrence) associated

with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug.

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 (NSADR) 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

a. 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.

Worsening of underlying disease or other pre-existing conditions

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

If progressive disease occurs and is associated with symptoms , the term “Progressive Disease” should not be reported as AE, however, signs and symptoms of progressive disease will be reported as an (S)AE (if applicable). Exception to this: Death due to progressive disease and where no signs or symptoms are available should be reported as “malignant neoplasm progression”.

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 occurred from the signing date on ICF to 28 days after last administration date of medication need to be collected, documented and reported to the sponsor using the AE reporting form of eCRF (Attachment 1). All SAEs must be reported within 24 hours of occurrence via telephone/fax to the Local PV Manager (LPVM) 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.

Non-serious ADR must be reported using eCRFs and NIS AE form within 7 calendar days, and all other Adverse Events must be reported using eCRFs within 2 weeks to the Sponsor.

Contact details:

Local PV Manager

Tel:

Fax:

Address:

Pregnancy

Rarely, patients taking part in regulatory non interventional studies can get pregnant. Once a patient enrolled into the study and exposed to GIOTRIF® 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 LPVM. 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 Assessment of other safety parameters

This section is not applicable.

5.2 EFFECTIVENESS

5.2.1 Endpoints of effectiveness

Disease Assessment will be based on the assessment of cancer related symptoms and, if available, radiologic assessments as per standard of care at the site.

Data regarding tumour assessments that are performed according to local standard of care for NSCLC may contribute to:

- Progression-Free Survival (PFS), defined as time from the date of the first administration of afatinib to the date of progression or to the date of death, whichever occurs first
- Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD) will be assessed by the investigator according to local standard pattern of care for NSCLC.
- Overall Survival (OS), defined as time from the date of the first administration of afatinib to the date of death.

No specific tumour measurements are required per trial protocol.

5.2.2 Assessment of effectiveness

Data of Disease Assessment to be collected at each visit; Visit 1: Baseline / Visit 2 : 8±2weeks / Visit 3 : 24±2weeks / Visit 4 : 48±2weeks.

In the case of OS data of the survived subject at the end of the study (Visit 4) is not available, the information should be collected by telephone, letter contact with the patient at the end of the PMS study period.

5.3 ITEMS OF INVESTIGATION

5.3.1 Demographic data

For demographic evaluation, following background information of subjects shall be recorded:

- Subject signed date
- Subject study number
- Gender
- Pregnancy
- Height
- Weight
- Year/month of birth (age)
- Smoking

5.3.2 Medical/surgical history and pre-treatment experience

The medical/surgical history to be collected and the treatment experience prior to administration of this drug includes:

- Date of diagnosis
- Date of EGFR test
- Medical history
- Previous surgical experience for the medical history
- Previous chemotherapy
- Previous radiotherapy

5.3.3 Concomitant medication

Information on concomitant medication that is to be collected includes:

- Brand name or generic name
- Daily dose
- Unit
- Indication
- Start date
- Date of discontinuation or continuation

5.3.4 Drug administration status

Information on the drug administration status includes:

- Dose
- Start date
- Date of discontinuation or continuation
- Dose changes

5.3.5 Information on the site

Information on the site includes:

- Hospital name
- Department
- Physician name

5.3.6 Main points of study and details of study method

If a particular trend or change associated with safety is found from spontaneous adverse event report during this study, special investigation into the relevant item shall be planned and implemented. Also, the situations of occurrence of any unexpected adverse drug reactions or adverse events whose causal relationship with the drug has not been established and frequency is extremely low, which have not appeared in the course of development of the drug during the study period, shall be intensively observed and investigated.

5.4 ENDPOINTS OF SUBJECTS EVALUATION

5.4.1 Subject evaluation items

5.4.1.1 Number of cases who accepted the study

This number means the planned number of cases as specified in the contract concluded with the investigator (physician) prior to initiation of the study.

5.4.1.2 Number of cases subject who collected CRF

This number means the number of cases who signed the informed consent form to participate in the study as subject, and have record of taking GIOTRIF® once at least.

5.4.1.3 Number of dropouts

These cases include those who signed the informed consent form to participate in this study as subject but did not meet any of the inclusion criteria, do not have any prescription record of GIOTRIF® , have prescription record but have not been followed up by the physician following prescription, and started administration prior to the signed date.

5.4.1.4 Number of cases subject to safety evaluation

These cases include those who signed the informed consent form to participate in this study as subject, took GIOTRIF® according to the approved label once at least, and were followed up via phone/mail/visit by the physician once or more.

5.4.1.5 Number of cases subject to efficacy evaluation

These cases include those who signed the informed consent form to participate in this study as subject, visited as per the study schedule, took GIOTRIF®, and were evaluated for the efficacy.

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 1: Baseline / Visit 2 : 8±2weeks / Visit 3 : 24±2weeks / Visit 4 : 48±2weeks). The procedures are further described below.

6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in periods

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

6.2.2 Treatment periods

As per regulations, enrolled patients will be followed up for 8 or 24 or 48 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 enrolment, the following will be recorded on the patient's eCRF.

- Visit date
- Informed consent form ; Date of Informed consent
- Diagnosis: date of the diagnosis of locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR mutation(s) or patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy
- Inclusion/exclusion criteria
- Medical history
- Demographic data: year of birth(age), gender, pregnancy, height, weight, smoking statusBaseline visit Concomitant medications: Record all medications have been taken at least once since one month prior to the baseline visit
- Physical examination
- Safety Laboratory Tests: laboratory testing is optional at this visit and may be performed at the discretion of the investigator and in accordance to the current standard of care.
- Dose of GIOTRIF® given

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

6.2.2.2 Visit 2 (8±2 weeks from Visit 1)

After 8±2 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the eCRF:

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

6.2.2.4 Visit 4 (48±2 weeks from Visit 1)

After 48±2 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the eCRF:

- Visit date
- Physical examination
- Concomitant medications including new medications taken since last visit: any change in the concomitant medications (dose and dosing intervals)
- Any change of GIOTRIF® given
- Effectiveness endpoints : Disease Assessment
- Any changes in laboratory tests if there is any lab result which was clinically significant compared to data before GIOTRIF® therapy (This data is collected on the basis of medical need, i.e. independent of the NIS)
- 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 discontinuati on of GIOTRIF® 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 th at no further follow-up is necessary. The survived subject at the end of the study (Visit 4) is not available, the information should be collected by telephone, letter contact with the patient at the end of the PMS study period.

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. Data of characteristics and other status of patients will be described and proportions including the confidence intervals will be provided.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No hypotheses are tested. (See Section 7.1)

7.3 PLANNED ANALYSES

7.3.1 Demographics and Baseline Characteristics analyses

Data for the demographics and baseline characteristics in safety analysis set is demonstrated by descriptive statistics. In the descriptive statistics, number of subjects, mean, standard deviation, median, minimum and maximum will be calculated for continuous variables, and frequency and percentage will be presented for categorical variables.

The following demographics and baseline characteristics will be reported.

< Demographic information >
- Age, Gender, Pregnancy, Height, Weight, Smoking status, Pediatric group (Under 19 years), Geriatric group (65 years or older), Other medical history and its classification, Kidney disorder, Liver disorder, Subjects whose drug administration period of long-term (24 weeks or more)

< Medication information >
- Giotrif administration status (Total administration period of Giotrif, Total administration dose of Giotrif), Concomitant medication and its classification,Reason of prematurely study withdrawal.

7.3.2 Safety analyses

Demographic 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 GIOTRIF® based on the current authorized label in Korea. However, if data for patients who have been treated with GIOTRIF® 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. Each endpoint will be analyzed by each indication ('locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s)' or 'locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy').

In the safety analysis set, the number of subjects with AEs and the number of AEs will be calculated. Also, the incidence proportion of AEs will be estimated with its 95% confidence interval.

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.

7.3.2.1 Adverse Events by Demographics and Baseline Characteristics

For the AE(s) by demographics and baseline characteristics in the safety analysis set:

- The number of subjects to whom AE occurred and the number of AEs will be calculated.

- The incidence proportion of AEs and its 95% confidence interval will be estimated. Chi-square test or Fisher's exact test will be used for comparing between subcategories of each demographics and baseline characteristics.

- If necessary, analysis for the impact of the safety may be carried out using logistic multiple regression analysis. In general, the variables corresponding to the baseline characteristics listed in section 7.3.1 are used as an independent variable. However, as considering the structure and characteristics of the collected data, the variables used for the actual analysis can be added or subtracted.

7.3.2.2 Adverse Events by Preferred Terms

All AEs recorded in the CRF will be classified by body organs and terms under the classification standard of MedDRA terms, and all AEs excluding the AEs where causal relationship with Giotrif is "Unlikely" will be treated as AEs which causality cannot be excluded (hereafter "Adverse Drug Reaction (ADR)").

For subjects to whom AE occurred, the incidence proportion of AEs and the number of AEs will be summarized. Details are as follows.

① The frequency and percentage of the number of AEs according to serious adverse event, intensity, outcome of the event, action taken, causality, therapy of the event will be calculated.

② All AEs will be classified into the preferred terms according to serious adverse event, intensity, outcome of the event, action taken, causality, therapy of the event. The frequency and percentage of the number of each AE will also be calculated.

③ The number of subjects and the number of AE/ADR, Serious AE/Serious ADR, unexpected AE/ADR, unexpected Serious AE/unexpected Serious ADR will be calculated according to the preferred terms. In this case, the following subgroups are presented separately. Also, the incidence proportion and its 95% confidence interval will be estimated.

④ Preferred terms of Serious AE/Serious ADR, unexpected AE/ADR will be presented respectively according to the proportion of AE in the local product document.

⑤ For subjects excluded from the safety analysis set†, the number of subjects and the number of AE/ADR, Serious AE/Serious ADR, unexpected AE/ADR, unexpected Serious AE/unexpected Serious ADR will be calculated according to the preferred terms. Also, the incidence proportion and its 95% confidence interval will be estimated.

†Subject excluded from safety analysis set: 'Subjects who have not taken Giotrif' and 'Follow-up failure' of patients excluded from safety analysis sets will be excluded (Reflecting the Ministry of Food and Drug Safety (MFDS) guideline).

7.3.3 Main analyses of effectiveness

Effectiveness analysis shall be conducted for subjects of the effectiveness analysis set. Each endpoint will be analyzed by each indication ('locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s)' or 'locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy').
The final effectiveness assessment of "Improved" will be classified as "Effective", "Unchanged" will be classified as "No changed", and "Worsening of symptoms due to cancer" will be classified as "Worsened". The effectiveness rate and its 95% confidence intervals will be estimated with exact method

7.3.3.1 Progression-free survival

Progression-free survival is the time from start of treatment to the date of disease progression or death, whichever comes first.

<u>For patients with known date of progression:</u>

Progression-free survival [days] = date of progression (or of death if no earlier progression) – (date of start of treatment) + 1

For patients known not to have progressed, i.e., those remaining on trial drug:
Progression-free survival (censored) [days] = date of last contact showing no disease progression or death - (date of start of treatment) + 1.
Patients with unknown progression status or unknown date of progression will be censored at the last contact date, refer to Section 7.4 for more detail.

Kaplan-Meier estimates and 95% confidence intervals for the 25th, median, and 75th percentiles of the survival distribution will be calculated for progression-free survival, using Greenwood's standard error estimate. Kaplan-Meier curves will be produced without confidence intervals.

7.3.3.2 Tumour response according to investigator's assessment

Each patient will be assigned to one of the following categories:

1. Complete response (CR)
2. Partial response (PR)
3. Stable disease (SD)
4. Progressive disease (PD)
5. Not evaluable for response, reasons to be specified (e.g. early death, tumour assessments incomplete, etc.)

Time to tumour response is defined as the time from the start of treatment to the date of first recorded CR or PR.

The duration of tumour response is the time from first documented CR or PR to the time of progression or death (or date of censoring for PFS).

Patients whose best assessment is stable disease, partial, or complete response will be considered to have achieved disease control. Duration of disease control will be the same as time to progression, but restricted to patients who achieve disease control.

Descriptive statistics will be calculated for the duration of objective tumour response and disease control. Finally, the proportion of patients in each response category will be tabulated, if feasible (confirmation of response not required). Two-sided 95% confidence intervals will be given for the calculated best response rate. Best response is defined as the best individual response from the date of the first administration until the earliest recording of PD, death or end of treatment (as long as no other anti-cancer therapy has been given).

7.3.3.3 Overall Survival

Overall Survival (OS), defined as time from the date of the first administration of afatinib to the date of death.

For patients with known date of death:
OS [days] = date of death – (date of start of treatment) + 1

For patients known not death case:
OS (censored) [days] = date of last contact showing no death - (date of start of treatment) + 1.

Kaplan-Meier estimates and 95% confidence intervals for the 25th, median, and 75th percentiles of the survival distribution will be calculated for OS, using Greenwood's standard error estimate. Kaplan-Meier curves will be produced without confidence intervals.

7.3.3.4 Demographics and Baseline Characteristics analyses of effectiveness

The effectiveness by factor was classified into 3 categories of 'Improved', 'Unchanged', and 'Worsened' based on the evaluation of cancer-related symptoms at last visit to evaluate the improvement rate.

The improvement rate will be analyzed according to the baseline characteristics listed in below Chisquare test or Fisher's exact test will be used for comparing between subcategories of each baseline characteristic and will be estimated with its 95% confidence interval.

- Age, Gender, Pregnancy, Height, Weight, Smoking status, Pediatric group (Under 19 years), Geriatric group (65 years or older), Other medical history and its classification, Kidney disorder, Liver disorder, Subjects whose drug administration period of long-term (24 weeks or more)

If necessary, analysis for the impact of the change from baseline to last visit may be carried out using multiple regression analysis. In general, the variables corresponding to the baseline characteristics listed in section 7.3.1 are used as an independent variable. However, as considering the structure and characteristics of the collected data, the variables used for the actual analysis can be added or subtracted.

The effectiveness rate will be analyzed according to the baseline characteristics listed in section 7.3.1 Chi-square test or Fisher's exact test will be used for comparing between subcategories of each baseline characteristic and will be estimated with its 95% confidence interval.

7.3.4 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

Missing or incomplete AE dates are imputed according to BI standards.

- For PFS, if a patient is known to have progressed, but the date of progression is not attainable, the last date when the patient was assessed will be used as date of progression.

For PFS, if a patient's vital status or progression status is unknown at the follow-up visit, the patient will be censored at the last contact date.

7.5. RANDOMISATION

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

7.6 DETERMINATION OF SAMPLE SIZE

With sample size of 1,149, ADR with an incidence of 0.26% can be detected in at least one patient with a probability of 95%, including interstitial lung disease(ILD, incidence 0.7%) listed in Korean FPI for GIOTRIF®

In case of Japan GIOTRIF® rPMS, planned sample size was 1,500. To detect an ADR with an incidence of 0.20% (or 0.30%) or greater in at least one patient with a probability of 95% (or 99%), at least 1500 patients needed to be entered and have at least one observation after treatment. The following AEs listed in the Risk Management Plan for GIOTRIF®: diarrhoea, rash/acne, nail effect and interstitial lung disease (include ILD-like event)

As per regulation, long-term surveillance is necessary for the indication. Since locally advanced or metastatic non-small cell lung cancer (NSCLC) is chronic disease, it might be restrictive to collect safety and effectiveness data in short-term (8±2weeks) period, all patients will be enrolled for longer-term (24±2weeks and 48±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 Ministry of Food And Drug Safety (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 patient 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 patient consent and any additional patient-information form retained by the NIS physician as part of the study records. A signed copy of the patient 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.

All AEs will be reported in accordance with Section 5.1.2.2.

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 GIOTRIF® tablets. The investigator will determine the relationship of GIOTRIF® 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

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R06-1394 Doroshow JH. Targeting EGFR in non-small-cell lung cancer. N Engl J Med. 2005; 353(2): 200-202.

9.2 UNPUBLISHED REFERENCES

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U13-1625-01 LUX-Lung 6: A randomised, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR-activating mutation. 24 April 2013.

U12-1482-01 Clinical Summary: Afatinib film-coated tablets, 20 mg, 30 mg, 40 mg, 50 mg. 25 July 2012.

10. APPENDICES

10.1 ELECTRONIC CASE REPORT FORM

Please refer to “ELECTRONIC CASE REPORT FORM” in site file or in electronic CRF web page for the latest version.

10.2 SAE/ SPECIAL INTEREST OF AE REPORT FORM / NON-SERIOUS ADVERSE REACTION REPORT

Please refer to “SAE/ NON-SERIOUS ADVERSE REACTION REPORT” in site file or in electronic CRF web page for the latest version.

10.3 PREGNANCY MONITORING FORM

Please refer to “PREGNANCY MONITORING FORM” in site file or in electronic CRF web page for the latest version.

10.4 LIST OF ALWAYS SERIOUS ADVERSE EVENTS

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

10.5 GIOTRIF® PRESCRIPTION INFORMATION FOR KOREA

Please refer to “GIOTRIF® Prescription Information for Korea” 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		1
Date of Protocol modification		30-Jul-2014
BI Trial number		1200.235
BI Product(s)		Afatinib
Title of protocol		A regulatory requirement post-marketing surveillance study to monitor the safety and efficacy of GIOTRIF®(afatinib dimaleate, 20mg, 30mg, 40mg, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutations
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		3.1.2 Study method
Description of change		*Was added to :* This study will be carried out in the manner of successive survey that the investigator will be asked to successively write in the case report forms(CRFs) from the subject who was initially administered the drug following the study start date to the requested number of subjects without omission. Prior to initiation of the study, written contract shall be concluded, and this contract shall be concluded with the head of the site or the investigator with his/her

		consent.
Rationale for change		Request by Korea Authorities (MFDS)
Section to be changed		3.3.5 Subjects of special investigation
Description of change		*Was added to :* Any Investigation for the elderly, pregnant women, and patients with renal impairment and hepatic impairment will not be separately conducted, and further investigation into cases collected from this study may be taken into account according to the outcome of retrospective analysis.
Rationale for change		Request by Korea Authorities (MFDS)
Section to be changed		5.3 OTHER
Description of change		5.3 OTHER This section is not applicable. 5.3.1 Demographic data This section is not applicable. *Was changed to :* 5.3 Items of investigation 5.3.1 Demographic data For demographic evaluation, following background information of subjects shall be recorded: Subject signed date Subject study number Gender Pregnancy Height Weight Year/month of birth (age) Smoking 5.3.2 Medical/surgical history and pre-treatment experience The medical/surgical history to be collected and the treatment experience prior to administration of this drug includes: Date of diagnosis Date of EGFR test Medical history Previous surgical experience for the medical

		history Previous chemotherapy Previous radiotherapy 5.3.3 Concomitant medication Information on concomitant medication that is to be collected includes: Brand name or generic name Daily dose Unit Indication Start date Date of discontinuation or continuation 5.3.4 Drug administration status Information on the drug administration status includes: Dose Start date Date of discontinuation or continuation Dose changes 5.3.5 Information on the site Information on the site includes: Hospital name Department Physician name 5.3.6 Main points of study and details of study method If a particular trend or change associated with safety is found from spontaneous adverse event report during this study, special investigation into the relevant item shall be planned and implemented. Also, the situations of occurrence of any unexpected adverse drug reactions or adverse events whose causal relationship with the drug has not been established and frequency is extremely low, which have not appeared in the course of development of the drug during the study period, shall be intensively observed and investigated.
Rationale for change		Request by Korea Authorities (MFDS)

Section to be changed		5.4 APPROPRIATENESS OF MEASUREMENTS
Description of change		5.4 APPROPRIATENESS OF MEASUREMENTS This section is not applicable. *Was changed to :* 5.4 Endpoints of subjects Evaluation 5.4.1 Subject evaluation items 5.4.1.1 Number of cases who accepted the study This number means the planned number of cases as specified in the contract concluded with the investigator (physician) prior to initiation of the study. 5.4.1.2 Number of cases subject who collected CRF This number means the number of cases who signed the informed consent form to participate in the study as subject, and have record of taking GIOTRIF® once at least. 5.4.1.3 Number of dropouts These cases include those who signed the informed consent form to participate in this study as subject but did not meet any of the inclusion criteria, do not have any prescription record of GIOTRIF® , have prescription record but have not been followed up by the physician following prescription, and started administration prior to the signed date. 5.4.1.4 Number of cases subject to safety evaluation These cases include those who signed the informed consent form to participate in this study as subject, took GIOTRIF® once at least, and were followed up by the physician once or more. 5.4.1.5 Number of cases subject to efficacy evaluation These cases include those who signed the informed consent form to participate in this study as subject, visited as per the study schedule, took GIOTRIF®, and were

		evaluated for the efficacy.
Rationale for change		Request by Korea Authorities (MFDS)

Number of Protocol modification		2
Date of Protocol modification		01-Oct-2014
BI Trial number		1200.235
BI Product(s)		Afatinib
Title of protocol		A regulatory requirement post-marketing surveillance study to monitor the safety and efficacy of GIOTRIF®(afatinib dimaleate, 20mg, 30mg, 40mg, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutations
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		All pages
Description of change		Doc. No.: c02597942-02 *Was changed to:* Doc. No.: c02597942-03
Rationale for change		Changed document number in the BIRDS
Section to be changed		All pages
Description of change		Date : 30 Jul 2014 *Was changed to:* Date : 01 Oct 2014
Rationale for change		As per Protocol Amendment

Section to be changed		Cover page
Description of change		Version : 2 *Was changed to:* Version : 3
Rationale for change		As per Protocol Amendment
Section to be changed		3.3.2 Inclusion criteria
Description of change		• Age ≥ 18 years at enrolment *Was deleted*
Rationale for change		As per local prescribing information
Section to be changed		5.1.2.2 Adverse event and serious adverse event reporting
Description of change		All adverse events occurring from the start of GIOTRIF® 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). *Was changed to :* All adverse events occurred from the signing date on ICF to 28 days after last administration date of medication need to be collected, documented and reported to the sponsor using the AE reporting form of eCRF (Attachment 1).
Rationale for change		Comments from the Local PV

Number of Protocol modification		3
Date of Protocol modification		04-Oct-2014
BI Trial number		1200.235
BI Product(s)		Afatinib
Title of protocol		A regulatory requirement post-marketing surveillance study to monitor the safety and efficacy of GIOTRIF®(afatinib dimaleate, 20mg, 30mg, 40mg, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutations

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		All pages
Description of change		Doc. No.: c02597942-03 *Was changed to:* Doc. No.: c02597942-04
Rationale for change		Changed document number in the BIRDS
Section to be changed		All pages
Description of change		Date : 01 Oct 2014 *Was changed to:* Date : 04 Oct 2014
Rationale for change		As per Protocol Amendment
Section to be changed		Cover page
Description of change		Version : 3 *Was changed to:* Version : 4
Rationale for change		As per Protocol Amendment
Section to be changed		3.1 OVERALL DESIGN AND PLAN
Description of change		However, active enrolment is to be initiated in May 2015 after finalizing the re-imbursement agreement with the authority. *Was changed to:* However, active enrolment is to be initiated in Oct 2014 after finalizing the re-imbursement

		agreement with the authority.
Rationale for change		Change of the date for the reimbursement agreement

Number of Protocol modification		4
Date of Protocol modification		17-Oct-2014
BI Trial number		1200.235
BI Product(s)		Afatinib
Title of protocol		A regulatory requirement post-marketing surveillance study to monitor the safety and efficacy of GIOTRIF®(afatinib dimaleate, 20mg, 30mg, 40mg, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutations
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		3.3.2 Inclusion Criteria
Description of change		• Patients who have been started on GIOTRIF® in accordance with the approved label in Korea • Patients who have signed on the data release consent form *Was changed to:* • Patients who have been started on GIOTRIF® in accordance with the approved label in Korea • Age ≥ 19 years at enrolment

		• Patients who have signed on the data release consent form
Rationale for change		Request by Korea Authorities (MFDS)

Number of Protocol modification		5
Date of Protocol modification		01-Sep-2017
BI Trial number		1200.235
BI Product(s)		Afatinib
Title of protocol		A regulatory requirement post-marketing surveillance study to monitor the safety and efficacy of GIOTRIF®(afatinib dimaleate, 20mg, 30mg, 40mg, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutations or patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy
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		All pages
Description of change		Doc. No.: c02597942-05 *Was changed to:* Doc. No.: c02597942-06
Rationale for change		Changed document number in the BIRDS
Rationale for change		All pages
Section to be changed		Date : 17 Oct 2014

		Was changed to: Date : 01 Sep 2017
Description of change		As per Protocol Amendment
Section to be changed		All pages
Description of change		Version no.: 5 *Was changed to:* Version no.: 6
Rationale for change		As per Protocol Amendment
Section to be changed		All corresponding pages
Description of change		Change of Title of Protocol A regulatory requirement post-marketing surveillance study to monitor the safety and efficacy of GIOTRIF®(afatinib dimaleate, 20mg, 30mg, 40mg, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutations *Was changed to:* A regulatory requirement post-marketing surveillance study to monitor the safety and efficacy of GIOTRIF®(afatinib dimaleate, 20mg, 30mg, 40mg, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutations or patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy
Rationale for change		Product label updated.
Section to be changed		Cover page
Description of change		Phone: Fax: *Was changed to:*

		Phone: Fax:
Rationale for change		Change of Trial Clinical Monitor
Section to be changed		All corresponding pages
Description of change		Diagnosis: - Patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s) *Was changed to:* - Patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s) - Patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy
Rationale for change		Product label updated.
Section to be changed		All corresponding pages
Description of change		data release consent form *Was changed to:* patient consent form
Rationale for change		To be consistent with a consent form title in use.
Section to be changed		1.2 DRUG PROFILE
Description of change		For the treatment of EGFR TKI-naïve NSCLC patients, the recommended dose of afatinib is 40 mg orally once daily. *Was changed to:* For the treatment of EGFR TKI-naïve NSCLC patients or patients with NSCLC of squamous histology progressing on or after platinum-

		based chemotherapy, the recommended dose of afatinib is 40 mg orally once daily.
Rationale for change		Product label updated.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		The physicians indicate doses and timing. *Was changed to:* The physicians indicate doses and timing based on the current authorized label in Korea..
Rationale for change		As this is a regulatory PMS to report cases within approved label, the concerning sentence was revised to avoid a confusion.
Section to be changed		Protocol Synopsis 5.1.1 Endpoints of safety
Description of change		All reported adverse events in patients who take at least one dose of GIOTRIF® will be noted. *Was changed to:* All reported adverse events in patients who take at least one dose of GIOTRIF® based on the current authorized label in Korea will be noted.
Rationale for change		As this is a regulatory PMS to report cases within approved label, the concerning sentence was revised to avoid a confusion.
Section to be changed		5.1.2.1 Definitions of adverse events
Description of change		**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. *Was changed to:* **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
Rationale for change		As per MFDS guideline on re-examination of

		new drugs, the 6 categories of AE causality are included.
Section to be changed		5.4.1.4 Number of cases subject to safety evaluation
Description of change		These cases include those who signed the informed consent form to participate in this study as subject, took GIOTRIF® once at least, and were followed by the physician once or more. *Was changed to:* These cases include those who signed the informed consent form to participate in this study as subject, took GIOTRIF® according to the approved label once at least, and were followed up via phone/mail/visit by the physician once or more.
Rationale for change		As per MFDS guideline on re-examination of new drugs, the detailed methods on safety follow up are included.
Section to be changed		7.3.1 Safety analyses
Description of change		Safety analyses will be based on all patients treated, i.e. all patients who received at least one dose of GIOTRIF®. *Was changed to:* Safety analyses will be based on all patients treated, i.e. all patients who received at least one dose of GIOTRIF® based on the current authorized label in Korea.
Rationale for change		As this is a regulatory PMS to report cases within approved label, the concerning sentence was revised to avoid a confusion.

Number of Protocol modification		6
Date of Protocol modification		20-Nov-2018
BI Trial number		1200.235
BI Product(s)		Afatinib
Title of protocol		A regulatory requirement post-marketing surveillance study to monitor the safety and efficacy of GIOTRIF®(afatinib dimaleate,

		20mg, 30mg, 40mg, q.d) in Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutations or patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy
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		All pages
Description of change		Doc. No.: c02597942-06 *Was changed to:* Doc. No.: c02597942-07
Rationale for change		Changed document number in the BIRDS
Rationale for change		All pages
Section to be changed		Date : 01 Sep 2017 Was changed to: Date : 20 Nov 2018
Description of change		As per Protocol Amendment
Section to be changed		All pages
Description of change		Version no.: 6 *Was changed to:* Version no.: 7

Rationale for change		As per Protocol Amendment
Section to be changed		Title page
Description of change		Phone: Fax: *Was changed to:* Phone: Fax:
Rationale for change		Change of Trial Clinical Monitor
Section to be changed		Flow Chart
Description of change		Add: Baseline Platinum-based chemotherapy
Rationale for change		MFDS comment refer to Product label updated.
Section to be changed		Flow Chart
Description of change		Add: Overall survival follow up
Rationale for change		MFDS comment refer to Product label updated.
Section to be changed		3.3 SELECTION OF POPULATION
Description of change		A total of 3000 patients *Was changed to :* A total of 1,149 patients
Rationale for change		No. of patients amendment
Section to be changed		5.2.1 Endpoints of effectiveness
Description of change		Add:

		• Overall Survival (OS), defined as time from the date of the first administration of afatinib to the date of death.
Rationale for change		MFDS comment refer to Product label updated.
Section to be changed		5.1.2.2 Adverse event and serious adverse event reporting
Description of change		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 Local PV Manager (LPVM) of BI Korea using the SAE report form (Attachment2).
Rationale for change		Delete
Section to be changed		5.1.2.2 Adverse event and serious adverse event reporting
Description of change		*Add :* Non-serious ADR must be reported using eCRFs and NIS AE form within 7 calendar days
Rationale for change		In accordance with NIS protocol SOP (001-MCS-90-118_RD-01_7.0)
Section to be changed		5.2.2 Assessment of effectiveness
Description of change		Add: In the case of OS data of the survived subject at the end of the study (Visit 4) is not available, the information should be collected by telephone, letter contact with the patient at the end of the PMS study period.
Rationale for change		MFDS comment refer to Product label updated.
Section to be changed		6.2.2.1Visit 1 – Baseline Visit
Description of change		• Demographic data: year of birth(age), gender, pregnancy, height, weight, smoking status~~, alcohol consumption (units and alcoholism diagnosis)~~
Rationale for change		Delete

Section to be changed		6.2.3 End of trial and follow-up period
Description of change		Add: The survived subject at the end of the study (Visit 4) is not available, the information should be collected by telephone, letter contact with the patient at the end of the PMS study period.
Rationale for change		MFDS comment refer to Product label updated.
Section to be changed		7.3.1 Demographics and Baseline Characteristics analyses
Description of change		Add: Data for the demographics and baseline characteristics in safety analysis set is demonstrated by descriptive statistics. In the descriptive statistics, number of subjects, mean, standard deviation, median, minimum and maximum will be calculated for continuous variables, and frequency and percentage will be presented for categorical variables. The following demographics and baseline characteristics will be reported. < Demographic information > - Age, Gender, Pregnancy, Height, Weight, Smoking status, Pediatric group (Under 19 years), Geriatric group (65 years or older), Other medical history and its classification, Kidney disorder, Liver disorder, Subjects whose drug administration period of long-term (24 weeks or more) < Medication information > - Giotrif administration status (Total administration period of Giotrif, Total administration dose of Giotrif), Concomitant medication and its classification,Reason of prematurely study withdrawal.
Rationale for change		MFDS comment - specific analysis plan
Section to be changed		7.3.2 Safety analyses
Description of change		Add: Each endpoint will be analyzed by each

		indication (‘locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s)’ or ‘locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy’). In the safety analysis set, the number of subjects with AEs and the number of AEs will be calculated. Also, the incidence proportion of AEs will be estimated with its 95% confidence interval.
Rationale for change		MFDS comment refer to Product label updated. MFDS comment - specific analysis plan
Section to be changed		7.3.2.1 Adverse Events by Demographics and Baseline Characteristics
Description of change		Add: For the AE(s) by demographics and baseline characteristics in the safety analysis set: - The number of subjects to whom AE occurred and the number of AEs will be calculated. - The incidence proportion of AEs and its 95% confidence interval will be estimated. Chi-square test or Fisher’s exact test will be used for comparing between subcategories of each demographics and baseline characteristics. - If necessary, analysis for the impact of the safety may be carried out using logistic multiple regression analysis. In general, the variables corresponding to the baseline characteristics listed in section 7.3.1 are used as an independent variable. However, as considering the structure and characteristics of the collected data, the variables used for the actual analysis can be added or subtracted.
Rationale for change		MFDS comment - specific analysis plan
Section to be changed		7.3.2.2 Adverse Events by Preferred Terms
Description of change		Add: All AEs recorded in the CRF will be classified by body organs and terms under the

		classification standard of MedDRA terms, and all AEs excluding the AEs where causal relationship with Giotrif is "Unlikely" will be treated as AEs which causality cannot be excluded (hereafter "Adverse Drug Reaction (ADR)"). For subjects to whom AE occurred, the incidence proportion of AEs and the number of AEs will be summarized. Details are as follows. ① The frequency and percentage of the number of AEs according to serious adverse event, intensity, outcome of the event, action taken, causality, therapy of the event will be calculated. ② All AEs will be classified into the preferred terms according to serious adverse event, intensity, outcome of the event, action taken, causality, therapy of the event. The frequency and percentage of the number of each AE will also be calculated. ③ The number of subjects and the number of AE/ADR, Serious AE/Serious ADR, unexpected AE/ADR, unexpected Serious AE/unexpected Serious ADR will be calculated according to the preferred terms. In this case, the following subgroups are presented separately. Also, the incidence proportion and its 95% confidence interval will be estimated. ④ Preferred terms of Serious AE/Serious ADR, unexpected AE/ADR will be presented respectively according to the proportion of AE in the local product document. ⑤ For subjects excluded from the safety analysis set†, the number of subjects and the number of AE/ADR, Serious AE/Serious ADR, unexpected AE/ADR, unexpected Serious AE/unexpected Serious ADR will be calculated according to the preferred terms. Also, the incidence proportion and its 95% confidence interval will be estimated. †Subject excluded from safety analysis set: 'Subjects who have not taken Giotrif' and

		'Follow-up failure' of patients excluded from safety analysis sets will be excluded (Reflecting the Ministry of Food and Drug Safety (MFDS) guideline).
Rationale for change		MFDS comment - specific analysis plan
Section to be changed		7.3.3 Main analyses of effectiveness
Description of change		Add: Effectiveness analysis shall be conducted for subjects of the effectiveness analysis set. Each endpoint will be analyzed by each indication ('locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s)' or 'locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy'). The final effectiveness assessment of "Improved" will be classified as "Effective", "Unchanged" will be classified as "No changed", and "Worsening of symptoms due to cancer" will be classified as "Worsened". The effectiveness rate and its 95% confidence intervals will be estimated with exact method.
Rationale for change		MFDS comment refer to Product label updated.
Section to be changed		7.3.3.3 Overall Survival
Description of change		Add: Overall Survival (OS), defined as time from the date of the first administration of afatinib to the date of death. <u>For patients with known date of death:</u> OS [days] = date of death – (date of start of treatment) + 1 <u>For patients known not death case:</u> OS (censored) [days] = date of last contact showing no death - (date of start of treatment) + 1. Kaplan-Meier estimates and 95% confidence intervals for the 25th, median, and 75th

		percentiles of the survival distribution will be calculated for OS, using Greenwood's standard error estimate. Kaplan-Meier curves will be produced without confidence intervals.
Rationale for change		MFDS comment refer to Product label updated.
Section to be changed		7.3.3.4 Demographics and Baseline Characteristics analyses of effectiveness
Description of change		The effectiveness by factor was classified into 3 categories of 'Improved', 'Unchanged', and 'Worsened' based on the evaluation of cancer-related symptoms at last visit to evaluate the improvement rate. The improvement rate will be analyzed according to the baseline characteristics listed in below Chisquare test or Fisher's exact test will be used for comparing between subcategories of each baseline characteristic and will be estimated with its 95% confidence interval. - Age, Gender, Pregnancy, Height, Weight, Smoking status, Pediatric group (Under 19 years), Geriatric group (65 years or older), Other medical history and its classification, Kidney disorder, Liver disorder, Subjects whose drug administration period of long-term (24 weeks or more) If necessary, analysis for the impact of the change from baseline to last visit may be carried out using multiple regression analysis. In general, the variables corresponding to the baseline characteristics listed in section 7.3.1 are used as an independent variable. However, as considering the structure and characteristics of the collected data, the variables used for the actual analysis can be added or subtracted. The effectiveness rate will be analyzed according to the baseline characteristics listed in section 7.3.1 Chi-square test or Fisher's exact test will be used for comparing between subcategories of each baseline characteristic

		and will be estimated with its 95% confidence interval.
Rationale for change		MFDS comment - specific analysis plan
Section to be changed		7.6 DETERMINATION OF SAMPLE SIZE
Description of change		Sample size of 3000 patients is based on the requirement of the local regulatory authority (Ministry of Food and Drug Safety). As per regulation, long-term surveillance is necessary for the indication. Since locally advanced or metastatic non-small cell lung cancer (NSCLC) is chronic disease, it might be restrictive to collect safety and effectiveness data in short-term (8±2weeks) period, all patients will be enrolled for longer-term (24±2weeks and 48±2weeks) surveillance. *Was changed to :* With sample size of 1,149, ADR with an incidence of 0.26% can be detected in at least one patient with a probability of 95%, including interstitial lung disease(ILD, incidence 0.7%) listed in Korean FPI for GIOTRIF® In case of Japan GIOTRIF® rPMS, planned sample size was 1,500. To detect an ADR with an incidence of 0.20% (or 0.30%) or greater in at least one patient with a probability of 95% (or 99%), at least 1500 patients needed to be entered and have at least one observation after treatment. The following AEs listed in the Risk Management Plan for GIOTRIF®: diarrhoea, rash/acne, nail effect and interstitial lung disease (include ILD-like event)
Rationale for change		No. of patients amendment, Rationale update
Section to be changed		8.4.1 Time windows
Description of change		*Deleted :* Any SAE, whether or not considered related to GIOTRIF® tablets, or whether or not GIOTRIF® tablets has been administered, must be reported immediately via eCRF and

		SAE/Special interest of AE Report Form. *Add :* All AEs will be reported in accordance with 5.1.2.2.
Rationale for change		Delete duplication