Boehringer Ingelheim Pharma GmbH & Co. KG	
Follow-up Plan Non-interventional Study (NIS)	Boehringer Ingelheim Pharma GmbH & Co. KG

BI No.:	1200.205
Medicinal Product:	GIOTRIF® (Afatinib)
Title:	**GIDEON:** GIOTRIF® as first-line treatment for advanced NSCLC with activating EGFR mutations (original: ***G****IOTRIF® **i**n **d**er **E**rstlinientherapie des f**o**rtgeschrittenen **N**SCLC mit aktivierenden EGFR-Mutationen*)
Clinical Monitor:	
Follow-up plan date:	01 July 2014
Planned duration of the NIS:	FPI: April 2014 LPO: October 2017
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Confidential	

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List of abbreviations

AMG	German Medicinal Products Act (original: *Arzneimittelgesetz der Bundesrepublik Deutschland*)
AE	Adverse Event
BfArM	German Federal Institute for Drugs and Medical Devices (original: *Bundesinstitut für Arzneimittel und Medizinprodukte*)
CR	Complete Remission
CRF	Case Report Form
DCR	Disease Control Rate
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
GCP	Good Clinical Practice
ITT	Intent to Treat
NIS	Non-Interventional Study
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall response rate
PFS	Progression-Free Survival
PR	Partial Remission
PRO	Patient Reported Outcome
QoL	Quality of Life
SD	Stable Disease
SAE	Severe Adverse Event
TKI	Tyrosine Kinase Inhibitor
TSAP	Trial Statistical Analysis Plan

1. Introduction

1.1 Medical Background

Lung and bronchial carcinoma is one of the most common cancer disorders in Germany, as well as around the world. Bronchial carcinoma is ranked third among tumour disorders in Germany with over 49,000 newly diagnosed cases in 2008 (34,000 men, 15,500 women) (1). At 26%, it also by far the most frequent cancer-related cause of death in men (29,500) and at 13% the third most frequent cancer-related cause of death in women (13,000) in 2008.
In contrast to other tumour disorders, due to the clinical course of the disease, which is initially asymptomatic for a long-period of time and usually associated with a non-specific constellation of symptoms, lung cancer is first diagnosed at an advanced stage in the majority of patients (2). Symptoms include coughing (with or without haemoptysis), respiratory distress, chronic lung inflammation, pain in the breast and shoulders, constant tiredness and exhaustion (fatigue) or anorexia (3). The relative 5-year survival rate for lung cancer in Germany is stated as approximately 15% in men and 18% for women and varies depending on the staging of the tumour disorder when the diagnosis is made (3). The median survival time for patients treated with chemotherapy alone in advanced stage IV (Union for International. Cancer Control UICC, 7th Edition) is limited and amounts to a median period of 8 - 12 months. The objectives of treatment are reduction of tumour-related symptoms and prolonged survival time.

Non-small cell small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) can be differentiated histologically, based on differences in biological behaviour, prognosis and therapeutic options. Approximately 80 - 85% of lung cancers are NSCLC, which are differentiated into three main histological subgroups: Adenocarcinoma, squamous cell carcinoma and large cell carcinoma (4). The fact that lung cancers also can be differentiated genetically has also emerged during the last few years. Accordingly, approximately half of adenocarcinomas exhibit so-called driver mutations that are important for malignant transformation. A study of 516 patients with an adenocarcinoma of the lung showed that one form of these driver mutations could be proven in 280 (54%) of the patients and 17% occurred in the epidermal growth factor receptor (EGFR) (5). These activating EGFR mutations are present in approximately 10% of all NSCLC in Western patient cohorts and approximately 40% of all Asian NSCLC patients (6). These mutations occur frequently in female patients, non-smokers and adenocarcinoma of the lungs (7). EGFR mutations lead to a constitutive activation of intracellular tyrosine kinase, thereby leading to overactivation – irrespective of the presence of EGFR ligands - of the downstream signal cascades (8). Most mutations occur in the EGFR tyrosine kinase region (exon 18 - 21). Deletions in exon 19 and the point mutation L858R in exon 21 should be mentioned here, since they represent the most common activating mutations at approximately 85-90%. Mutations appear more rarely in exons 18 and 20 (9). EGFR-mutated lung cancer was first described in 2004 and is currently the most studied NSCLC subtype (10). These tumours exhibit a better prognosis than those with non-mutated, so-called wild type EGFR (11). The mean survival time of patients with advanced EGFR-mutated NSCLC is more than two years if they are treated with a tyrosine kinase inhibitor (TKI) targeting the EGFR (12). These TKIs bind with a high affinity to the mutated EGFR and as a result, these types of genetic changes are considered to be a positive predictive factor for the efficacy of this substances (10). Accordingly, TKIs are much more effective than platinum-based combination chemotherapy as first-line treatment for advanced or metastatic NSCLC in patients testing positive for EGFR mutations in terms of the response rate and progression-free survival (PFS) (13-20). A prerequisite for this treatment is molecular pathology evidence of activating EGFR mutations in the tumour tissues. Patients with one of these mutations could benefit from targeted treatment with an EGFR-TKI, such as gefitinib, erlotinib or afatinib, due to improved efficacy and tolerability in comparison to chemotherapy.

These substances block the receptor EGFR tyrosine kinase. This receptor belongs to the ErbB family of receptors. The ErbB family is considered to be one of the most commonly dysregulated systems in the signal transduction of malignant tumours (8). The discovery of other receptor tyrosine kinases in this family as potential target molecules, such as the receptors HER2 (ErbB2), ErbB3 and ErbB4, enable an extended therapeutic approach. After ligand binding, the ErbB family receptors are dimerised into homo- or heterodimers and this process is paralleled by activation of signal transduction (8). Since the signal transduction for the receptors occurs by means of various compound homo- and heterodimers, the blockade of a single ErbB family receptor may not be sufficient to effectively and continuously inhibit tumour growth and infiltration (21-23). Afatinib (GIOTRIF®) is a TKI that binds covalently and therefore irreversibly to the intracellular tyrosine kinase domains in EGFR, ErbB2 and ErbB4, which prevents them from being phosphorylated and prevents the transphosphorylation of ErbB3. These three ErbB family members are therefore inhibited directly, while ErbB3 is also inhibited indirectly (19, 20). This new mechanism of action therefore clearly differentiates these products from reversible TKIs, such as erlotinib and gefitinib, which only target EGFR and only permit reversible receptor binding. During NSCLC oncogenesis, however, multiple members of the ErbB family could play an important role due to their mutation (8).

Patients with advanced NSCLC and activating EGFR mutations could benefit from first-line treatment with afatinib in several respects (20). During the marketing authorisation study LUX-Lung 3, the patients exhibited, in addition to significant prolongation of PFS during treatment with afatinib, also a significantly improved quality of life (QoL) and significant extended period of symptomatic control in comparison to chemotherapy (21).** **re-read sentence, check words** During this international, multicentre study, 230 patients with advanced adenocarcinoma of the lung and activating EGFR mutations received afatinib, while 115 received cisplatin/pemetrexed. During the course of a central and independent evaluation, treatment with afatinib resulted in a significant prolongation of the median PFS from 11.1 months vs. 6.9 months for chemotherapy (HR = 0.58; p = 0.001) for the total study population. The percentage of patients who survived after 12 months and had experienced no disease progression was more than doubled by afatinib and amounted to 47% vs. 22% for chemotherapy. In the predefined subgroup analysis of the patients with the frequent EGFR mutations Del19 and L858R (89% of the total population), the increase in PFS for afatinib even more pronounced at a median of 13.6 vs. 6.9 months (HR 0.47; p = 0.001). This increase in PFS was seen in virtually all subgroups investigated, irrespective of sex, age, ethnicity, performance status or smoking history. There were also significantly higher objective response rates in those treated with afatinib, compared to those treated with chemotherapy (56% vs. 23%, p = 0.001). During the LUX-Lung 3 study, QoL and tumour-related symptoms as patient-reported outcomes (PRO) were evaluated using two-part standardised questionnaires (EORTC QLQ-C30 and QLQ-LC13). During the evaluation, afatinib fared significantly better than cisplatin/pemetrexed with regard to the general QoL (p = 0.015) as well as the physical (p<0.001), cognitive functions (p = 0.007) and the role function (p = 0.004). Patients reported clinically relevant improvement in disease-specific symptoms in comparison to chemotherapy when using afatinib: Coughing (p = 0.244), dyspnoea (p = 0.010) and pain (p = 0.051). The time until deterioration of coughing (p = 0.007) and dyspnoea (p = 0.015) was significantly longer in the patients treated with afatinib than those treated with chemotherapy treatment. Time until deterioration of pain tended to be longer (p = 0.190). Adverse events (AE) with a therapy-related toxicity grade ≥3 occurred in 49% of those treated with afatinib in comparison to 48% of those treated with cisplatin/pemetrexed. A total of 8% of those treated with afatinib and 12% of those treated with chemotherapy discontinued treatment due to treatment-related AEs. The grade ≥3 AEs that occurred frequently during treatment with afatinib were diarrhoea (14.4%), skin rash/acne (16.2%), stomatitis/mucositis (8.7%) and paronychia (11.4%).

Current data for the LUX-Lung 6 study confirms the results of the LUX-Lung 3 study (22). This phase III study performs a comparative investigation of the platinum duo cisplatin/gemcitabine and afatinib monotherapy in exclusively Asian patients (n = 364) with advanced adenocarcinoma of the lungs and activating EGFR mutations. Independent analysis of the primary endpoint revealed a median PFS of 11.0 months for afatinib and 5.6 months for chemotherapy (HR 0.28; p<0.0001). The independent analysis also showed a significantly higher response to afatinib when compared to chemotherapy (67% vs. 23%; p<0.0001). The tumour response to afatinib treatment correlated to a significantly prolonged time until deterioration of the disease-associated symptoms of dyspnoea, coughing and pain. Furthermore, the patients treated with afatinib had a significantly better QoL than the patients treated with chemotherapy. The most common treatment-related AEs (grade ≥3) during the LUX-Lung 6 study during afatinib treatment were skin reactions (14.2%), diarrhoea (5.4%) and stomatitis/mucositis (5.4%). There are consistent results in this regard from two large, prospective phase III studies, which prove the efficacy of afatinib as first-line treatment in this patient population.

1.2 Rationale

Marketing authorisation in Europe was granted to afatinib in September 2013 as monotherapy for EGFR-TKI-naive, adult patients with locally advanced and/or metastasised non-small cell small cell lung cancer (NSCLC) with activating EGFR mutations.
A non-interventional study (NIS) is particularly suitable for capturing additional data about efficacy, tolerability, safety, QoL and symptom control under everyday treatment conditions in the general patient population and to extend the level of knowledge of treatment with afatinib in routine practice using documentation. There is still no existing data from medical practice in this regard for afatinib in advanced NSCLC. The NIS instrument appears to be most suitable for prospectively investigating the open questions from routine treatment without influencing them. Elderly patients (> 65 years) and patients with an ECOG performance score of 2 in particular, who comprise the majority of the patients in clinical practice, are frequently not included or are under-represented in clinical trials.
Patients at locally, widely-advanced or metastatic stages who no longer have any treatment options are treated with palliative intent. Treatment is symptom-orientated, i.e. in addition to the prolongation of survival time, achieving QoL and symptom control are at the foreground of treatment. Of particular interest in this NIS, therefore, is whether the data with regard to effectiveness, tolerability, safety, symptom control and QoL from the LUX-Lung 3 marketing authorisation study can be transferred to everyday clinical practice in Germany.

2. Study objective

2.1 Type of Investigation

This investigation is a prospective, non-interventional study of afatinib as first-line treatment for patients with locally advanced or metastatic NSCLC and activating EGFR mutations. The treatment is given as part of the marketing authorisation of afatinib as first-line treatment of EGFR TKI-naive patients. The usual treatment regimen remains unchanged by participation in this NIS. No diagnostic or therapeutic measures are required that exceed the otherwise required scope. The decision of those administering treatment with regard to diagnosis and treatment before, during or at the end treatment are not affected by this NIS.

2.2 Objectives of the Investigation

The objective is to capture and document data to extend the knowledge about the efficacy and tolerability, QoL and symptom control reported by the patient when using afatinib as first-line treatment for locally advanced or metastatic NSCLC with activating EGFR mutations under routine conditions in everyday clinical practice. In addition to the primary inquiry, additional information should be captured regarding the course of treatment and management of treatment-related adverse reactions in everyday clinical practice:

Primary endpoint:

- The percentage of patients without tumour progression after 12 months (progression-free survival rate after one year, %).

Secondary endpoints:

- Determination of the objective remission rate (CR + PR, %)
- The percentage of patients with tumour control (CR + PR + SD, %)
- Progression-free survival (PFS, months)
- Safety data (incidence of SAEs and AEs)
- Toxicity/side effect profile (frequency and severity of diarrhoea, skin reactions, stomatitis and paronychia)
- Duration of treatment and modifications (dose adjustments, treatment withdrawals and interruptions)
- Symptom control (coughing, dyspnoea and pain) using EORTC questionnaires QLQ-C30/LC13

3. Patient cohorts/patient descriptions

3.1 Patient population

EGFR-TKI-naive adult patients with locally advanced and/or metastasised non-small cell small cell lung cancer (NSCLC) with activating EGFR mutations could be included during the course of marketing authorisation of afatinib as first-line treatment. Patient EGFR mutation status must be determined using a validated and robust procedure in order to avoid false-negative or false-positive results. The patient population consists of adult participants of both sexes.

There is insufficient data for afatinib in pregnant and breastfeeding women. For this reason, it is urgently recommended that pregnant women and all women and men who are not using a reliable method of contraception do not use afatinib.

The decision to treat occurs irrespective of participation in this NIS and is made by the attending doctor before considering participation.

3.2 Number of patients and number of participating doctors

A total of n = 150 patients in 50 oncology centres within Germany were included. The number of patients is based on the assumptionα= 0.05 (two-sided) and an expected PFS rate over 12 months of 47% (see chapter 6).

3.3 Inclusion criteria

Patients who meet all of the following criteria can be included:

- EGFR-TKI-naive men and women with pathologically confirmed NSCLC, Stage IV (UICC, 7th edition) with activating EGFR mutations (exons 18 - 21)
- Age ≥ 18 years
- No diagnostic or therapeutic measures are required that go beyond the scope of clinical routine practice.
- The usual treatment regimen remains unchanged.
- A signed declaration of informed consent must be present before inclusion in the NIS.

3.4 Exclusion criteria:

- Known hypersensitivity reaction to afatinib and its excipients
- Concurrent participation in another NIS or interventional clinical study during the treatment phase or within the last 30 days
- Previous treatment with systemic chemotherapy, except during the course of (neo)adjuvant therapy (within 12 months after treatment completion).
- Previous treatment with therapy targeted towards EGFR
- Patients unwilling or unable to complete questionnaires about their QoL
- Patients with absent or diminished capacity
- Pregnancy

The decision to treat occurs irrespective of participation in this NIS and is made by the attending doctor before considering participation.

The contraindications are to be observed prior to starting afatinib treatment. Also see the current scientific information for afatinib.

3.5 Representativity

The distribution of participating centres throughout the country and the number of patients guarantees that the data obtained will be representative. University medical centres, hospitals and registered doctors active in the field of oncology can participate in the NIS. The study will also strive for recruitment that is as equivalent as possible at the centres through contractual definition of a maximum number of three (3) patients. The number can be increased if necessary during the course of the study. The only centres considered during selection were those that were expected to enrol 3 patients based on the patient characteristics specified in this NIS.

4. Treatment

4.1 Posology and method of administration

Afatinib film-coated tablets each contain 50, 40, 30 or 20 mg of active substance (as afatinib dimaleate) and lactose (as monohydrate) as an excipient with known effects. Please consult the scientific information for the full list of excipients.

Patient EGFR mutation status must be determined using a validated and robust procedure in order to avoid false-negative or false-positive results.

In accordance with the scientific information, the recommended dose of afatinib during the course of first-line treatment is 40 mg once daily. Afatinib should not be taken together with food. Afatinib should be taken at least 1 hour before or 3 hours after a meal. Afatinib is taken orally and the tablets are to be taken whole with water. In patients who cannot swallow afatinib tablets whole, they should be dissolved in approximately 100 ml of uncarbonated drinking water. Do not use any other fluids for this purpose. These tablets are added to the water whole without crushing. Occasionally stir for up to 15 minutes thereafter, until the tablet has completely dissolved into small particles. Drink the suspension immediately, rinse the glass with approximately 100 ml of water and drink this water as well. This suspension can be administered through a gastric tube. A forgotten afatinib dose should still be taken on the same day, as soon as the patient remembers. If the period until the next planned dose is less than 8 hours, however, the forgotten dose must not be taken.

Treatment with afatinib should be continued until there is progression of the disease or the patient no longer tolerates the medication. A dose increase up to a maximum of 50 mg/day can be considered in patients who tolerate the dose of 40 mg/day well (i.e. no onset of diarrhoea, skin rash, stomatitis or other medication-related events of CTCAE grade >1). No dose increase should occur after a dose reduction. The maximum daily dose is 50 mg.

4.2 Dose adjustments in the event of adverse reactions

Symptomatic side effects (e.g. severe/persistent diarrhoea or skin side effects) can be treated successfully by withdrawing the treatment, dose reduction **or** drug holidays from afatinib:

Side effects according to the CTC[1]	**Recommended afatinib dose**	
Grade 1 or grade 2	No interruption[2]	No dose adjustment
Grade 2 (longer term[3] or intolerable) or Grade $\geq$3	Interruption up to grade 0/1[2]	Restarting treatment with dose reduction in 10 mg steps[4]

1. NCI Common Terminology Criteria for Adverse Events
2. If diarrhoea occurs, anti-diarrhoeals (e.g. loperamide) should be taken **immediately**, and in the event of persistent diarrhoea, their intake should be continued until the soft stools stop.
3. Diarrhoea >48 hours and/or skin rash >7 days
4. If the patient does not tolerate 20 mg/day, permanent discontinuation of treatment with afatinib should be considered.

4.3 Special warnings and precautions for use

Diarrhoea has been reported in patients treated with afatinib, including severe cases. Diarrhoea can lead to dehydration (with or without impairment of kidney function), which may lead to death in rare cases. Diarrhoea occurred as a rule in the first two weeks of treatment and grade 3 diarrhoea usually occurred in the first 6 weeks of treatment. Therefore, you must proactively treat patients with sufficient hydration and anti-diarrhoeals from the appearance of the first signs, particularly in the first 6 weeks of treatment. In addition, the dose of the anti-diarrhoeals (e.g. loperamide) used should be increased to the highest recommended authorised dose if required. Anti-diarrhoeals must be quickly accessible to the patients, so that they can start and continue treatment from the first signs of diarrhoea independently, until they have had no further soft stools for a minimum of 12 hours. If severe diarrhoea occurs, an interruption of treatment with afatinib, a dose reduction or completely withdrawal of treatment may be required. Dehydrated patients require intravenous electrolyte and fluid replacement where necessary. These patients are therefore advised to start anti-diarrhoeal treatment independently if diarrhoea occurs and to inform the attending doctor of this immediately.

Skin rash/acne have been reported in patients treated with afatinib. The skin rash in question is usually a mild to moderate, erythematous, acneiform rash that may appear in areas of skin exposed to light or be more prominent there. Early treatment of dermatological reaction (e.g. with skin care agents, antibiotics) increases the probability that treatment can be continued. If severe skin reactions occur, temporary interruption of treatment, dose reductions other therapeutic interventions or transfer to a specialist with experience treating these types of dermatological reactions is required.

If acute or deteriorating respiratory symptoms occur, interstitial lung disease should be considered and the treatment with afatinib is to be withdrawn until detailed investigation takes place. If a diagnosis of interstitial lung disease is confirmed, treatment with afatinib must be discontinued and suitable treatment should be started.

Afatinib is not recommended for patients with severely impaired kidney function (< 30 ml/min) with liver function (Child-Pugh class C).
An increased afatinib plasma level has been observed in women, patients with low body weight and patients with impaired kidney function. This increases the risk of side effects such as diarrhoea, skin rash/acne and stomatitis. Strict monitoring of patients with these risk factors is recommended. The respective prescribing information is to be observed in this regard, particularly the sections “Contraindications”, “Special warnings and precautions for use”, “Interactions with other medicinal products” and “Fertility, Pregnancy and Lactation”.

Additional information about afatinib can be obtained from the enclosed scientific information.

5. Description of follow-up and implementation

5.1 Follow-up

No appointments for special doctor’s visits are required for the NIS. After the decision to introduce first-line treatment with afatinib for the treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations and before prescribing the substance, the doctor considers whether the patient is suitable for participating in the NIS, taking the scientific information provided into consideration. The doctor explains the nature of the study and includes the written declaration of informed consent for processing the patient information for the purpose of this study and source data verification. It is important that this

step occur before the patient is enrolled in the NIS and the observations are entered into the eCRF. The fact that informed consent was obtained from the patient before the start of follow-up is to be documented in the eCRF.

5.2 Documentation

The following parameters are captured using an internet-based data capturing system (eCRF):

Basic Documentation

- general anonymised patient information (year of birth, sex, height, weight), vital parameters, laboratory parameters, blood profile, diagnosis date, location of the primary tumour, location of the metastases, risk factors, medical history, associated disorders, associated medication, ECOG performance score, histology, TNM status and EGFR mutation analysis (investigation methodology and biomarker analysis)
- Determination of co-morbidity using the Charlson score
- Operation: Date, nature of the procedure and outcome

- Previous treatment during the course of neo- or adjuvant therapy: Time, duration, chemotherapeutic agents used or radiotherapy
- QoL and symptom control (coughing, dyspnoea and pain) using EORTC QLQ-C30 and LC13 questionnaires

Documentation of the clinical course

- Use of afatinib (dose, time, duration, dose adjustments) are captured during each visit (1x month)
- ECOG performance status
- Vital parameters, laboratory parameters and blood profile
- Adverse events and severe adverse events (nature of the event, clinical course and measures taken)
- Therapeutic management of skin reactions and diarrhoea (prophylactic or reactive measures, treatment plan, duration of treatment and clinical course)
- QoL and symptom control using the EORTC questionnaires QLQ-C30 and LC13 every 8 weeks (= 2 months of treatment) or at the end of treatment
- Response (imaging procedures according to what is normally done at the centre)
- Patient status at the end of treatment with afatinib (date treatment ended, reason for ending treatment, date disease progressed, location of the progression or the recurrence, new secondary disorders and/or comorbidities, cause and date of death)

Follow-up Documentation

The following parameters are captured 12 and 24 months after first-line treatment with afatinib has ended:

- Patient status (patient living/deceased, ECOG performance score, date disease progressed, location of new metastases, date of death)
- Ongoing treatment (number, nature, response, duration of treatment)

If intolerable side effects occur during treatment with afatinib that require treatment to be withdrawn, treatment is to be discontinued.

The patient QoL and tumour symptoms are determined using the EORTC QLQ-C30 and LC13 questionnaires, which the patient should complete before the start of treatment and every 8 weeks during the course of treatment (= 2 months of treatment), irrespective of staging and treatment. The two standardised EORTC questionnaires contain a total of 43 questions.

The attending doctor hands each patient one copy of to EORTC QLQ-C30 and LC13 at enrolment (baseline) and then every 8 weeks (= 2 months of treatment). Before or during the appointment, Each patient is requested to answer questions 1 to 28 and 31 to 43 by making a tick mark on a scale from 1 to 4 (“not at all applicable” to “very applicable”) independently and to estimate their current general condition of health/QoL (questions 29 and 30) by making a cross on a scale from 1 (“very bad”) to 7 (“excellent”).

5.3 Survey period and procedure

First patient enrolment:	April 2014
Last patient enrolment:	December 2015
Duration of treatment:	until progression of the disease or until the occurrence of intolerable, severe toxicities or until revocation of informed consent
Follow-up period:	24 Months
Database closure/lock:	December 2017
Final report:	December 2018

The survey period of this NIS should amount to a total of 4 years. The follow-up period per patient is a maximum of 3 years from the time that they are enrolled in the NIS. An extension of the follow-up deadline for individuals or all patients is possible through consultation.

5.4 Termination of the Study

The individual patient has the right to revoke their consent to participate in the NIS. Termination of the NIS has no influence on the routine treatment of the patients.

After one or all of the following events occur, the study can be terminated at the discretion of the sponsor:

- The presence of medical or ethical reasons that may influence the continuation of the study in the interest of the patient
- Problems with recruitment

It is assumed that recruitment of less than 1/4 of the planned patients 1 year after the start of recruitment is insufficient for achieving the study objectives. Should, as a consequence, less than 40 patients be enrolled in the study one year after recruitment, a decision will be taken about a premature termination of the study.

5.5 Adverse events (AEs)

All adverse events that occur during the course of this NIS are captured in eCRF. Adverse events are all harmful, pathological or inadvertent changes to anatomical, physiological or

metabolic functions, recognisable by physical signs, symptoms and/or changes in laboratory values that occur during the course of the NIS, irrespective of whether there is an association to the medicinal product. This also includes the deterioration of existing disorders or events that appear in the interim or interactions between medicinal products. Expected daily fluctuations during the clinical course of a disease or a progression of the disorder under investigation must not be considered to be an adverse event.

The documentation of all adverse events in the eCRF must take place during treatment with afatinib and in the 30 days soon after the last intake of afatinib.
The capturing of changes in the laboratory values is done using the documentation for the laboratory values; these must not be separately documented as adverse events.

Exceptions to this are changes in the laboratory values that represent a severe adverse event (SAE)

5.6 Serious adverse events (SAEs)

A severe adverse event is any adverse event that

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation (excluding for the purpose of chemotherapy or tumour staging, or before the start of an elective hospital stay)
- results in persistent or significant disability or incapacity,
- malignant disorder or a birth defect (in the descendants)
- is medically significant

Abuse and overdose of medicinal products is to be considered severe, even if it does not fulfil the above-mentioned criteria.

Events that are associated with “progression of the underlying disease” must not be reported as SAEs, even if the criteria for severity (e.g. hospitalisation) are fulfilled. Tumour progression, however, is documented in eCRF as a primary endpoint.

SAEs must be reported to the pharmacovigilance department at Boehringer Ingelheim within 24 hours. AEs must be documented in the eCRF within 14 days. All adverse events (SAE and AE) are automatically reported to the pharmacovigilance department at Boehringer Ingelheim according to the documentation in the eCRF within 24 hours in the form of a PDF file. The Boehringer Ingelheim SAE/AE form is generated from the eCRF.

If there is no Internet access on the reporting date, a fax must be sent to the following address as an alternative:

Boehringer Ingelheim Pharma GmbH & Co. KG
Pharmacovigilance Germany (PV Germany)
Binger Straße 173
55216 Ingelheim
Fax: +49 (6132) 72 - 141522
PV_local_Germany@boehringer-ingelheim.com

The causal relationship of the event to afatinib should be evaluated by the attending doctor.

5.7 Adverse reactions unknown to date

The significant adverse reactions of afatinib are diarrhoea (in over 95% of patients, all grades), skin reactions (89%), stomatitis (70%) and paronychia (58%).

The frequency of adverse reactions is defined using the following convention:
very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000) and very rare (<1/10,000)

Infections and infestations
Very common: Paronychia
Common: Cystitis
Metabolism and nutrition disorders
Very common: Decreased appetite
Common: Dehydration, hypokalaemia
Nervous system disorders
Common: Dysgeusia
Eye disorders
Common: Conjunctivitis, dry eye
Uncommon: Keratitis.
Respiratory, thoracic and mediastinal disorders
Very common: Epistaxis
Common: Rhinorrhoea
Uncommon: Interstitial lung disease.
Gastrointestinal disorders
Very common: Diarrhoea, stomatitis
Common: Dyspepsia, cheilitis
Hepatobiliary disorders
Common: Increased alanine aminotransferase (ALT) values
Increased aspartate aminotransferase (AST) values
Skin and subcutaneous tissue disorders
Very common: Rash, acneiform dermatitis, pruritus, dry skin
Common: Palmar plantar erythrodysesthesia
Musculoskeletal and connective tissue disorders
Common: Muscle spasms
Renal and urinary disorders
Common: Impaired renal function, renal failure
General disorders and administration site conditions
Common: Fever
Investigations
Common: Weight loss

Additional information can be obtained from the enclosed scientific information.

6. Statistical Analysis

6.1 Description of the encoding, the data capturing and inspection

Coding

Adverse events are coded using the current version of MedDRA. Medications are coded in accordance with the WHO-DD.

Data capturing

The data is captured using an electronic documentation (eCRF).

Data validation

Data checks are performed automatically in eCRF directly during electronic entry. Source data verification is planned.

6.2 Description of the statistical analysis including objectives and planned analyses

Sample size

A PFS rate of 47% was determined after 12 months in the afatinib arm in the marketing authorisation study. A sample size of 150 patients is required to confirm this rate with a precision of ± 8% (two-sided 95% confidence interval based on normal approximation of the sampling distribution). This calculation justifies the assumption ofα= 0.05 (two-sided) and an expected PFS rate of 47% over 12 months.

Handling of missing value

Based on the non-interventional nature of the study, only data that are routinely used by the doctor should be made available. The data completeness in the documentation questionnaire will therefore vary from doctor to doctor. All available information is used. There is no planned imputation of missing values during the course of the statistical analysis.

Evaluation of the Study Data

The evaluation is based on all the patients enrolled in the study (i.e. all patients who signed the declaration of informed consent and have entered data for the doctor). The following statistical parameters are reported for constant variables in descriptive tables: N/Mean/Standard Deviation/Minimum/Q1 (25% quantile)/Median/Q3 (75% quantile)/Maximum. Frequency tables for categorical variables will represent all possible categories and will report the number of observations and the percentage per manifestation. Percentages are rounded to two decimal places. The number of patients with missing values, as well as the percentage they make up of the total sample size, is also shown (if required). A 95% confidence interval is also determined. All analyses are represented in the total population. These analyses are additionally performed according to the subgroups sex, smoking status and EGFR mutation status, or in the case of special interests, also according to other subgroups. The details of the statistical analyses are described in the trial statistical analysis plan (TSAP), which is prepared in complete form before the database lock.

Primary Analyses

The primary endpoint of this NIS is the progression-free survival (PFS) rate after one year. This is defined as relative frequency of the patients, who have no tumour progression and survive after 12 months of treatment. The Kaplan-Meier survival rate with two-sided 95% confidence interval after 12 months is shown. The Greenwood estimator of variance was used to calculate the confidence interval.

Secondary Analyses

Each patient is allocated into one of the following categories based on their response to treatment:

1 = CR (complete response)
2 = PR (partial response)
3 = SD (stable disease)
4 = PD (progressive disease)
9 = unknown (cannot be evaluated, insufficient data available).

Objective remission rate

Patients in the categories 1 and 2 (CR and PR) have objective remission. The objective remission rate is the relative frequency of patients with objective remission and is calculated together with the exact 95% confidence interval.

Tumour control rate

Patients in the categories 1 - 3 (CR, PR, SD) have tumour control. The tumour control rate is the percentage of patients from the total population with tumour control. They are calculated together with the exact 95% confidence interval.

Progression-free survival (PFS)

Progression-free survival is the time from the start of treatment until progression occurs or until death. The date of progression is the earliest date from:

(1) Date of the investigation that showed progression or
(2) Date given by the doctor for progression

If the date of progression is known, the PFS is calculated using the following formula:

PFS [days] = date of progression (or death, if not progression occurred) – date of the start of treatment + 1.

The censored PFS was calculated for patients without progression:

PFS (censored) [days] = date of the last investigation – date of the start of treatment +1.

Kaplan-Meier estimators and 95% confidence intervals are shown.

Duration of treatment and modifications

Treatment schedules, duration of treatment and treatment interruptions are shown. The number of patients with no/one/two or more dose modifications are shown.

Symptom control

The duration until deterioration of the following clinically-relevant symptoms is calculated:

- Coughing (question 1 in the QLQ-C30 questionnaire)
- Dyspnoea (total of the questions 3 - 5 in the QLQ-LC13 questionnaire)
- Pain (total of the questions 9 and 19 in the QLQ-C30 questionnaire)

Deterioration occurs when the score increases by 10 points in comparison to baseline during a transformation according to EORTC with possible value of 0 to 100. Details are described in the TSAP.

Safety Analyses

All patients who have received at least one dose of afatinib are included in the safety analyses. All analyses were conducted descriptively. Adverse events are classified according to the CTCAE (version 4.3).
The safety analyses include:

- Frequency, severity and causal relationship of adverse events
- Frequency, severity and causal relationship of diarrhoea, skin reactions, stomatitis and paronychia

SAEs are shown in the table. In addition, significant adverse events and adverse events that lead to dose reduction or withdrawal of treatment are investigated.

Descriptive statistics are performed to describe changes in laboratory values during the course of the study. All abnormalities of potential clinical relevance are reported. In general, potential clinical relevance is defined as a CTCAE grade ≥2 or an increase in the CTCAE classification by at least one grade in comparison to baseline.

7. Medical Evaluation and Report Creation

7.1 Regulations for report creation including biometric and medical evaluation

The analysed data will be documented within the usual period in the form of a report and published in an appropriate form. An entry in the publicly accessible database clinicaltrials.gov is planned.

7.2 Responsibility Regulations

The clinical monitor and principal investigator of the NIS are responsible for evaluating the medical data and creating the NIS report.

8. Administrative Specifications

This NIS is conducted in accordance with the recommendations from the German Federal Institute for Drugs and Medical Devices and the Paul-Ehrlich Institute for Planning, conducting and evaluation of observational studies (24) and definitive Boehringer Ingelheim Pharma GmbH & Co. KG standard operating procedures.

8.1 Contract Administration

The participating doctor is obliged to conduct the NIS responsibly in accordance with the agreements made in the contract. The rights and obligations of the participating doctor and Boehringer Ingelheim Pharma GmbH & Co. KG are stipulated in the contract concluded regarding the implementation of this NIS.

8.2 Remuneration

Boehringer Ingelheim Pharma GmbH & Co. KG grants the participating doctor remuneration/compensation in accordance with the specifications in the contract.

8.3 Quality Assurance Measures

The validity of the data obtained is guaranteed by the validations integrated into the documentation system, which notify the documenter/doctor of missing or illogical entries. Additionally a random source data comparison is conducted by a monitor appointed by at the participating study centre.

All participating doctors are obliged to record the participation of patients in the NIS in the patient's original documents. In the event of possible queries, the participating doctor must be able to identify the patient who was followed up. Medical information about the patients must only be communicated and analysed using the patient number. By signing the agreement, the participating centre gives its consent to source data verification, which will take place at the participating centres. Then, a source data verification from 100% of the patients enrolled in the NIS takes place at a participating centre. Additional inspection/review of the quality assurance for this NIS may be conducted. The monitor appointed by will have access to all treatment documentation, the files and reports of the participating doctors relating to the NIS and the declaration of informed consent documents for this NIS.

8.4 Ethical and Legal Considerations and Requirements

This NIS is conducted in accordance with Section 67, paragraph 6 of the German Medicinal Products Act (*Arzneimittelgesetzes der Bundesrepublik Deutschland* or AMG) The medicinal product afatinib used during the course of this NIS has obtained marketing authorisation in Germany during the course of central European marketing authorisation. The medicinal product under observation is not provided by the pharmaceutical company, but instead is ordered by the participating doctor. The selection of treatment lies at the sole discretion of the doctor involved. The NIS has no influence on the treatment of patients. The decision to include a patient in an NIS is separate to ordering medicinal products. This means that there are no additional risks to the patient from participation in this NIS. There are no additional medical procedures required beyond the scope that the patient would obtain if they were not enrolled in the NIS. The treatment, including the diagnosis and monitoring, are conducted in accordance with treatment during routine medical practice.
The patient is provided with a comprehensive explanation and provides their consent to participate and to the disclosure of their data. The NIS was approved by the ethics committee at Dresden University before the start of the study. The same applies to the implementation of changes. The ethics committees for the participating doctors are notified of the NIS.

8.5 Data protection

Before a patient can be enrolled in this NIS, they will be provided with an explanation of how their personal data will be handled and informed comprehensively about the disclosure of their data to involved third parties. They are requested to grant their informed consent in writing. The patient information is captured in anonymised form. The allocation occurs based on the year of birth and patient numbers stated in the participating study centre. All information collected during the NIS is always handled confidentially. Data regarding medical history and therapeutic measures, adverse reactions that occur and the clinical course of the disease is captured from patients during the course of this NIS. All data was used to answer the above-mentioned questions and was captured in accordance with GCP using electronic documentation system (eCRF).

8.6 Duty to inform

The commercial medicinal product GIOTRIF® (afatinib) is used during the course of the NIS, which is used or prescribed by a doctor in a medical practice and procured from a pharmacy. The NIS is conducted in accordance with Section 67, paragraph 6 of the German Medicinal Products Act, the Central Federal Association of Health Insurance Funds and the competent federal authorities shown by Boehringer Ingelheim Pharma GmbH & Co. KG or the institution appropriately commissioned by them**.** In terms of the National Association of Statutory Health

Insurance Physicians, the Central Federal Association of Health Insurance Funds and the Association of Private Health Insurance Funds, the doctors involved are also stated by name with the nature and amount of the compensation given to them and a certified copy of their concluded contracts should be sent over. In addition, an entry corresponding to the notification from the German Association of Research-Based Pharmaceutical Companies (*Verbandes forschender Arzneimittelhersteller* or VFA) in the publicly accessible database clinicaltrials.gov is planned.

8.7 Storage

All study-specific documents are stored over a period of 10 years after the end of this NIS by Boehringer Ingelheim Pharma GmbH & Co. KG Ingelheim Pharma GmbH.

8.8 Publication

Boehringer Ingelheim Pharma GmbH & Co. KG endeavours to support the process of free exchange of relevant scientific information. Every publication resulting from this NIS must conform to the Boehringer Ingelheim Pharma GmbH & Co. KG publication guidelines. The rights of the monitoring doctors and Boehringer Ingelheim Pharma GmbH & Co. KG with regard to the publication of the results of this NIS are stipulated in a contract concluded with the doctor.

8.9 Responsibilities

Principal investigator of the NIS:

Clinical Monitor:

9. Signature regulations

The Follow-up Plan must be signed by the clinical monitor and by the statistician.

Trial Clinical Monitor:	01 July 2014	[signature]
Name:		
Trial Statistician:	01 July 2014	[signature]
Name:		

10. References

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Observational Plan
Non-interventional study
Local Amendment

Local Amendment Number:	Local Amendment 1 Country Germany		
Date:	01.08.2015	☐	To be implemented only after documented approval of the *IRB / IEC / Competent Authorities*
EudraCT No.: **BI Trial No.:**	n.a. 1200.205	☐	To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval
Investigational Product(s):	GIOTRIF® (Afatinib)	x	Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only
Title:	GIDEON: GIOTRIF® in der Erstlinientherapie des fortgeschrittenen NSCLC mit aktivierenden EGFR-Mutationen		

Rationale for Local Amendment:	After ca. 15 months of site and patient recruitment it becomes evident that the targeted patient number of 150 will not be met within the given timeframe of 20 months recruitment time until December 2015. Recruitment time will thus be prolonged to 32 months (FPI April 2014 to LPI December 2016). Study duration will also increase. LPO is now planned for December 2018. Other timelines will change accordingly. One exclusion criterion has been phrased mistakably and thus needs clarification. This will also be taken care of in this amendment. For readability reasons we marked changes in front page and sections 4.3 and 5.3. **bold**.

SIGNATURE PAGE(S)

This amendment

☒ concerns administrative matters only so that the coordinating investigator's signature will not be obtained.

☐ concerns matters dealing with design elements of the study, in- / exclusion criteria, observations, or safety or efficacy related study elements so that the coordinating investigator's signature needs to be obtained.

Trial Clinical Monitor

Date

Boehringer Ingelheim
Medical Affairs Germany

Trial Statistician

Date

Boehringer Ingelheim
Boehringer Ingelheim
Biometrics & Data Management

Team Member Medicine

Date

Boehringer Ingelheim
Corporate Medical Affairs

Local Clinical Monitor

Date

Boehringer Ingelheim
Medical Affairs Germany

CHANGE 1: SHORT DESCRIPTION OF CHANGE

Section of the protocol: Front page

Planned duration of the NIS:	FPI: April 2014 LPO: October 2017

Was changed to:

Planned duration of the NIS:	FPI: April 2014 LPO: December 2018

Reason(s) for change 1:

After ca. 15 months of site and patient recruitment it becomes evident that the targeted patient number of 150 will not be met within the given timeframe of 20 months recruitment time until December 2015.

Recruitment time will thus be prolonged to 32 months (FPI April 2014 to LPI December 2016). Study duration will also increase. LPO is now planned for December 2018.

CHANGE 2: SHORT DESCRIPTION OF CHANGE

Section of the protocol: 3.4. Exclusion criteria

- Previous treatment with systemic chemotherapy, except during the course of (neo)adjuvant therapy, previous treatment with therapy targeted against EGFR **(within 12 months after treatment completion)**.

Was changed to:

- Previous treatment with systemic chemotherapy, except during the course of (neo)adjuvant therapy, previous treatment with therapy targeted against EGFR

Reason for change 2:

The exclusion criterion has been phrased mistakably and thus needs clarification.

CHANGE 3: SHORT DESCRIPTION OF CHANGE

Section of the protocol: 5.3. Survey period and procedure

Last patient enrolment: December 2015

Database closure/lock: December 2017
Final report: December 2018

The survey period of this NIS should amount to a total of 4 years.

Was changed to:

Last patient enrolment: December 2016

Database closure/lock: **March 2018**
Final report: **December 2019**

The survey period of this NIS should amount to a total of 5 years.

Reason for change 3:

After ca. 15 months of site and patient recruitment it becomes evident that the targeted patient number of 400 will not be met within the given timeframe of 20 months recruitment time until December 2015.

Recruitment time will thus be prolonged to 32 months (FPI April 2014 to LPI December 2016). Study duration will also increase. LPO is now planned for December 2018.

Other timelines will change accordingly.

Observational Plan
Non-interventional study
Local Amendment

Local Amendment Number:	Local Amendment 2 Country Germany		
Date:	11.07.2016	☐	To be implemented only after documented approval of the *IRB / IEC / Competent Authorities*
EudraCT No.: **BI Trial No.:**	n.a. 1200.205	☐	To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval
Investigational Product(s):	GIOTRIF® (Afatinib)	x	Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only
Title:	GIDEON: GIOTRIF® in der Erstlinientherapie des fortgeschrittenen NSCLC mit aktivierenden EGFR-Mutationen		

Rationale for Local Amendment:	One exclusion criterion prohibiting simultaneous participation in other NIS recently showed not to reflect clinical reality. New registries and NIS have been implemented by Boehringer Ingelheim or scientific collaboration groups, in which to include also GIDEON patients is of scientific interest. The parallel inclusion will not interfere with the primary endpoints of the respective NIS or registry. Patient data will be documented for both projects after receiving written informed consent for the respective study. This exclusion criterion will thus be rephrased. For readability reasons we marked changes in front page and sections 4.3 and 5.3. **bold**.

CHANGE 1: SHORT DESCRIPTION OF CHANGE

Section of the protocol: 3.4. Exclusion criteria

- …
- Concurrent participation in another NIS or interventional clinical study during the treatment phase or within the last 30 days

Was changed to:

- …
- Concurrent participation in an **interventional clinical study** during the treatment phase or within the last 30 days

Reason for change:

The exclusion criterion was rephrased to better reflect clinical reality.

SIGNATURE PAGE(S)

This amendment

☒ concerns administrative matters only so that the coordinating investigator's signature will not be obtained.

☐ concerns matters dealing with design elements of the study, in- / exclusion criteria, observations, or safety or efficacy related study elements so that the coordinating investigator's signature needs to be obtained.

Trial Clinical Monitor

Date

Boehringer Ingelheim
Medical Affairs Germany

Trial Statistician

Date

Boehringer Ingelheim
Boehringer Ingelheim
Biometrics & Data Management

Team Member Medicine

Date

Boehringer Ingelheim
Corporate Medical Affairs

Local Clinical Monitor

Date

Boehringer Ingelheim
Medical Affairs Germany