Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

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Name of company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
Name of finished medicinal product: Giotrif®			
Name of active ingredient: afatinib dimaleate			
Report date: 05Feb2021	**Study number:** 1200-0235	**Version/Revision:** 1.0/Not applicable	**Version/Revision date:** Not applicable

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
Keywords:	Observational prospective, non-interventional, open-label, multi-centre national study
Rationale and background:	According to the local regulations, when a new chemical entity (NCE) is registered, a regulatory non interventional study (NIS) of an extended period (4 or 6 years) should be conducted. Such NIS can provide supplementary data to monitor the safety of NCEs in a real-life situation. Data collected in randomized clinical study with strict inclusion/exclusion criteria and rigorous monitoring schemes have limitations.
Research question and 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. <u>Primary Objective</u> 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.. <u>Secondary Objective</u> 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.

Study design:	This was a single arm study with GIOTRIF®. GIOTRIF® was prescribed according to the local label and at the discretion of the treating physician. Since this was a non-interventional study, the drug was not be supplied by the sponsor. Furthermore, the sponsor did not cover the expenses related to other medications taken by the patient, interventions, procedures, or diagnostic test.
Setting:	Patients were managed according to the local practice guidelines. The choice of treatment was solely at the discretion of the participating physician. GIOTRIF® was administered according to the approved label in Korea. GIOTRIF® is indicated as 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. <u>Inclusion criteria:</u> • 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 <u>Exclusion criteria:</u> • 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®
Subjects and study size, including dropouts:	A total of 1,149 patients were planned to be enrolled at approximately 50 sites by as many as 50 or more NIS physicians.
Variables and data sources:	<u>Endpoints of safety</u> All reported adverse events in patients who take at least one dose of GIOTRIF® based on the current authorized label in Korea were noted. Endpoints pertaining to safety werepresented 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 <u>Endpoints of effectiveness</u>

<table>
<tr><td></td><td>Disease Assessment was 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.</td></tr>
<tr><td>Results:</td><td>Subjects and Compliance with Protocol:
During this re-examination period, case report forms (CRFs) were retrieved from a total of 1,272 subjects. Among these, 1,221 subjects were included in the safety assessment, after excluding 1 subject 'who consented prior to the contract date', 2 subjects 'who have not taken GIOTRIF', 5 subjects with 'follow-up failure', and 43 subjects 'who have violated the inclusion/exclusion criteria'; and of the subjects in the safety assessment set, 1,000 subjects were included in the effectiveness assessment, after excluding 221 subjects whose 'effectiveness assessment were missing: the evaluation of cancer-related symptoms at Visit 2, Visit 3, and Visit 4 were all missing'.
<table><tr><td>Number of subjects whose CRFs were retrieved</td><td>1,272</td></tr><tr><td>Number of subjects included in the safety analysis set</td><td>1,221</td></tr><tr><td>Number of subjects included in the effectiveness analysis set</td><td>1,000</td></tr></table>
Demographic information:
Of the 1,220 subjects in the safety assessment set, 54.26% (662/1,220 subjects) were 'Female', and 45.74% (558/1,220 subjects) were 'Male'. The mean (±std) age of the 1,220 subjects in the safety assessment set was 66.26±10.78 years, ranging from 31.00 to 95.00 years. Looking at age group, the most common was '≥ 70 years' with 42.54% (519/1,220 subjects), followed by '60 years ~ 69 years' with 29.84% (364/1,220 subjects), '50 years ~ 59 years' with 20.90% (255/1,220 subjects), and '< 50 years' with 6.72% (82/1,220 subjects). There was no pregnant subject.

Race and Ethnicity:
Not collected

Safety Results:</td></tr>
</table>

	All participants whose CRFs were retrieved during the re-examination period (29 Jan 2014 - 28 Jan 2020) and who did not violate the inclusion/exclusion criteria. 1 subject was excluded from the set based on disease indication. There was no interim analysis conducted. Among the 1,220 subjects in the safety assessment set, AEs occurred in 94.10% (1,148/1,220 subjects, 5,984 cases), while ADRs in which causal relationship to the study medication could not be ruled out occurred in 89.92% (1,097/1,220 subjects, 4,353 cases). The most common ADRs were 'Diarrhoea' (870/1,220 subjects, 71.31%), 'Rash' (501/1,220 subjects, 41.07%), and 'Stomatitis' (385/1,220 subjects, 31.56%). SAEs occurred in 35.66% (435/1,220 subjects, 660 cases) and SADRs in 10.98% (134/1,220 subjects, 176 cases). The most common SADRs were 'Diarrhoea' (52/1,220 subjects, 4.26%), 'Acute kidney injury' (12/1,220 subjects, 0.98%), and 'Vomiting' (9/1,220 subjects, 0.74%). Unexpected AEs occurred in 64.10% (782/1,220 subjects, 1,999 cases) and unexpected ADRs in 33.93% (414/1,220 subjects, 665 cases). The most common unexpected ADRs were 'Asthenia' (37/1,220 subjects, 3.03%), 'Folliculitis' (28/1,220 subjects, 2.30%), and 'Skin lesion' (22/1,220 subjects, 1.80%). Unexpected SAEs occurred in 32.05% (391/1,220 subjects, 539 cases) and unexpected SADRs in 5.08% (62/1,220 subjects, 73 cases). The most common SADRs were 'Acute kidney injury' (12/1,220 subjects, 0.98%), 'Asthenia' (6/1,220 subjects, 0.49%), and 'Dyspnoea' and 'Hypophagia' (each in 4/1,220 subjects, 0.33%). Looking at the CTCAE grade of 22 unexpected SADRs of the total of 73 unexpected SADRs, excluding 51 recovered cases, the specific SADRs in CTCAE grade 4 and grade 5 were 'Acute kidney injury', 'Neutropenia', 'Pulmonary fibrosis', and 'Malignant neoplasm progression'. The most frequently occurring unexpected SADR was 'Acute kidney injury'. While this was not reflected in the approved label for the study medication, Romanidou et al.'s research on the EGFR inhibitor Gefitinib showed rapid deterioration in renal function from the introduction of Gefitinib in patients with chronic renal impairment, and improvement in sCr and creatinine clearance with the discontinuation of Gefitinib. Zhuang et al. showed that EFGR inhibitor could increase renal damage in acute renal failure using mice models. Thus it is deemed possible that acute kidney injury could be causally related to study medication use. However, given the nature of non-interventional studies, it would be difficult to confirm causal relationship between the study medication and acute kidney failure from the results of this post marketing surveillance alone. The severity of the 5,984 AEs that occurred was 'Mild' in 4,138 cases, 'Moderate' in 1,659 cases, and 'Severe' in 187 cases, while CTCAE grade was 'Grade 1' in 3,630 cases, 'Grade 2' in 1,874 cases, 'Grade 3' in 409 cases, 'Grade 5' in 44 cases, and 'Grade 4' in 27 cases. Action taken to study medication following AE was 'Continue' in 3,910 cases, 'Reduced' in 1,508 cases, 'Discontinued' in 352 cases, 'Discontinued and reintroduced' in 153 cases, 'Not applicable' in 56 cases, and 'Increased' in 5 cases. AE outcome was 'Recovered' in 3,661 cases, 'Not yet recovered' in 2,102 cases, 'Unknown' in 111 cases, 'Sequlae' in 57 cases, and 'Fatal' in 53 cases. Causal relationship between AE and study medication was 'Possible' in 1,882 cases, 'Probable/Likely' in 1,758 cases, 'Unlikely' in 1,631 cases,

	'Certain' in 692 cases, 'Conditional /unclassified' in 12 cases, and 'Unassessible/unclassifiable' in 9 cases. Treatment was given for the AE in 4,778 cases, and not given for the AE in 1,206 cases. In a logistic regression analysis, the factors of 'squamous cell carcinoma' in NSCLC histological classification, total administration period of study medication, mean daily dose of study medication, and presence of concomitant medication were found to have statistically significant impact on safety. The OR of AE incidence were 434.63 times higher for subjects with NSCLC histological classification of 'squamous cell carcinoma' than for subjects with 'large cell/undifferentiated carcinoma', 1.01 times higher with each additional day of study medication administration, 0.72 times lower with each 1 mg/day increase in mean daily dose, and 10.84 times higher in subjects taking concomitant medication compared to those not taking concomitant medication. Although statistically significant increases were observed in subjects with NSCLC histological classification of 'squamous cell carcinoma', there was no consistent significance in AE incidence compared to other histological classifications used in the analysis, and thus clinical significance could not be derived from this outcome. Furthermore, the proportion of subjects with the indication of 'adenocarcinoma' was 95.82%, indicating an impact of subject distribution on the statistical comparison of AE incidence with other indication. However, it is deemed unlikely that this has clinical significance. For total administration period, AE incidence increased by 1.01 times for each additional day, but early termination for 'Worsening or AE of underlying cancer disease' was rare (1.55%) among subjects terminating the study early, and dose adjustment and rechallenge were conducted for AE incidences, thus it is deemed that the termination of the study medication was not due to ADR. For mean daily dose of study medication, the initial dose is 40 mg/day on the approved label, and dose adjustment is recommended in the case of AE occurrence. As subjects experiencing AEs were given doses lowered by 10 mg compared to the previous dose, they fell under the 30 mg/day and 20 mg/day groups, resulting in higher AE incidence for these dose decreased groups. As for concomitant medication, the concomitant medication may have been either the cause or outcome of AE. Thus, while there is statistical significance, it cannot be seen as a significant factor clinically. **Effectiveness / Other Results:** The effectiveness assessment was conducted based on the assessment of cancer-related symptoms and, if applicable, radiologic assessments as per standard medical procedure of study institution. Based on the assessment of cancer-related symptoms and radiologic assessment, the effectiveness assessment was analyzed to tumor assessment at last visit, overall clinical benefit at last visit, duration of response, best response, best clinical benefit, duration of disease control, survival analysis of PFS, and overall survival. Tumor response at last visit was 'Stable Disease' in 57.05%, followed by 'Partial Response' in 29.98%, 'Progressive Disease' in 9.54%, 'Complete Response' in 2.28%, and 'Not Evaluable' in 1.14%. Overall clinical benefit, which was defined as clinical response, or absence of progression or symptom improvement at last visit, was ‘Yes’ in 88.60%.

	The duration of tumor response in 115 subjects excluding 385 subjects for whom CR or PR were not found and 498 subjects with CR or PR but no disease progression or death was 162.20±109.84 days. To assess duration of response including all subjects with response, result of analyzing tumor response including 498 subjects with CR or PR but no disease progression or death, mean (±std) duration of tumor response was 199.33±125.54 days. The best response in 964 subjects who had completed the tumor assessment was 'Partial Response' in 60.89%, followed by 'Stable Disease' in 32.26%, 'Progressive Disease' in 3.22%, 'Complete Response' in 2.90%, and 'Not Evaluable' in 0.73%. The best clinical benefit defined as 'Stable Disease', 'Partial Response', and 'Complete Response' at any timepoint during the observation period based on best response, was 96.06%. The mean (±std) disease control duration of 181 subjects excluding 745 subjects that did not experience disease progression or death was 223.50±99.76 days. To assess duration of response including all subjects with response, result of analyzing mean (±std) disease control duration including 745 subjects that did not experience disease progression or death was 269.15±118.27 days. Disease progression or death occurred in 216 subjects among 1,000 subjects, and the median of the median (50% PFS) was 1,051.00 days. However low maturity should be considered as there are 784 subjectscensored in the analysis . The PFS rate at 48 weeks was 73.74%. The overall survival was not estimated because death occurred only in 30 subjects among the 1,000 subjects in the effectiveness assessment set. The data for OS and PFS was calculated using the Kaplan-Meier estimates. Classifying the cancer-related symptoms assessment at last visit into the categories: 'Improve' for "Improved", 'Stable' for "Unchanged", and 'Worse' for "Worsening of symptoms due to cancer", 'Improve' occurred in 34.10% (341/1,000 subjects) of the effectiveness assessment set, 'Stable' in 60.70% (607/1,000 subjects), and 'Worse' in 5.20% (52/1,000 subjects). In a logistic regression analysis, the factors that showed statistically significant impact on improvement rate were total administration period of study medication and early termination. Specifically, the OR of improvement rate increased by 1.00 times with each additional day of study medication use, while the OR of improvement rate was 1.59 times higher in subjects that did not terminate the study early, compared to subjects that did terminate the study early. In the case of early termination, 'Progressive disease' was the most common reason for early termination in 35.54% of early termination subjects, and these subjects showed an improvement rate of 22.03%, lower than the 34.07% improvement rate among subjects who did not terminate the study early. Therefore, subjects who terminated the study medication use due to disease progression were included in the early termination group, resulting in higher improvement rate for subjects in the non-early termination group. The same goes for the

	higher improvement rate for longer study medication use period, as subjects who continued using the study medication without early termination had longer total administration periods, thus showing a similar outcome.
Discussion:	As a result of this re-examination period, in conclusion, the post-marketing surveillance of Giotrif® Tablet showed 'Acute kidney injury' as the most frequently occurring unexpected SADR not reflected in the approved label. However, due to the non-interventional nature of the post-marketing surveillance which relies only on data from routine clinical practice, it cannot be considered a significant issue affecting safety and effectiveness based on this data alone. Incidence of AEs and their causal relationship to the study medication will be continuously monitored in future surveillance.
Marketing Authorisation Holder(s):	[redacted] Korea
Names and affiliations of principal investigators:	Multi-centre study(51 sites/ 59 Principal investigators)
Study status	Completed