Boehringer Ingelheim

# Protocol for non-interventional studies based on existing data

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| **Document Number:** | **c14668275-03** |
| **BI Study Number:** | 1200-0286 |
| **BI Investigational Product(s):** | Gi(l)otrif® (afatinib) |
| **Title:** | GioTag: Real-world data study on sequential therapy with Gi(l)otrif®/ afatinib as first-line treatment followed by osimertinib in patients with EGFR mutation positive advanced non-small cell lung cancer |
| **Lay Title:** | The GioTag study observes how long patients with non-small cell lung cancer (NSCLC) take afatinib as first-line treatment and osimertinib as second-line treatment. |
| **Protocol version identifier:** | 3.0 |
| **Date of last version of protocol:** | 06 Mar 2019 |
| **PASS:** | No |
| **EU PAS register number:** | EUPAS21037 |
| **Active substance:** | afatinib<br>Antineoplastic agents, tyrosine kinase inhibitors<br>ATC code: L01XE13 |
| **Medicinal product:** | Gi(l)otrif® 50mg, 40mg, 30mg, 20mg tablet |
| **Product reference:** | 20mg: EU/1/13/879/001, EU/1/13/879/002, EU/1/13/879/003<br>30mg: EU/1/13/879/004, EU/1/13/879/005, EU/1/13/879/006<br>40mg: EU/1/13/879/007, EU/1/13/879/008, EU/1/13/879/009<br>50mg: EU/1/13/879/010, EU/1/13/879/011, EU/1/13/879/012 |
| **Procedure number:** | EMEA/H/C/002280 |
| **Joint PASS:** | No |
| **Research question and objectives:** | Primary objective:<br>To determine the time on treatment of afatinib (Gi(l)otrif®) as first-line therapy in Epidermal Growth Factor Receptor (EGFR) mutation-positive followed by osimertinib in case the T790M resistance mutation was developed in real-world setting. Time on treatment is defined from the start of the first-line treatment until the end of the second-line treatment.<br>Secondary objective: |

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| | To collect data on acquired resistance mechanism to osimertinib. |
| **Country(-ies) of study:** | Austria, Canada, Germany, Israel, Italy, Japan, Singapore, Slovenia, Spain, Taiwan and USA. |
| **Author:** | Phone:<br>Fax:<br>e-mail: |
| **Marketing authorisation holder(s):** | |
| **Date:** | 06 Mar 2019 |

# 1. TABLE OF CONTENTS

# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| ADRs | Adverse Drug Reactions |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| BI | Boehringer Ingelheim |
| CA | Competent Authority |
| CML | Local Clinical Monitor |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| CUP | Compassionate Use Program |
| EAP | Early Access Program |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EGFR | Epidermal Growth Factor Receptor |
| EU | European Union |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GEP | Good Epidemiological Practice |
| GPP | Good Pharmacoepidemiology Practice |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| IV | Intravenous |
| MAH | Marketing Authorization Holder |
| NIS | Non-Interventional Study |
| NSCLC | Non-Small Cell Lung Cancer |
| PFS | Progression free Survival |
| PD | Progressive Disease |
| PS | Performance Score |
| RDC | Remote Data Capture |
| RWD | Real World Data |
| SAE | Serious Adverse Event |
| SOP | Standard Operating Procedures |
| SEAP | Statistical and Epidemiological Analysis Plan |
| SmPC | Summary of Product Characteristics |
| SUSARs | Suspected Unexpected Serious Adverse Reactions |
| TCM | Trial Clinical Monitor |
| TKI(s) | Tyrosine Kinase Inhibitor(s) |
| TMF | Trial Master File |
| WHO | World Health Organisation |

# 3. RESPONSIBLE PARTIES

The study is sponsored by Boehringer Ingelheim (BI).

Boehringer Ingelheim has appointed a Trial Clinical Monitor (TCM), responsible for coordinating the activities required in order to manage the study in accordance with applicable regulations and internal standard operating procedures (SOPs), directing the study team in the preparation, conduct, and reporting of the study, order the materials as needed for the study, ensures appropriate training and information of internal Local Clinical Monitors (CML), Clinical Research Associates (CRAs) or external Contract Research Organisation (CRO) members (CRO Project Managers and/or CRO CRAs), and investigators of participating countries.

The organisation of the study in the participating countries will be done by a CRO with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the study.

Data Management and Statistical evaluation will be performed by a CRO which is appointed by the sponsor.

Tasks and functions assigned in order to organise, manage, and evaluate the study will be defined according to BI SOPs. A list of responsible persons and relevant local information (as protocol reference if applicable) are in the Investigator Site File (ISF) and in the Trial Master File (TMF) document.

A coordinating investigator will be nominated to coordinate investigators at different sites participating in this multicentre study. Tasks and responsibilities for the coordinating investigators will be defined in a contract filed before initiation of the study.

Relevant documentation on the participating (Principal) investigators and other important participants (e.g. their curricula vitae) will be filed in the ISF. An ISF containing all relevant study related documentation will be maintained according to local regulations and BI SOPs at each study site. A copy of the ISF documents will also be kept as an electronic TMF at BI according to BI SOPs.

Coordinating investigator:

Phone:
Fax:
E-mail:

# 4. ABSTRACT

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|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | | |
| **Name of finished medicinal product:**<br>Gi(l)otrif® | | | |
| **Name of active ingredient:**<br>afatinib<br>Antineoplastic agents, tyrosine kinase inhibitors<br>ATC code: L01XE13 | | | |
| **Protocol date:**<br>04 May 2017 | **Study number:**<br>1200-0286 | **Version/Revision:**<br>3.0 | **Version/Revision date:**<br>06 Mar 2019 |
| **Title of study:** | GioTag: Real-world data study on sequential therapy with Gi(l)otrif®/ afatinib as first-line treatment followed by osimertinib in patients with EGFR mutation positive advanced non-small cell lung cancer | | |
| **Rationale and background:** | Afatinib (Gi(l)otrif®), an irreversible ErbB family blocker, is approved in EGFR-TKI (Tyrosine Kinase Inhibitor) naïve patients. Afatinib showed a median progression-free survival (PFS) of 11.1~13.6 months in previous clinical trials (LUX-Lung 3, LUX-Lung 6 and LUX-Lung 7). However, resistance develops for most of patients and the most common mechanism of resistance to EGFR TKIs (> 50%) is the emergence of a second-site EGFR-mutation, the T790M.<br><br>Osimertinib, a third-generation EGFR TKI, was approved for these patients whose tumours have developed the EGFR T790M mutation in several countries/regions (e.g. USA, EU and Japan).<br>Data for osimertinib in TKI-naïve setting are expected to come soon from the FLAURA trial. However, resistance mechanisms of osimertinib indicate limited options for subsequent targeted therapy.<br><br>Whether osimertinib will extend PFS versus available therapies if used as front-line therapies remains unknown. Investigating the time from start of first-line afatinib (Gi(l)otrif®) until the end of second-line osimertinib in this study provides insights on treatment sequence that can inform on the most beneficial treatment sequence for the patients. | | |
| **Research question and objectives:** | To determine the time on treatment of afatinib (Gi(l)otrif®) as first-line therapy in patients with EGFR mutation-positive NSCLC followed by osimertinib in case the T790M resistance mutation was developed in real-world setting and to collect data on osimertinib's resistance mechanisms (when available). | | |

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|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | | |
| **Name of finished medicinal product:**<br>Gi(l)otrif® | | | |
| **Name of active ingredient:**<br>afatinib<br>Antineoplastic agents, tyrosine kinase inhibitors<br>ATC code: L01XE13 | | | |
| **Protocol date:**<br>04 May 2017 | **Study number:**<br>1200-0286 | **Version/Revision:**<br>3.0 | **Version/Revision date:**<br>06 Mar 2019 |
| **Study design:** | Non-interventional, multi-country, multi-centre study based on existing data from medical records of patients treated with afatinib (Gi(l)otrif®) as the first-line treatment followed by osimertinib in case the T790M resistance mutation was developed. | | |
| **Population:** | Site selection:<br>Sites in countries meeting the following criteria:<br>- Afatinib launch dates prior 2015 and known to prescribe afatinib (Gi(l)otrif®) on a regular basis<br>- Osimertinib used in patients with EGFR T790M mutation-positive NSCLC within an early access program/ compassionate use program (EAP/CUP) or regular clinical practice; osimertinib provided via a clinical trial is not permitted.<br><br>Main inclusion criteria:<br>1. Patients with common EGFR mutations (Del19, L858R) advanced NSCLC being treated with afatinib (Gi(l)otrif®) in the first-line setting and for acquired T790M mutation with osimertinib in the second line; patients must have completed afatinib (Gi(l)otrif®) treatment and must have started osimertinib treatment at least 10 months prior to data entry.<br>2. Patients treated with osimertinib within an EAP/CUP or regular clinical practice; patients treated with osimertinib via a clinical trial are excluded.<br>3. Age ≥ 18 years<br><br>Main exclusion criteria:<br>1. Patients who received drug(s) other than osimertinib as the second-line treatment and/or patients who received drug(s) other than afatinib (Gi(l)otrif®) as the first-line treatment.<br>2. Patients with active brain metastases at start of treatment (either afatinib/Gi(l)otrif® or osimertinib). | | |

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|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | | |
| **Name of finished medicinal product:**<br>Gi(l)otrif® | | | |
| **Name of active ingredient:**<br>afatinib<br>Antineoplastic agents, tyrosine kinase inhibitors<br>ATC code: L01XE13 | | | |
| **Protocol date:**<br>04 May 2017 | **Study number:**<br>1200-0286 | **Version/Revision:**<br>3.0 | **Version/Revision date:**<br>06 Mar 2019 |
| **Variables:** | Primary Outcome(s):<br>Time on treatment with afatinib (Gi(l)otrif®) followed by osimertinib.<br><br>Secondary Outcome(s):<br>Type and proportion of acquired resistance mutations after osimertinib. | | |
| **Safety criteria:** | All adverse drug reactions (ADRs), adverse events (AEs) with fatal outcome and drug exposure during pregnancy will be collected retrospectively for pharmacovigilance. There is no intention to analyse the safety data in this non-interventional study (NIS) based on existing data. Safety data will be reviewed and analysed as part routine global pharmacovigilance procedures. | | |
| **Data sources:** | Non-interventional study (NIS) based on existing data from medical records of patients. | | |
| **Study size:** | Total enrolled: at least 190 patients | | |
| **Data analysis:** | Time on treatment will be analysed using Kaplan-Meier method, and the median along with two-sided 90% confidence interval will be displayed.<br>The different types and proportion of patients with acquired resistance mutations after osimertinib will be summarized descriptively. | | |
| **Milestones:** | Start of data collection in Dec 2017<br>End of data collection in May 2018<br>Final report of study results expected in Sep 2018<br>Note: Additional follow-up data collection for additional data analyses will be performed at least 10 months after the end of data collection of study primary outcomes. | | |

# 5. AMENDMENTS AND UPDATES

| | | |
|---|---|---|
| **Number of global amendment** | | 1 |
| **Date of protocol revision** | | 11-Sep-2017 |
| **EudraCT number** | | NA |
| **BI Study number** | | 1200-0286 |
| **BI Active substance** | | afatinib |
| **Title of protocol** | | GioTag: Real-world data study on sequential therapy with Gi(l)otrif®/ afatinib as first-line treatment followed by osimertinib in patients with EGFR mutation positive advanced non-small cell lung cancer |
| | | |
| **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** | | Title Page (Change 1) |
| **Description of change** | | Change 1: Revising the countries of the study<br><br><u>Title Page:</u> Wording changed.<br>Austria, **Canada,** Germany, **Israel,** Italy, Japan, **Singapore, Slovenia,** Spain, **Taiwan** and USA. |
| **Rationale for change** | | Change 1: To change the targeted countries according to the results of further evaluation on current real-world patient population. |
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| **Section to be changed** | | Section 4 (Change 2)<br>Section 9.1 (Change 2)<br>Section 9.2 (Change 2)<br>Section 9.5 (Change 2) |

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| **Number of global amendment** | | 1 |
| **Description of change** | | Change 2: Revising sample size and study population information<br><br>Section 4: Information and wording revised<br>Sample size:<br>Total enrolled: **at least 190** patients<br><br>Section 9.1: Information and wording revised<br>In total, **at least 190** eligible patients are planned to be enrolled to this study.<br><br>Section 9.2: Information and wording revised<br>It is planned that around **65** study centres in **11** countries will be participating in this non-interventional study and **at least 190** consecutive eligible patients will be enrolled to the study.<br><br>Section 9.2: Information and wording revised<br>It is expected that approximately **3** patients will be enrolled at each study centre.<br><br>Section 9.5: Information and wording revised<br>Based on the assumption that time on treatment follows an exponential distribution, a sample size of **171** patients are expected to ensure at 80% chance to observe a width of the 90% confidence interval of median time on treatment smaller or equal to **10** months, which is considered as a reasonable estimation precision. Assuming 10% of censored observations a total of **190** patients are included in the study. |
| **Rationale for change** | | Change 2: To change the targeted study sample size according to the results of further evaluation on current real-world patient population. Other study population information is changed due to the change of study sample size and study timeline. |
| | | |
| **Section to be changed** | | Section 4 (Change 3)<br>Section 9.7.1 (Change 3) |
| **Description of change** | | Change 3: Adding additional descriptions about how to handle the collected safety data<br><br>Section 4: Wording added |

<table>
<tr><td>Number of global amendment</td><td></td><td>1</td></tr>
<tr><td></td><td></td><td>Safety Criteria: All adverse drug reactions (ADRs), adverse events (AEs) with fatal outcome and drug exposure during pregnancy will be collected retrospectively for pharmacovigilance. There is no intention to analyse the safety data in this non-interventional study (NIS) based on existing data. Safety data will be reviewed and analysed as part routine global pharmacovigilance procedures.<br><br>Section 9.7.1: Wording revised and added<br>This descriptive non-interventional study based on existing data is conducted within the conditions of the approved marketing authorization and there is no intention to analyse the safety data collected retrospectively in the study as part of the study analysis. The safety data from this study will be reviewed and analysed as part of routine global pharmacovigilance processes.</td></tr>
<tr><td>Rationale for change</td><td></td><td>Change 3: To specify that the review and analysis of collected safety data will be part of company routine processes.</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Section to be changed</td><td></td><td>Section 4 (Change 4)<br>Section 6 (Change 4)</td></tr>
<tr><td>Description of change</td><td></td><td>Change 4: Revising the study timeline<br><br>Section 4: Information revised<br>Milestones:<br>Start of data collection in Dec 2017<br>End of data collection in May 2018<br>Final report of study results expected in Sep 2018<br><br>Section 6: Information revised
<table>
<tr><th>Milestone</th><th>Planned Date</th></tr>
<tr><td>Start of data collection</td><td>31 Dec 2017</td></tr>
<tr><td>End of data collection</td><td>31 May 2018</td></tr>
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| **Number of global amendment** | | 1 |
| | | Registration in the EU PAS register: EU PAS register number not yet assigned as the study is not yet registered in the EU PAS Register. The study will be registered shortly before the start of data collection.<br>Final report of study results: **30 Sep 2018** |
| **Rationale for change** | | Change 4: Study timeline is revised based on the revised sample size and the evaluation results of current real-world patient population. |
| | | |
| **Section to be changed** | | Section 4 (Change 5)<br>Section 9.7.1 (Change 5) |
| **Description of change** | | Change 5: Wording revised (administrative changes)<br><br><u>Section 4:</u> Wording revised<br>Data analysis: Time on treatment will be **analysed** using Kaplan-Meier method, and the median along with two-sided 90% confidence interval will be displayed.<br><br><u>Section 9.7.1:</u> Wording revised<br>Time on treatment will be **analysed** using Kaplan-Meier method, and the median along with two-sided 90% confidence interval will be displayed (use the Greenwood's formula for estimation of standard errors).<br><br>Baseline conditions and demographics will be **analysed** with descriptive statistics.<br><br>This descriptive non-interventional study based on existing data is conducted within the conditions of the approved marketing authorization and there is no intention to **analyse** the safety data collected retrospectively in the study. |
| **Rationale for change** | | Change 5: Administrative changes |
| | | |
| **Section to be changed** | | Section 9.8 (Change 6) |

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| **Number of global amendment** | | 1 |
| **Description of change** | | Change 6: Adding the patient replacement rule<br><br>Section 9.8: Wording added<br>**Patient replacement may be considered if there are major quality issues identified from the collected data. The decision of whether or not to enforce a patient replacement will be made by the sponsor/study team after evaluations. Data of the replaced patients will not be included in the final data analysis.** |
| **Rationale for change** | | Change 6: To exclude the data without acceptable quality level to ensure the quality and credibility of the study outcome. |
| | | |
| **Section to be changed** | | Section 11.2 (Change 7) |
| **Description of change** | | Change 7: Revising the wordings of AE and SAE collection and reporting section<br><br>Section 11.2: Wording revised<br>**Collection of AEs**<br>The following must be collected by the investigator in the eCRF from start of data collection **once** informed consent **is signed** (if required**, or waiver for informed consent obtained**) onwards until the end of the study (end of data collection):<br><br>**Expedited Reporting of AEs and Drug Exposure During Pregnancy**<br>The following must be reported by the investigator on the NIS AE form from start of data collection **once** informed consent **is signed** (if required**, or waiver for informed consent obtained**) onwards until the end of the study: |
| **Rationale for change** | | Change 7: To specify that data collection will be started after obtaining the signed informed consent if there is no waiver for informed consent given by IRB/IEC. Data collection can be started without obtaining signed informed consent when waiver for informed consent is obtained. |

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|---|---|---|
| **Number of global amendment** | | 2 |
| **Date of protocol revision** | | 06-Mar-2019 |
| **EudraCT number** | | NA |
| **BI Study number** | | 1200-0286 |
| **BI Active substance** | | afatinib |
| **Title of protocol** | | GioTag: Real-world data study on sequential therapy with Gi(l)otrif®/ afatinib as first-line treatment followed by osimertinib in patients with EGFR mutation positive advanced non-small cell lung cancer |
| | | |
| **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** | | Section 4 (Change 1)<br>Section 6 (Change 1)<br>Section 9.9 (Change 1) |
| **Description of change** | | Change 1: Adding descriptions of the additional data collection<br><br>Section 4 and Section 6: Wording added<br>**Note: Additional follow-up data collection for additional data analyses will be performed at least 10 months after the end of data collection of study primary outcomes**.<br><br>Section 9.9: Wording added<br>**In addition, additional data collection for following up the time on treatment and patient's status of the sub-groups (i.e.** |

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|---|---|---|
| **Number of global amendment** | | 2 |
| | | **patients who were still on treatment and/or alive at the time of data collection) will be performed at least 10 months after the end of data collection of study primary outcomes.** |
| **Rationale for change** | | Change 1: The study enrolled patients who are still on treatment as long as patients started osimertinib treatment at least 10 months prior to data entry because osimertinib was approved by most of the regions no longer than 1 to 1.5 years by the time of data collection (See Section 9.9 for the details). For patients who were still under osimertinib treatment at the time of data collection, the time on treatment would be censored at the date of data collection.<br>The additional follow-up data collection may provide more mature real-world data on time on treatment of the sequential therapy with afatinib (Gi(l)otrif®) followed by osimertinib. |
| | | |
| **Section to be changed** | | Title Page (Change 2)<br>Section 6 (Change 2) |
| **Description of change** | | Change 2: Updating the EU PAS register number<br><br>Title Page and Section 6: Information update EU PAS register number: **EUPAS21037** |
| **Rationale for change** | | Change 2: To update the EU PAS register number |
| | | |
| **Section to be changed** | | Section 9.8 (Change 3) |
| **Description of change** | | Change 3: To clarify the quality control plan<br><br>Section 9.8: Wording added<br>For the further quality assurance of the documented patient observations, a sample-size based source data verification will be performed on about 30% of included patients **(not including the additional data collected for follow-up analyses).** |
| **Rationale for change** | | Change 3: To clarify that there will be no source data verification planned for the |

| | | |
|---|---|---|
| **Number of global amendment** | | 2 |
| | | additional data collection for follow-up analyses. |
| | | |
| **Section to be changed** | | Section 11.2 (Change 4) |
| **Description of change** | | Change 4: To specify that AE reporting is not required during the additional data collection period for follow-up analyses<br><br>Section 11.2: Wording revised<br>**<u>Collection of AEs</u>**<br>The following must be collected by the investigator in the eCRF from start of data collection once informed consent is signed (if required, or waiver for informed consent obtained) onwards until the end of data collection **of study outcomes, but will not be collected during the additional data collection period for follow-up analysis. For the additional data collection period for follow-up analyses, study outcome events will be collected in the CRF only for the purpose of analysis.**<br>• all ADRs (serious and non-serious)<br>• all AEs with fatal outcome<br>• for Japan: an AE which possibly leads to disability will be reported as an SAE<br><br>The investigator carefully assesses whether an AE constitutes an ADR using the information below.<br><br>Section 11.2: Wording added<br>**<u>Expedited Reporting of AEs and Drug Exposure During Pregnancy</u>**<br>The following must be reported by the investigator on the NIS AE form from start of data collection once informed consent is signed (if required, or waiver for informed consent obtained) onwards until the end of the **data collection of study outcomes**:<br><br>**Additional data collection period for follow-up analyses will be performed at least 10 months after the end of data** |

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| **Number of global amendment** | | 2 |
| | | **collection of study primary outcomes. All subjects would have discontinued afatinib (Gi(l)otrif®) for 10 months prior to study enrollment.**<br><br>**For the additional data collection period for follow-up analyses, study outcome events will be collected in the CRF only for the purpose of analysis and will not be collected and reported on the NIS AE form.**<br><br>**However, the investigator is encouraged to report all AEs related to any BI drug other than afatinib (Gi(l)otrif®) according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.** |
| **Rationale for change** | | Change 4: To clarify the AE reporting rule for the additional data collection period and specify that AEs will not be collected and reported on the NIS AE form during the additional data collection period as all subjects would have discontinued afatinib (Gi(l)otrif®). |
| | | |

# 6. MILESTONES

| Milestone | Planned Date |
|---|---|
| Start of data collection | 31 Dec 2017 |
| End of data collection | 31 May 2018 |
| Registration in the EU PAS register | EUPAS21037 |
| Final report of study results: | 30 Sep 2018 |

Note: Additional follow-up data collection for additional data analyses will be performed at least 10 months after the end of data collection of study primary outcomes.

# 7. RATIONALE AND BACKGROUND

Metastatic epidermal growth factor receptor (EGFR)-mutant lung cancers are sensitive to first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib and afatinib (P14-03814).

Afatinib is an irreversible ErbB family blocker and the first marketing approval of afatinib was granted on 12 Jul 2013 in the US (trade name Gilotrif®) for the indication of first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an Food and Drug Administration (FDA)-approved test. It was approved in the European Union (EU) on 25 Sep 2013 (trade name Giotrif®) as monotherapy indicated for the treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic NSCLC with activating EGFR mutation(s). In total, marketing authorisation for Gi(l)otrif® has been granted in 70 other countries world-wide as of today (c01802941-10).

On the clinical trials LUX-Lung 3 (P13-07382), LUX-Lung 6 (P14-00758) and LUX-Lung 7 (P16-04350), afatinib (Gi(l)otrif®) showed a median progression-free survival (PFS) of 11.1, 11.1 and 13.6 months, respectively, for patients with EGFR common mutations (Del19 and L858R) treatment-naïve. Time to treatment failure in LUX-Lung 7 was 13.7 months. Eventually, resistance develops for most patients and the most common mechanism of resistance to EGFR TKIs (>50%) is the emergence of a second-site EGFR-mutation, the T790M (R15-6101, P09-09950).
Explorative analysis of LUX-Lung 7 showed a median overall survival of not being reached for patients who started with afatinib (Gi(l)otrif®) and received subsequently osimertinib or olmutinib (follow-up period of 42.6 months) indicating a long-time benefit from this sequence (P16-13901).

Osimertinib, a third generation EGFR TKI, was approved for patients whose tumours have developed the EGFR T790M mutation by several countries. The first marketing approval of osimertinib was granted on 13 Nov 2015 in the US (R16-5838). The EU and Japan also gave a similar approval on 03 Feb 2016 and 29 Mar 2016 separately (P16-15191, P16-15190).

In addition, osimertinib has been studied in the first-line treatment in an expansion cohort from AURA trial, whose reported result looked promising (median PFS for the 80 mg cohort had not yet been reached but for the 160 mg cohort was shown to be 19.3 months) (R16-5840). Confirmation of these results in a phase III randomized trial is still needed to define the role of osimertinib in the treatment of patients with EGFR mutation-positive. FLAURA is comparing osimertinib to either gefitinib or erlotinib in EGFR mutant NSCLC treatment naïve patients and results are expected to be presented during 2017 (R16-5841).

Whether osimertinib will extend PFS versus available therapies if used as front-line therapies remains unknown. Investigating in this real-world data (RWD) study the time from start of first-line afatinib (Gi(l)otrif®) until the end of second-line osimertinib in this study provides insights on treatment sequence that can inform on the most beneficial treatment sequence for the patients.

# 8. RESEARCH QUESTION AND OBJECTIVES

Data from real-world setting would inform on the most beneficial treatment sequence in patients diagnosed with advanced EGFR mutation-positive NSCLC.

**Primary objective:**
To determine the time on treatment of afatinib (Gi(l)otrif®) as first-line therapy in patients with EGFR mutation-positive NSCLC followed by osimertinib in case the T790M resistance mutation was developed in real-world setting. Time on treatment is defined from the start of the first-line treatment until the end of the second-line treatment or death date by any cause.

**Secondary objective:**
To collect data on acquired resistance mechanism to osimertinib.

# 9. RESEARCH METHODS

## 9.1 STUDY DESIGN

This is a non-interventional, multi-country, multi-centre cohort study based on existing data from medical records of patients with EGFR mutation-positive advanced NSCLC treated with afatinib (Gi(l)otrif®) as the first-line treatment followed by osimertinib in case the T790M resistance mutation was developed.

In total, at least 190 eligible patients are planned to be enrolled to this study.

Key study outcome:

- The time on treatment with afatinib (Gi(l)otrif®) followed by osimertinib.

## 9.2 SETTING

It is planned that around 65 study centres in 11 countries will be participating in this non-interventional study and at least 190 consecutive eligible patients will be enrolled to the study. Every patient who fulfils inclusion and exclusion criteria and agree to participate in the study (if a written informed consent is required for this NIS by local regulation and legal requirement) will be selected until the required sample size is achieved. Deceased patients should be enrolled whenever possible. This has to be discussed with the local authorities. It is expected that approximately 3 patients will be enrolled at each study centre. Investigators who fail to enrol at least one patient in the first 8 weeks of the study may be excluded from further participation. If enrolment is delayed additional countries and centres may be recruited.

To avoid differential centre influence on study results, permission to enrol more than 15 patients per site must be obtained from the TCM.

Recruiting of patients for this study is competitive, i.e., recruitment will stop at all centres when it is determined that a sufficient number of patients have been enrolled. Investigators will be notified when the appropriate number of patients has been enrolled and recruitment is complete, and will not be allowed to recruit additional patients for this study.

### 9.2.1 Selection of study population

**Site selection:**

Sites in countries meeting the criteria below:

- Sites in countries with afatinib launch dates prior to 01 Jan 2015 and known to prescribe afatinib (Gi(l)otrif®) on a regular basis
- Osimertinib used in patients with EGFR T790M mutation-positive NSCLC within an early access program/ compassionate use program (EAP/CUP) or regular clinical practice; osimertinib provided via a clinical trial is not permitted.

**Inclusion criteria:**

1. Patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC)
2. The tumour harbours common EGFR mutations (Del19, L858R) at start of first-line treatment
3. Patients who initiated second-line osimertinib treatment for acquired T790M mutation at least 10 months prior to data entry, AND who were treated with afatinib (Gi(l)otrif®) in the first-line
4. Patients treated with osimertinib within an EAP/CUP or regular clinical practice
5. Age ≥ 18 years
6. Signed and dated written informed consent per regulations (Exemption of a written informed consent for NIS based on existing data in countries per local regulations and legal requirements)

**Exclusion criteria:**

1. Patients who received drug(s) other than osimertinib as the second-line treatment and/or patients who received drug(s) other than afatinib (Gi(l)otrif®) as the first-line treatment
2. Patients with active brain metastases at start of treatment (either afatinib/Gi(l)otrif® or osimertinib)

Patients treated with afatinib (Gi(l)otrif®) and/or osimertinib in interventional trials are excluded to ensure the non-interventional setting of this study. Real-world studies such as ASTRIS are not affected by this exclusion (R17-0754). The threshold of start of osimertinib at least 10 months prior to data entry was chosen based on the median PFS result of AURA-3 (R17-0221) to avoid early censoring and enable collection of mature data on adverse drug reactions (ADRs) and treatment duration. All patients fulfilling inclusion and exclusion criteria from a site will be entered to avoid bias.

A log of all patients included into the study will be maintained in the ISF at the investigational site.

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

1. Failure to meet expected enrolment goals overall or at a particular study site.
2. Violation of Good Clinical Practice (GCP) (as applicable), the Study Protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study.

## 9.3 VARIABLES

The following data will be collected from medical records and will be recorded in the electronic case report form (eCRF) by investigators (or designees) during the study period:

- Informed consent
- Demographics: age at start of afatinib (Gi(l)otrif®) treatment, gender, ethnicity
- Stage of disease (IIIb or IV) at start of afatinib (Gi(l)otrif®) treatment
- Type of mutations at initial diagnosis
- Sites of metastases at start of afatinib (Gi(l)otrif®) treatment
- Body weight and height at start of afatinib (Gi(l)otrif®) treatment

- Eastern Cooperative Oncology Group (ECOG) performance score (PS) (if available) at start of afatinib (Gi(l)otrif®) treatment
- Date of start and end of afatinib (Gi(l)otrif®) treatment
- Starting dose of afatinib (Gi(l)otrif®)
- Afatinib (Gi(l)otrif®) dose modification(s) and date(s)
- ECOG PS (if available) at start of osimertinib treatment
- Type of mutations at start of osimertinib treatment
- Sites of metastases at start of osimertinib treatment
- Date of start and end of osimertinib treatment
- Starting dose of osimertinib
- Osimertinib dose modification(s) and date(s)
- Reason for discontinuation of each treatment (e.g. progressive disease (PD), adverse event (AE))
- If osimertinib was provided within an EAP/CUP or prescribed as clinical practice
- ADRs
- AEs with fatal outcome
- Type of mutations at stop of osimertinib if available (EGFR mutations: T790M, C797S [if positive: in cis or in trans], Del19, L858R, other EGFR sensitizing mutation (to be specified), non-EGFR: to be specified) (R16-1552, P15-11024)
- Date of death (if available)

### 9.3.1 Exposures

Afatinib (Gi(l)otrif®):
Patients were treated with afatinib (Gi(l)otrif®) 50mg or 40mg or 30mg or 20mg tablet once daily as indicated in the approved labels of afatinib (Gi(l)otrif®).

Osimertinib:
Patients were/are treated with osimertinib 80 mg or 40 mg tablets once daily as indicated in the approved labels of osimertinib.
Patients who started osimertinib treatment at least 10 months prior to data entry are eligible.

The Summaries of Product Characteristics on Gi(l)otrif® and Osimertinib are contained in the ISF in the "Summary of Product Characteristics" (SmPC) section.

### 9.3.2 Outcomes

#### 9.3.2.1 Primary outcomes

Time on treatment with afatinib (Gi(l)otrif®) followed by osimertinib. This will be assessed as the time from start of afatinib (Gi(l)otrif®) as first-line treatment until the end of the second-line treatment (the last dose of osimertinib) or death date by any cause.

#### 9.3.2.2 Secondary outcomes

Type and proportion of acquired resistance mutations after osimertinib.

### 9.3.3 Covariates

NA

## 9.4 DATA SOURCES

Data will be collected from patients' medical records and recorded in (e)CRFs.

### 9.4.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.
The investigator may need to request previous medical records or transfer records, current medical records must be available.

For (e)CRFs all data must be derived from source documents.

### 9.4.2 Records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor or appointed CRO via remote data capture (RDC) system or Electronic Data Capture (EDC) system.

### 9.4.3 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, Institutional Review Board (IRB) / Independent Ethics Committee (IEC) review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. FDA). The CRA/on site monitor and auditor may review all eCRFs, and written informed consents (if applicable). The accuracy of the data will be verified by reviewing the documents described in Section 9.4.1.

### 9.4.4 Storage of records

Study site (s):
The study site(s) must retain the source documents and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the study (whatever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

## 9.5 STUDY SIZE

It is assumed that the median time on treatment from start of the first-line treatment until the end of the second-line treatment or death date by any cause is 24 months (based on: 13.6 months median PFS with afatinib (Gi(l)otrif®) in LUX-Lung 3, 13.7 months time to treatment failure with afatinib (Gi(l)otrif®) in LUX-Lung 7 plus 10.1 months median PFS of osimertinib in AURA-3, 13.2 months in the AURA study phase 2 extension component) (P17-01960, P17-03000). Based on the assumption that time on treatment follows an exponential distribution, a sample size of 171 patients are expected to ensure at 80% chance to observe a width of the 90% confidence interval of median time on treatment smaller or equal to 10 months, which is considered as a reasonable estimation precision. Assuming 10% of censored observations a total of 190 patients are included in the study.

## 9.6 DATA MANAGEMENT

Data will be gathered in Remote Data Capture (RDC) system or Electronic Data Capture (EDC) system prepared by sponsor or appointed CRO. The details of data management procedures to ensure the quality of the data will be described in the Statistical and Epidemiological Analysis Plan (SEAP) available in eTMF.

## 9.7 DATA ANALYSIS

### 9.7.1 Main analysis

The primary endpoint is time on treatment, which is defined as time in months from the start of date of afatinib (Gi(l)otrif®) treatment to the end date of osimertinib treatment or death date due to any cause. Time on treatment will be analysed using Kaplan-Meier method, and the median along with two-sided 90% confidence interval will be displayed (use the Greenwood's formula for estimation of standard errors).
In the analyses of time-to-event endpoint, missing or incomplete data are managed by standard survival analysis techniques. For patient still on treatment, time on treatment will be censored at the date of data collection. We do not expect missing start dates of afatinib (Gi(l)otrif®) treatment.

Baseline conditions and demographics will be analysed with descriptive statistics. The frequency of treatment interruption and dose reduction of both afatinib (Gi(l)otrif®) and

osimertinib will be summarized through descriptive statistics. This descriptive non-interventional study based on existing data is conducted within the conditions of the approved marketing authorization and there is no intention to analyse the safety data collected retrospectively in the study as part of the study analysis. The safety data from this study will be reviewed and analysed as part of routine global pharmacovigilance processes.

## 9.8 QUALITY CONTROL

All entries in the eCRF will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the eCRF. To improve and ensure data quality, data checks will be performed automatically in the eCRF directly on electronic entry at the study site.

Plausible value ranges for numerical data entries and logical data and list entries will be filed in the eCRF. The tests for consistency and completeness based on this will be performed during entry in the eCRF. The validity of the recorded data will therefore be ensured by the validations incorporated in the documentation system, which highlight incorrect or implausible entries to the data entry clerk/doctor.

If corrections are necessary after the data are saved, these will be documented in an audit trail.
For the further quality assurance of the documented patient observations, a sample-size based source data verification will be performed on about 30% of included patients (not including the additional data collected for follow-up analyses).

Patient replacement may be considered if there are major quality issues identified from the collected data. The decision of whether or not to enforce a patient replacement will be made by the sponsor/study team after evaluations. Data of the replaced patients will not be included in the final data analysis.

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Boards/ Independent Ethics Committees (IRBs/IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

## 9.9 LIMITATIONS OF THE RESEARCH METHODS

Potential limitations of the study design:
1. Site selection:

The study is restricted to the sites using afatinib (Gi(l)otrif®) on a regular basis and to the sites which are able to use osimertinib for T790M mutation tumours. By the time of data collection, osimertinib has been approved (and reimbursed) in most regions not longer than 1 to 1.5 years, which limits the number of patients being treated with osimertinib.
To overcome this feasibility limitation, patients who have received osimertinib treatment within an EAP/CUP are eligible as well as patients who started osimertinib treatment at least 10 months prior to data entry, increasing the pool of eligible sites and potential patients.
In addition, additional data collection for following up the time on treatment and patient's status of the sub-groups (i.e. patients who were still on treatment and/or alive at the time of data collection) will be performed at least 10 months after the end of data collection of study primary outcomes.

2. Patient population:
Firstly, there is an immortal time bias as patients that die on afatinib (Gi(l)otrif®) will not be included in this study. Because of that immortal time bias, the results of the study (i.e. median duration from start of afatinib (Gi(l)otrif®) until the end of osimertinib) will not be generalizable to all patients starting first line treatment with afatinib (Gi(l)otrif®).

Secondly, there is some bias as patients with long-term benefit from afatinib (Gi(l)otrif®) have a lower likelihood of being included in this study. Because of bias, the results of the study (i.e. median duration from start of afatinib (Gi(l)otrif®) until the end of osimertinib) will not be generalizable to all patients starting first-line treatment with afatinib (Gi(l)otrif®).

Thirdly, the treatment approach investigated in this non-interventional study (NIS) provides a treatment solution for around 50% of the patients who start with afatinib (Gi(l)otrif®) treatment (as only these are expected to develop the acquired resistance T790M following an EGFR TKI). Currently, patients who did not acquired the T790M resistance mutation seems to be treated heterogeneously with no available standard of treatment so these patients are not included in this non-interventional study.

This study has no comparator group limiting the interpretability of the results as they cannot be put into perspective. The only reasonable control group could be patients treated with the sequence of first-line osimertinib followed by afatinib (Gi(l)otrif®) however this group does not exist in real clinical practice as frontline use of osimertinib in EGFR-mutant NSCLC is not currently approved.

## 9.10 OTHER ASPECTS

### 9.10.1 Statement of confidentiality

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

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principle 6 and 12 of the World Health Organisation (WHO) GCP handbook.

Data generated as a result of the study need to be available for inspection on request by the participating investigators, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

### 9.10.2 Patient completion

The collection of the data of patients will continue until end of data collection or withdrawal of consent (if applicable) which occurs first.

### 9.10.3 Completion of study

The end of the study will occur when the end of data collection of the last patient's data. No further data will be collected afterwards.

<For Japan>
When the study is completed, the principal investigator should inform the head of the study site of the completion in writing, and the head of the study site should promptly inform the IRB and sponsor of the completion in writing.

<For EU member states>
The IEC/ competent authority (CA) in each participating EU member state will be notified about the study milestones according to the respective laws.
A final report of study data will be written only after all patients have completed the study in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final study results within one year from the end of a study as a whole, regardless of the country of the last patient (EU or non-EU).

## 9.11 SUBJECTS

Please refer to Section 9.2.1 Section of study population.

### 9.11.1 Cases

NA

### 9.11.2 Controls

NA

## 9.12 BIAS

Methodological efforts have been taken to minimize selection bias: these efforts including only consecutive patients meeting each of the inclusion criteria and none of the exclusion criteria.

ECOG PS might not be recorded in all medical records and it means that not only patients with good performance status (PS 0-1) will be included in this study.

In addition, the study is not including the impact of the patients who died during first-line treatment, introducing immortal time bias. Based on clinical trials LUX-Lung 3 and LUX-Lung 6, from the 6% of the patients who have died during afatinib (Gi(l)otrif®) treatment, assuming that on 50% of those the T790M mutation would be detected, this NIS analysis is excluding results of 3% of the patients (who started the first-line treatment but did not reach the second-line treatment), which is not expected to be a significant impact on the study results. There is some bias as patients with long-term benefit from afatinib (Gi(l)otrif®) have a lower likelihood of being included in this study. Please refer to the Section 9.9 for the details.

# 10. PROTECTION OF HUMAN SUBJECTS

## 10.1 DATA PROTECTION AND STUDY RECORDS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline for GCP (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI SOPs <For Japan> and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating investigator of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol, ICH GCP <For Japan> and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997)..

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalisation of the Study Report.

### 10.1.1 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 competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

In some countries, NIS based on existing data can be exempt from a written informed consent per local regulations and legal requirements, IRB / IEC often grants a waiver of consent for retrospective chart review studies. In order to avoid bias by exclusion of subjects that cannot be given informed consent for any reason like death, missing contact information etc., exempt from a written informed consent should be asked for such situations. Additionally, permission to include deceased patients should be requested by the local authorities.

In case such a waiver is not given, prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country.

Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed 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 medical records may be examined by authorised monitors (CML / CRA or CRO monitors) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

## 10.2 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF STUDY RELATED INJURY

In the event of health injury associated with marketed product in routine medical practice, the sponsor is not responsible for compensation.

# 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

## 11.1 DEFINITIONS OF ADVERSE EVENTS

**Adverse event**

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**Adverse reaction**

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

**Serious adverse event**

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect,

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.
Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

For Japan, an AE which possibly leads to disability will be reported as an SAE.

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

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

No AESIs have been defined for this study.

## 11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

**Collection of AEs**

The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the eCRF from start of data collection once informed consent is signed (if required, or waiver for informed consent obtained) onwards until the end of data collection of study outcomes, but will not be collected during the additional data collection period for follow-up analysis. For the additional data collection period for follow-up analyses, study outcome events will be collected in the CRF only for the purpose of analysis.

- all ADRs (serious and non-serious)
- all AEs with fatal outcome
- for Japan: an AE which possibly leads to disability will be reported as an SAE

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

**Causal relationship of AEs**

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event (AE). An adverse reaction, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug

- The event is known to be caused by or **attributed to the drug class**.
- **A plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

**Intensity of AEs**

The intensity of the AE should be judged based on the following:

| | |
|---|---|
| Mild: | Awareness of sign(s) or symptom(s) which is/are easily tolerated |
| Moderate: | Enough discomfort to cause interference with usual activity |
| Severe: | Incapacitating or causing inability to work or to perform usual activities |

**Pregnancy**

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken afatinib (Gi(l)otrif®) the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.
The ISF will contain the Pregnancy Monitoring Form for Studies (Part A and Part B).

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

**Expedited Reporting of AEs and Drug Exposure During Pregnancy**

The following must be reported by the investigator on the NIS AE form from start of data collection once informed consent is signed (if required, or waiver for informed consent obtained) onwards until the end of data collection of study outcomes:

Additional data collection period for follow-up analyses will be performed at least 10 months after the end of data collection of study primary outcomes. All subjects would have discontinued afatinib (Gi(l)otrif®) for 10 months prior to study enrollment.

For the additional data collection period for follow-up analyses, study outcome events will be collected in the CRF only for the purpose of analysis and will not be collected and reported on the NIS AE form.

However, the investigator is encouraged to report all AEs related to any BI drug other than afatinib (Gi(l)otrif®) according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

| Type of Report | Timeline |
|---|---|
| All **Serious Adverse Drug Reactions** (SADRs) associated with afatinib (Gi(l)otrif®) | immediately within 24 hours |
| All **AEs with fatal outcome** in patients exposed to afatinib (Gi(l)otrif®) | immediately within 24 hours |
| For Japan: AE which possibly leads to disability in patients exposed to afatinib (Gi(l)otrif®) | immediately within 24 hours |
| All **non-serious ADRs** associated with afatinib (Gi(l)otrif®) | 7 calendar days |
| All **pregnancy monitoring** forms | 7 calendar days |

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the physician could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

**Information required**

For each reportable AE, the investigator should provide the information requested on the appropriate eCRF pages and the NIS AE form.

**Reporting of related AEs associated with any other BI drug**

The investigator is encouraged to report all AEs related to any BI drug other than Gi(l)otrif® according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure,

lack of effect, and unexpected benefit.

## 11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the Marketing Authorization Holder (MAH) according to local and international regulatory requirements.

# 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalisation of the Study Report.

BI intends to use data from this study to prepare peer-reviewed publications and other scientific communications such as abstracts, posters, and podiums presentations.

# 13. REFERENCES

## 13.1 PUBLISHED REFERENCES

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# ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

1. Informed Consent Form
2. Statistical and Epidemiological Analysis Plan (SEAP)

The stand-alone documents listed above will be archived in the electronic Trial Master File.

# ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

## ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

**Study title:**
GioTag: Real-world data study on sequential therapy with Gi(l)otrif®/ afatinib as first-line treatment followed by osimertinib in patients with EGFR mutation positive advanced non-small cell lung cancer

**Study reference number:**
BI 1200-0286
Note: EU PAS register number not yet assigned as the study is not yet registered in the EU PAS Register. The study will be registered shortly before the start of data collection.

| Section 1: Milestones | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 6 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 6 |
| 1.1.3 Study progress report(s) | ☐ | ☒ | ☐ | NA |

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

| **Section 1: Milestones** | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 1.1.4 Interim progress report(s) | ☐ | ☒ | ☐ | NA |
| 1.1.5 Registration in the EU PAS register | ☒ | ☐ | ☐ | 6 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 6 |

Comments:

Item 1.1.3 and 1.1.4: There is no study progress report and interim progress report planned for this non-interventional study based on existing data.

| **Section 2: Research question** | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | ☒ | ☐ | ☐ | 7 and 8 |
| 2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 7 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 8 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 9.2.1 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | NA |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | NA |

Comments:

Item 2.1.4 and 2.1.5: This real-world data study is designed to help people to understand the time on treatment of the sequential therapy in targeted patients. There is no hypothesis and priori hypothesis to be tested in this study.

| **Section 3: Study design** | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design) | ☒ | ☐ | ☐ | 9.1 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 9.1 and 9.3.2 |
| 3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk) | ☐ | ☒ | ☐ | NA |
| 3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☐ | ☒ | ☐ | NA |
| 3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 11 |

Comments:

Item 3.3 and 3.4: There is no measure of occurrence and association designed for this non-interventional study based on existing data.

**ENCePP Checklist for Study Protocols (Revision 3)**

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 9 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period? | ☒ | ☐ | ☐ | 6 |
| 4.2.2 Age and sex? | ☒ | ☐ | ☐ | 9.2.1 |
| 4.2.3 Country of origin? | ☒ | ☐ | ☐ | 9.2.1 |
| 4.2.4 Disease/indication? | ☒ | ☐ | ☐ | 9.2.1 |
| 4.2.5 Duration of follow-up? | ☐ | ☐ | ☒ | NA |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 9.2.1 |

Comments:

Item 4.2.5: There is no need to have a follow-up period designed for this non-interventional study based on existing data.

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure,) measurement of dose and duration of drug exposure | ☒ | ☐ | ☐ | 9 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☒ | ☐ | ☐ | 9 |
| 5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use) | ☒ | ☐ | ☐ | 9 |
| 5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☐ | ☒ | NA |

Comments:

Item 5.4: The drug exposure in this study isn't classified based on biological mechanism of action.

| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☒ | ☐ | ☐ | 9.3.2 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3.2 |
| 6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☐ | ☐ | ☒ | NA |

**ENCePP Checklist for Study Protocols (Revision 3)**

| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management) | ☐ | ☒ | ☐ | NA |

Comments:

Item 6.3: The data related to study outcomes (e.g. start and end date of the treatments) will be collected from the existing data in patients' medical records in this non-interventional study.

Item 6.4: There is no endpoint relevant for Health Technology assessment designed for this study.

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol describe how confounding will be addressed in the study? | ☒ | ☐ | ☐ | 9.7.1 and 9.12 |
| 7.1.1. Does the protocol address confounding by indication if applicable? | ☒ | ☐ | ☐ | 9.12 |
| 7.2 Does the protocol address: | ☒ | ☐ | ☐ | 9.12 |
| 7.2.1. Selection biases (e.g. healthy user bias) | ☒ | ☐ | ☐ | 9.12 |
| 7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias) | ☒ | ☐ | ☐ | 9.12 |
| 7.3 Does the protocol address the validity of the study covariates? | ☐ | ☐ | ☒ | NA |

Comments:

Item 7.3: There is no covariate in this study.

| **Section 8: Effect modification** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | ☐ | ☒ | ☐ | |

Comments:

Item 8.1: No effect modifier or any sub-group analysis is addressed or planned for this study.

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | 9.3 and 9.4 |
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 9.3 and 9.4 |
| 9.1.3 Covariates? | ☐ | ☐ | ☒ | NA |

**ENCePP Checklist for Study Protocols (Revision 3)**

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 93 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 9.3 |
| 9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☐ | ☐ | ☒ | NA |
| 9.3 Is a coding system described for: | | | | NA |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☐ | ☐ | ☒ | NA |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA)) | ☐ | ☐ | ☒ | NA |
| 9.3.3 Covariates? | ☐ | ☐ | ☒ | NA |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☐ | ☐ | ☒ | NA |

Comments:

Item 9.1.3, 9.2.3 and 9.3.3: There is no covariate in this study.

Item 9.3: There is no safety outcome designed for this study and a coding system is not required in this study.

Item 9.4: No linkage method is required to be used in the study.

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | 9.7 |
| 10.2 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.7 |
| 10.3 Are stratified analyses included? | ☐ | ☒ | ☐ | NA |
| 10.4 Does the plan describe methods for adjusting for confounding? | ☒ | ☐ | ☐ | 9.7.1 |
| 10.5 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 9.7.1 |
| 10.6 Is sample size and/or statistical power estimated? | ☒ | ☐ | ☐ | 9.5 |

Comments:

Item 10.3: No stratified analysis is planned for this study.

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 9.8 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9.8 |
| 11.3 Is there a system in place for independent review of study results? | ☐ | ☐ | ☒ | NA |

**ENCePP Checklist for Study Protocols (Revision 3)**

Comments:

Item 11.3: There is no independent review system required for this study.

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | |
| 12.1.1 Selection bias? | ☒ | ☐ | ☐ | 9.12 |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 9.12 |
| 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | ☐ | ☐ | ☒ | NA |
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 9.1 and 9.2 |

Comments:

Item 12.1.3: There is no residual/unmeasured confounding in the study.

| **Section 13: Ethical issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☒ | ☐ | ☐ | 10 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☒ | ☐ | ☐ | 10 |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 10 |

Comments:

| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | ☒ | ☐ | ☐ | 5 |

Comments:

| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | ☒ | ☐ | ☐ | 12 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 12 |

Comments:

Name of the main author of the protocol: _____

**ENCePP Checklist for Study Protocols (Revision 3)**

Date: 04/April/2017

Signature: ___ _____

**ENCePP Checklist for Study Protocols (Revision 3)**

# ANNEX 3. ADDITIONAL INFORMATION

## ANNEX 3.1 ECOG PERFORMANCE STATUS

| Grade | Definition |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled, cannot carry on any self-care, totally confined to bed or chair |
| 5 | Dead |