Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	c28110847-03
BI Study Number:	1200-0316
BI Investigational Product(s):	Gi(l)otrif® (afatinib)
Title:	UpSwinG: Real World study on TKI activity in Uncommon mutations and Sequencing Giotrif®
Lay Title:	The study observes how long patients with non-small cell lung cancer (NSCLC) benefit from treatment with Epidermal Growth Factor Tyrosine Kinase Inhibitor (EGFR-TKI) when given either for uncommon mutations or for common mutations in the sequence afatinib followed by osimertinib
Protocol version identifier:	3.0
Date of last version of protocol:	23 July 2019
PASS:	Yes
EU PAS register number:	EUPAS32098
Active substance:	Afatinib (ATC code: L01XE13), gefitinib (L01XE02), erlotinib (L01XE03), osimertinib (L01XE35), Antineoplastic agents, tyrosine kinase inhibitors
Medicinal product:	Gi(l)otrif®: 50mg, 40mg, 30mg, 20mg tablet IRESSA®: 250mg tablet Tarceva®: 25mg, 100mg, 150mg tablet Tagrisso®: 40mg, 80mg
Product reference:	Gi(l)otrif®: 20mg: EU/1/13/879/001, EU/1/13/879/002, EU/1/13/879/003 30mg: EU/1/13/879/004, EU/1/13/879/005, EU/1/13/879/006 40mg: EU/1/13/879/007, EU/1/13/879/008, EU/1/13/879/009 50mg: EU/1/13/879/010, EU/1/13/879/011, EU/1/13/879/012 IRESSA®: 250mg: EU/1/09/526/001, EU/1/09/526/002 Tarceva®: 25mg: EU/1/05/311/001 100mg: EU/1/05/311/002 150mg: EU/1/05/311/003 Tagrisso®: 40mg: EU/1/16/1086/001, EU/1/16/1086/003 80mg: EU/1/16/1086/002, EU/1/16/1086/004

Procedure number:	Gi(l)otrif® : EMEA/H/C/002280 IRESSA®: EMEA/H/C/001016 Tarceva®: EMEA/H/C/000618 Tagrisso®: EMEA/H/C/004124
Joint PASS:	No
Research question and objectives:	Data from real-world setting would inform on the beneficial treatments in patients diagnosed with advanced NSCLC harbouring uncommon EGFR mutations and on the treatment sequence in patients diagnosed with advanced common EGFR mutation NSCLC. Primary objective: For both cohorts the study aims to describe the time on treatment until its end or death. More specifically, this will be evaluated for each cohort as follows: Uncommon mutation cohort To determine the time on treatment of EGFR-TKIs as first or second line therapy in NSCLC with uncommon Epidermal Growth Factor Receptor (EGFR) mutations. Time on treatment is defined from the start of EGFR-TKI until the end of EGFR-TKI treatment or death date by any cause. Sequencing cohort: 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. 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 objectives: To determine overall survival and time on treatment until failure of second-line (uncommon mutation cohort only). To determine overall response rate, and describe methodology and the material (liquid vs tissue) used for detection of uncommon/T790M mutation, These endpoints will be analysed descriptively.
Country(-ies) of study:	Up to 11 countries will participate in this study
Author:	[redacted] Tel.: [redacted] Mobil: [redacted] Fax: [redacted] email: [redacted]

Marketing authorisation holder(s):	[redacted]
Date:	20 June 2020
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2. LIST OF ABBREVIATIONS

ACT	Anatomical Therapeutic Chemical
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
CTL	Clinical Trial Leader
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
EHR	Electronic Health Record
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
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 Clinical Trial Leader (CTL), 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, ordering the materials as needed for the study, ensuring appropriate training and information of the internal study team and external Contract Research Organisation (CRO) team members (e.g. 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 signed 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 CRO and 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 Study Master File (Trial Master File, TMF).

A coordinating investigator and a co-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 contracts signed 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 CRO SOPs at each study site. A copy of the ISF documents, as applicable, will also be kept as an electronic TMF at the CRO according to CRO SOPs.

Coordinating investigator:

[redacted]

Co-coordinating investigator:

[redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Gi(l)otrif®			
Name of active ingredient: Afatinib (ATC code: L01XE13), gefitinib (L01XE02), erlotinib (L01XE03), osimertinib (L01XE35), Antineoplastic agents, tyrosine kinase inhibitors			
Protocol date: 31 May 2019	**Study number:** 1200-0316	**Version/Revision:** 3.0	**Version/Revision date:** 20 June 2020
Title of study:	UpSwinG: Real World study on TKI activity in Uncommon mutations and Sequencing Giotrif®		
Rationale and background:	Patients with non-small-cell lung cancer (NSCLC) represent a heterogeneous population; however, increased understanding of the molecular pathogenesis of the disease has allowed for new treatments using molecularly targeted anti-cancer agents. Currently, the most established target is the epidermal growth factor receptor (EGFR) (P15-00464). Four EGFR tyrosine kinase inhibitors (TKIs; erlotinib, gefitinib, afatinib and osimertinib) are currently globally available for the management of NSCLC. The two most common EGFR mutations (in-frame deletion in Exon 19 (Del19) and Point mutation in Exon 21 (L858R) account for >85% of all mutation-positive NSCLC cases and are known to confer sensitivity to EGFR TKIs (P14-02931), whereas the efficacy on uncommon mutation is still debated. Although several EGFR TKIs are available for the treatment of EGFR mutation-positive NSCLC, the development of acquired resistance is inevitable. It is therefore beneficial to consider the optimal sequence of EGFR TKIs in order to maximize their clinical benefit (P18-01208). There are limited real world data with regard to EGFR mutated, advanced NSCLC who are EGFR TKI naïve therefore the aim of this study will be to collect more information on the benefit of		

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	individual EGFR-TKIs treatment for the uncommon mutations and the overall benefit for the sequential EGFR TKI treatment with afatinib and osimertinib for the common EGFR mutations. These findings will allow for evidence-based therapy decision. Uncommon mutation cohort: There is convincing data for afatinib in many uncommon mutations (L861Q, G719X, and S768I) which resulted in regulatory approval by EMA and FDA. However, uncommon mutations are very heterogeneous and more information on the benefit of individual EGFR-TKIs is needed to allow for evidence-based therapy decision. Furthermore, little is known about the benefit of subsequent therapies and OS. Sequencing cohort: It is still unclear which therapy sequence is the most beneficial for patients with EGFR mutated NSCLC. A recent global real-world study (GioTag) provided some insights into the outcomes of patients treated with the sequence afatinib followed by osimertinib. This study enrolled mainly Caucasian patients; study timelines and availability of drugs led to limited enrolment of long-term responders and maturity of time to treatment failure was 52% and 31% for OS. Thus, more data from Asian patients and with meanwhile longer availability of both drugs will provide more robust data with an increased maturity. Various methodologies with different sensitivities can be used for mutational testing. The percentage of patients qualifying for		

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	the sequence afatinib followed by osimertinib patients is depending on the methodology used. Moreover, little is known about the sensitivity of the different techniques for uncommon or compound mutation. Thus, it is of interest to learn more about the methods that have been used to identify uncommon mutation (including T790M).		
Research question and objectives:	Data from real-world setting would inform on the beneficial treatments in patients diagnosed with advanced NSCLC harbouring uncommon EGFR mutations and on the treatment sequence in patients diagnosed with advanced common EGFR mutation NSCLC. Primary objective: For both cohorts the study aims to describe the time on treatment until its end or death. More specifically, this will be evaluated for each cohort as follows: Uncommon mutation cohort: To determine the time on treatment of EGFR-TKIs as first or second line therapy in NSCLC with uncommon Epidermal Growth Factor Receptor (EGFR) mutations. Time on treatment is defined from the start of EGFR-TKI until the end of EGFR-TKI		

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	treatment or death date by any cause. Sequencing cohort: 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. 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 objectives: To determine the overall response rate, and overall survival. To describe methodology and the material (liquid vs tissue) used for detection of uncommon/T790M mutation. To determine time on treatment until failure of second-line (uncommon mutation cohort only).		
Study design:	Non-interventional, multi-country, multi-centre study based on existing data from medical records or electronic health records		
Population:	Site selection: Sites with access to paper / electronic medical charts/EHR that have treated patients according to		

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	Inclusion criteria: 1. Adult patients 2. diagnosed with EGFR-TKI naïve advanced EGFR mutated NSCLC, 3. being treated for EGFR mutated NSCLC within regular clinical practice. 4. Informed and privacy consent signature must be obtained depending on local regulations. More specific inclusion criteria for each cohort are the following: Uncommon mutation cohort: 5. Patients harbouring uncommon or compound EGFR mutations 6. Patients who started with either afatinib (Gi(l)otrif®), gefitinib (Iressa), erlotinib (Tarceva), or osimertinib (Tagrisso) in the first- or second-line setting within regular clinical practice 7. Patients must have started EGFR-TKI treatment at least 12 months prior to data entry.		

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	Sequencing cohort: 5. Patients with common EGFR mutations (Del19, L858R) 6. Patients were treated with afatinib (Gi(l)otrif®) in the first-line setting and for acquired T790M mutation with osimertinib in the second line; 7. Patients must have started osimertinib treatment at least 10 months prior to data entry. Patients treated with osimertinib within an EAP/CUP are allowed Main exclusion criteria: 1. Patients treated for EGFR mutated NSCLC within a clinical trial or participated in GioTag study. 2. Patients with active brain metastases at start of EGFR-TKI therapy 3. For uncommon mutation cohort: Patients treated with osimertinib with no further uncommon mutation than acquired T790M		
Variables:	Primary Outcome(s):		

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	Time on treatment with EGFR-TKI(s) Secondary outcomes: Overall survival, ORR, methodology and material used for mutational testing. Uncommon cohort only: time on treatment until failure of second line (TTF2),		
Safety criteria:	Drug exposure during pregnancy, ADRs with causality to Gi(l)otrif (serious or non-serious) and all fatal AEs will be reported to PV on the NIS AE form/Pregnancy Monitoring Form - excluding deaths to PD of the underlying malignancy. Safety data will be reviewed and analysed as part of routine global pharmacovigilance procedures. All adverse events/reactions collected for the study per protocol will be summarised in the final study report.		
Data sources:	Non-interventional study (NIS) based on existing data from medical records/EHR of patients.		
Study size:	Total enrolled: at least 200 patients in the sequencing cohort and approximately 250 patients in the uncommon cohort		
Data analysis:	Time on treatment and overall survival will be analysed using Kaplan-Meier method, and the median along with two-sided 95% confidence interval will be displayed.		
Milestones:	• Start of data collection in December 2019		

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	• The end of data collection is determined by the sufficient number of patients enrolled and pertinent data entered in eDC. • Interim report: According to patients data availability the possibility to perform an Interim Analysis by the end of 2020 will be considered. • Final report of study results expected in 2021		

5. AMENDMENTS AND UPDATES

Number of global amendment		1
Date of protocol revision		23 July 2019
EudraCT number		Not applicable
BI Study number		1200-0316
BI Active substance		afatinib
Title of protocol		UpSwinG: Real World study on TKI activity in Uncommon mutations and Sequencing Giotrif®
Section to be changed		4.
Description of change		The numbering of the inclusion criteria was corrected: Sequencing cohort: ~~6.~~ **5.** Patients with common EGFR mutations (Del19, L858R) ~~7.~~ **6.** Patients were treated with afatinib (Gi(l)otrif®) in the first-line setting and for acquired T790M mutation with osimertinib in the second line; ~~8.~~ **7.** Patients must have started osimertinib treatment at least 10 months prior to data entry. ~~9.~~ Patients treated with osimertinib within an EAP/CUP are allowed
Rationale for change		Numbering of inclusion criterion was incorrect.
Section to be changed		4.
Description of change		One exclusion criterion was added for the uncommon mutations cohort: **3. For uncommon mutation cohort: Patients treated with osimertinib with no further uncommon mutation than acquired T790M.**
Rationale for change		Given the robust evidence for osimertinib in acquired T790M from randomized controlled trial AURA-3, no further data on EGFR-TKI effectiveness in this indication is needed and respective patients should not be included in this study.
Section to be changed		9.2.1
Description of change		The numbering of the inclusion criteria was

Number of global amendment		1
		corrected: Uncommon mutation cohort: ~~6.~~ 5. Patients harbouring uncommon or compound EGFR mutations ~~7.~~ 6. Patients who started with either afatinib (Gi(l)otrif®), gefitinib (Iressa), erlotinib (Tarceva), or osimertinib (Tagrisso) in the first- or second-line setting within regular clinical practice ~~8.~~ 7. Patients must have started EGFR-TKI treatment at least 12 months prior to data entry. Sequencing cohort: ~~6.~~ **5.** Patients with common EGFR mutations (Del19, L858R) ~~7.~~ **6.** Patients were treated with afatinib (Gi(l)otrif®) in the first-line setting and for acquired T790M mutation with osimertinib in the second line; ~~8.~~ **7.** Patients must have started osimertinib treatment at least 10 months prior to data entry. ~~9.~~ Patients treated with osimertinib within an early access program/compassionate use program are allowed
Rationale for change		Numbering of inclusion criterion was incorrect.
Section to be changed		9.2.1
Description of change		One exclusion criterion was added for the uncommon mutations cohort: **3. For uncommon mutation cohort: Patients treated with osimertinib with no further uncommon mutation than acquired T790M.**
Rationale for change		Given the robust evidence for osimertinib in acquired T790M from randomized controlled trial AURA-3, no further data on EGFR-TKI effectiveness in this indication is needed and respective patients should not be included in this study.
		2

Number of Global amendment		2
Date of protocol revision		20 June 2020
EudraCT number		Not Applicable
BI Study number		1200-0316
BI Active substance		afatinib
Title of protocol		UpSwinG: Real World study on TKI activity in Uncommon mutations and Sequencing Giotrif®
Section to be changed		**EU PASS**
Description of change		Information regarding EU PASS are updated
Rationale for change		EU Pass registration was completed and new information are now available
Section to be changed		**Safety criteria**
Description of change		The language has been changed to the following: Drug exposure during pregnancy, ADRs with causality to Gi(l)otrif (serious or non-serious) and all fatal AEs will be reported to PV on the NIS AE form/Pregnancy Monitoring Form - excluding deaths to PD of the underlying malignancy. Safety data will be reviewed and analysed as part of routine global pharmacovigilance procedures. All adverse events/reactions collected for the study per protocol will be summarised in the final study report.
Rationale for change		It is planned to summarize all adverse events/reactions collected for the study per protocol in the final study report as requested by health authorities.
Section to be changed		**Milestones**
Description of change		Study milestnes are updated
Rationale for change		Due to the unforeseen COVID-19 outbreak, milestones needed to be adjusted
Section to be changed		4.
Description of change		Study size in the uncommon cohort is

		increased from 200 to approximately 250 patients
Rationale for change		Sample size increased due to new feasibility data
Section to be changed		7.
Description of change		Sample size for the uncommon cohort was in creased from 200 patients to about 250 patients.
Rationale for change		Sample size increased due to new feasibility data
Section to be changed		9.1
Description of change		Number of eligible patients in the uncommon cohort is increased from 200 to approximately 250 patients
Rationale for change		Sample size increased due to new feasibility data
Section to be changed		9.2
Description of change		• Number of eligible patients in the uncommon cohort is increased from 200 to approximately 250 patients • "and Cohort" is added to thie section to read as the following "To avoid differential centre influence on study results, permission to enrol more than 15 patients per site and cohort must be obtained from the CTL."
Rationale for change		• Sample size increased due to new feasibility data • The previous language was not clear enough. Thus, a clarification is added.
Section to be changed		9.2.1
Description of change		"adverse drug reactions (ADRs)" is deleted from the section to read as the following: "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 (P17-01960) to avoid early censoring and enable collection of mature data on treatment duration.".
Rationale for change		An error in the previous protocol version is correct

Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		9.5
Description of change		Smaple size in the uncommon cohort was increased to approximately 250 patients. Number of patients with frequent uncommon mutations was increased from 90 to 110. Number of patients with exon20 insertions was increased from 60 to 70. Number of patients with compound mutations was increased from 25 to 35.
Rationale for change		Sample size increased due to new feasibility data
Section to be changed		9.7
Description of change		This sentence was deleted: There is no intention to collect and/or analyse safety data in this non-interventional study (NIS) based on existing data The following language is added: All adverse events/reactions collected for the study per protocol will be summarised in the final study report.
Rationale for change		It is planned to summarize all adverse events/reactions collected for the study per protocol in the final study report as requested by health authorities
Section to be changed		11.2
Description of change		This sentence was deleted:

		There is no intention to collect and/or analyse safety data in this non-interventional study (NIS) based on existing data The following language is added: All adverse events/reactions collected for the study per protocol will be summarised in the final study report.
Rationale for change		It is planned to summarize all adverse events/reactions collected for the study per protocol in the final study report as requested by health authorities

6. MILESTONES

Milestone	Planned Date
Start of data collection	December 2019
End of data collection	The end of data collection is determined by the sufficient number of patients enrolled and pertinent data entered in eDC.
Registration in the EU PAS register	October 2019
Interim report	According to patients data availability the possibility to perform an Interim Analysis by the end of 2020 will be considered.
Final report of study results	2021

7. RATIONALE AND BACKGROUND

Patients with non-small-cell lung cancer (NSCLC) represent a heterogeneous population; however, increased understanding of the molecular pathogenesis of the disease has allowed for new treatments using molecularly targeted anti-cancer agents. Currently, the most established target is the epidermal growth factor receptor (EGFR) (P15-00464). Four EGFR tyrosine kinase inhibitors (TKIs; erlotinib, gefitinib, afatinib and osimertinib) are currently globally available for the management of NSCLC.
The two most common EGFR mutations (in-frame deletion in Exon 19 (Del19) and Point mutation in Exon 21 (L858R)) account for >85% of all mutation-positive NSCLC cases and are known to confer sensitivity to EGFR TKIs (P14-02931), whereas the efficacy on uncommon mutation is still debated.

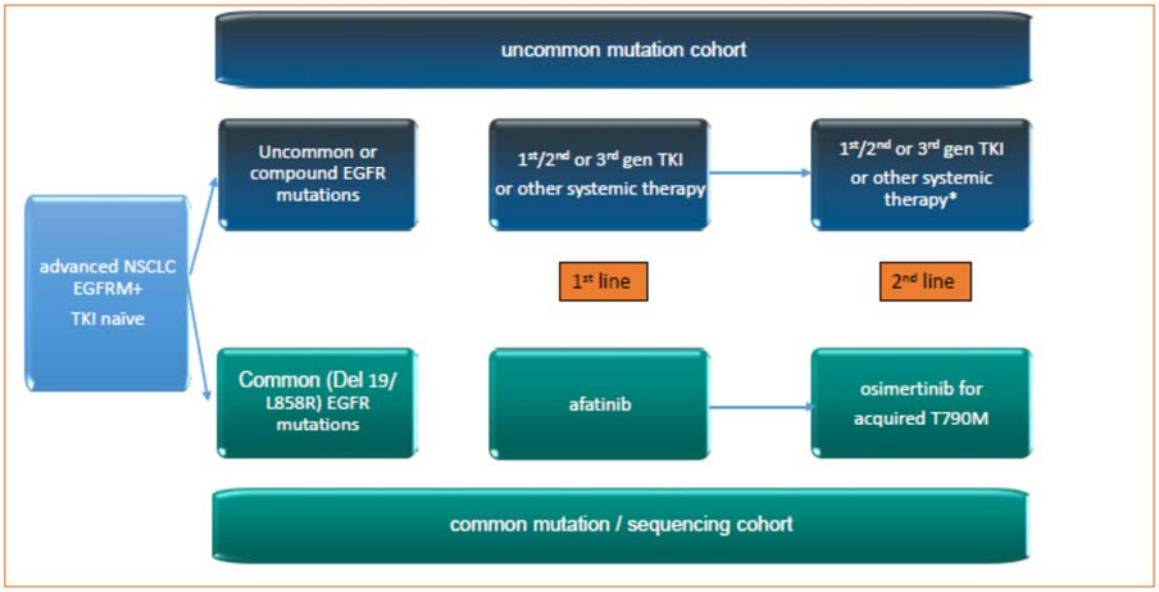
Although several EGFR TKIs are available for the treatment of EGFR mutation-positive NSCLC, the development of acquired resistance is inevitable. It is therefore beneficial to consider the optimal sequence of EGFR TKIs in order to maximize their clinical benefit (P18-01208)

There are limited real world data with regard to EGFR mutated, advanced NSCLC who are EGFR TKI naïve therefore the aim of this study will be to collect more information on the benefit of individual EGFR-TKIs treatment for the uncommon mutations and the overall benefit for the sequential EGFR TKI treatment with afatinib and osimertinib for the common EGFR mutations. These findings will allow for evidence-based therapy decision.

This global Real-World non-interventional, multi-country, multi-centre study will be collecting pre-existing data from medical records for the patient population: EGFR mutated, advanced NSCLC who are EGFR TKI naïve, in the following two cohorts:

1- **Uncommon mutation cohort**
Patient with uncommon EGFR mutations who started EGFR TKI (afatinib, gefinitib, erlotinib, osimertinib) in first or second line and with treatment initiated at least 12 months prior to data entry. About 250 eligible patients are planned to be enrolled.

2- **Sequencing cohort**
Patient with common EGFR mutations who started osimertinib in second line for acquired T790M at least 10 months prior to data entry. As first-line patients underwent afatinib. About 200 eligible patients are planned to be enrolled.



*Patient must have been treated with EGFR-TKI in either 1st or 2nd line, 2nd line treatment after 1st line EGFR-TKI is not mandatory.

Figure 7:1 Overview of the two cohorts

7.1 UNCOMMON MUTATION COHORT

In a retrospective analysis of 1632 patients with stage IIIB-IV NSCLC, uncommon mutations occurred in ~16% of EGFRm+ NSCLC cases: exon 20 insertions (9%), uncommon mutations with Del19 or L858R complex mutations (30%) [Del19 + 18G721D; Del19 + 19L732P; Del19+ 20L792P; Del19+ 20S768I + 20V774M; Del19 + 21L858R + 21K860I; 21L858R + 18E709X; 21L858R + 20S768I; 21L858R + 20V786E; 21L858R + 20T790M; 21L858R + 20 insertion; 21L858R + 21L833Vl 21L858R + 21K860I; 21L858R + 18G719X +20 insertion]; uncommon mutation alone or in combination with other uncommon mutations (61%) [18I715V; 18K716E; 18V717G; 18G719X; 19L747P; 19 insertion; 20A763_Y764 insFQEA; 20S768I; 20G779F; 21L861Q; 18G719X + 21L861Q; 18E709X + 18G719X; 18G719X + 20S768I; 20T790M + 21L861Q; 21M825L +21R831C; 18V703L + 18L707W +18G719X; 18E709X + 18T710S + 18G719X; 19V742F + 19A743 V + 20H773R] (P17-07438).

Recent improvements in detection methods have indicated that ‘uncommon’ EGFR mutations are more prevalent than previously thought. According to the catalogue of somatic mutations in cancer (COSMIC) database, in 2016, 594 types of EGFR mutation had been reported [P16-09907]. Categories of uncommon mutation include insertions in exon 19 (Ins19; 0.6% of all EGFR mutations) or 20 (Ins20; ~6%), as well as point mutations in exon 18 at position G719 (G719X; ~3%), exon 21 L861Q mutations (~1%) and exon 20 S768I mutations (~1% of EGFR mutations) [P16-09907]. In addition, it is becoming increasingly clear that some patients with EGFR mutation-positive NSCLC have tumors that harbor more than one type of EGFR mutation, predominantly in cis, in other words, within the same EGFR allele (so-called ‘compound’ mutations).(P19-02454, P18-10855).

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). On January 12, 2018, FDA granted approval to afatinib for a broadened indication in first-line treatment of patients with metastatic NSCLC whose tumours have non-resistant EGFR mutations as detected by an FDA-approved test (P19-04170). Approval was based on demonstration of durable responses in a subset of 32 afatinib-treated patients with metastatic NSCLC harbouring non-resistant EGFR mutations (S768I, L861Q, and/or G719X) other than exon 19 deletions or exon 21 L858R substitutions enrolled in one of three clinical trials (LUX-Lung 2 [NCT00525148], LUX-Lung 3 [NCT00949650], and LUX-Lung 6 [NCT01121393]). The confirmed overall response rate, as assessed by independent radiology review, was 66% (95% confidence interval 47, 81). Among the 21 responders, the proportion of patients with response duration of ≥12 months was 52% and the proportion with response durations of ≥18 months was 33%. Clinical benefit was lower in patients with de-novo Thr790Met and exon 20 insertion mutations. (P15-05932)

Gefitinib (IRESSA®) and erlotinib (Tarceva®) are first generation EGFR-TKIs and approved by EMA as monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK. FDA label is restricted to common mutations (Del19 and L858R).

Anecdotal data from erlotinib/gefitinib trials show variable and mainly limited responses to EGFR TKIs in a multitude of other EGFR mutations, eg, in Exons 18-21 or a combination of ≥2 EGFR mutations (P16-09907) Post-hoc analyses from the NEJ002 study comparing gefitinib with chemotherapy showed that patients with uncommon EGFR mutations had a significantly shorter OS (11.9 versus 29.3 months; $p < 0.001$). By contrast, OS was similar for uncommon mutations and common mutations in the CarboPac group (n = 111; 22.8 versus 28 months; $p = 0.358$)(R19-1656).

Osimertinib (Tagrisso®) is approved by EMA for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations, and for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. The FDA label restricts osimertinib in first line to common EGFR mutations. Data from a Korean phase 2 IIS showed benefit for osimertinib in 36 patients with G719A/C/D/S/X L861Q , S768I, and four other mutations. The overall response rate was 50.0% (95% CI 32.8-67.2) and DCR was 88.9% (95% CI 78.1-99.7) (R19-1672).

Given the robust evidence for osimertinib in acquired T790M from randomized controlled trial (AURA-3) (P17-01960), no further data on EGFR-TKI effectiveness in this indication is needed.

Dacomitinib (Vizimpro) is not approved outside common mutations and will therefore not be analysed.

The heterogeneity of EGFR mutations in EGFR mutation-positive NSCLC has potential clinical implications because different EGFR-targeted TKIs can have different activities against specific mutations. Therefore, treatment with EGFR TKIs that have limited efficacy against certain mutations may drive the clonal expansion of those insensitive mutations. A recent preclinical study assessed the activity of different EGFR-directed TKIs against

uncommon EGFR variants of unknown significance. By utilizing a high-throughput functional assay in Ba/F3 cells, Kohsaka et al. evaluated the sensitivity of over a hundred different variants of unknown significance, including compound mutations (P18-10855). Interestingly, afatinib showed activity against almost all mutations tested and, in many cases, was more potent than erlotinib and gefitinib. Afatinib also showed a broader spectrum of activity against uncommon EGFR variants compared with osimertinib, although, as expected, afatinib was less effective against T790M than osimertinib (P18-10855).

Various methodologies with different sensitivities can be used for detection of EGFR mutation. Little is known about the sensitivity for uncommon or compound mutation. Thus, it is of interest to learn more about the methods that have been used to identify patients harbouring tumours with uncommon mutations (R19-1655).

In summary, there seems to be only limited efficacy of first generation EGFR-TKI, and limited data on osimertinib who has furthermore only recently been approved for first line. In many countries, the labels for these drugs are restricted to common mutations, whereas afatinib's efficacy has been confirmed in clinical trials and being acknowledged by regulatory authorities. Given this, the uncommon mutation cohort should enrol at least 50% of patients who were treated with afatinib. Furthermore, as patients with EGFR mutations should be treated in first-line as recommended by NCCN and ESMO guidelines, at least 50% of enrolled patients should have been treated in first line.

Thus, more information on the benefit of individual EGFR-TKIs on individual uncommon mutations is needed to allow for evidence-based therapy decision. Furthermore, more information is needed on outcome with other systemic therapy and OS.

7.2 SEQUENCING COHORT

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 more than 80 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(P19-03125).

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 the FLAURA trial. Osimertinib significantly prolonged PFS compared to first generation TKIs (erlotinib or gefitinib). Median PFS by independent review was 17.7 months in patients with common mutations (R18-0130).Overall survival data are still immature and so far, only 29% of the patients treated first-line with osimertinib received a subsequent therapy. Furthermore, as more than 60% have no putative resistance mechanism and even those identified are not druggable with approved targeted therapies, the best sequencing strategy is still under discussion.

A recent global real-world study (GioTag) recruited from December 2017 to May 2018 and provided insights into the outcomes of patients treated with the sequence afatinib followed by osimertinib. Time on treatment for the sequence was 27.6 months and 2 year survival rate being 79% (P18-09968). This study enrolled mainly Caucasian patients (59%) and 63% of the patients came from USA, although incidence of EGFR mutated NSCLC is much higher in Asian countries (R19-1657). Study timelines and availability of drugs led to limited enrolment of long-term responders (10-12% of patients treated with afatinib are for 3 years and longer on drug) (P19-03124) and maturity of time to treatment failure was 52% and 31% for OS. Thus, more data from Asian patients and with meanwhile longer availability of both drugs will provide data that are more robust with an increased maturity. At least 60% of enrolled patients should have Asian ethnicity.

Various methodologies with different sensitivities can be used for T790M detection. Recently, it could be shown that in patients who progressed under treatment with an EGFR TKI, the T790M positivity rate was 66% using ddPCR, but only 24% using Cobas (P19-03686). Thus, it is of interest to learn more about the methods that have been used to identify patients qualifying for the sequence afatinib followed by osimertinib.

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 beneficial treatments in patients diagnosed with advanced NSCLC harbouring uncommon EGFR mutations and on the treatment sequence in patients diagnosed with advanced common EGFR mutation NSCLC.

Primary objective:

For both cohorts the study aims to describe the time on treatment until its end or death.

More specifically, this will be evaluated for each cohort as follows:

Uncommon mutation cohort:

To determine the time on treatment of EGFR-TKIs as first or second line therapy in NSCLC with uncommon Epidermal Growth Factor Receptor (EGFR) mutations. Time on treatment is defined from the start of EGFR-TKI until the end of EGFR-TKI treatment or death date by any cause.

Sequencing Cohort:
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. 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 objectives:

To determine the overall response rate, and overall survival. To describe the methodology and material (liquid vs tissue) used for detection of uncommon/T790M mutation. Uncommon mutation cohort only: To determine the time on treatment until the end of the second-line treatment.

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 (paper or electronic) or electronic health records of patients with advanced NSCLC harbouring EGFR mutations and treated with an EGFR-TKI.

In total, at least 200 eligible patients in the sequencing cohort and approximately 250 eligible patients in the uncommon cohort.

Key study outcome:
Time on treatment with EGFR-TKI(s)

The study will involve secondary use of data.
Since the collected data include also genetic data, the appropriate strategies to ensure data protection (such as strong authentication) will be implemented in the eCRF employed for data collection.

9.2 SETTING

It is planned that around 65 study centres in up to 11 countries will be participating in this non-interventional study and at least 200 consecutive eligible patients in the sequencing cohort and approximately 250 patients in the uncommon cohortfrom up to 80 sites will be enrolled to the study. Data extraction from local data bases might be used when possible. 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. 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 and cohorts must be obtained from the CTL.

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 with access to paper/electronic medical charts/electronic health record (EHR) that have treated patients according to inclusion criteria:

1. Adult patients
2. diagnosed with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI) naïve advanced EGFR mutated non-small cell lung cancer (NSCLC),
3. treated for Epidermal Growth Factor Receptor (EGFR) mutated NSCLC within regular clinical practice.
4. Informed and privacy consent signature must be obtained depending on local regulations.

More specific inclusion criteria for each cohort are the following:

Uncommon mutation cohort:

5. Patients harbouring uncommon or compound EGFR mutations
6. Patients who started with either afatinib (Gi(l)otrif®), gefitinib (Iressa), erlotinib (Tarceva), or osimertinib (Tagrisso) in the first- or second-line setting within regular clinical practice
7. Patients must have started EGFR-TKI treatment at least 12 months prior to data entry.

Sequencing cohort:

5. Patients with common EGFR mutations (Del19, L858R)
6. Patients were treated with afatinib (Gi(l)otrif®) in the first-line setting and for acquired T790M mutation with osimertinib in the second line;
7. Patients must have started osimertinib treatment at least 10 months prior to data entry.

   Patients treated with osimertinib within an early access program/ compassionate use program (EAP/CUP) are allowed

Main exclusion criteria:

1. Patients treated for EGFR mutated NSCLC within a clinical trial or participated in GioTag study.
2. Patients with active brain metastases at start of EGFR-TKI therapy (independent of treatment line)
3. For uncommon mutation cohort: Patients treated with osimertinib with no further uncommon mutation than acquired T790M

Deceased patients fulfilling the eligibility criteria should be enrolled whenever possible.

Uncommon mutation cohort: Patients treated with EGFR-TKI in interventional trials are excluded to ensure the non-interventional setting of this study. The threshold of start of treatment at least 12 months respectively prior to data entry was chosen based on the median PFS reported for patients being treated with afatinib in the LUX-Lung 2, -3, -and 6 trials (P15-05932) 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.

Sequencing cohort: 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 (P17-01960) to avoid early censoring and enable collection of mature data on 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 (where applicable)
- Demographics: age at start of first-line treatment, gender, ethnicity
- Stage of disease (IIIb or IV) at start of first-line treatment
- Type of mutations at initial diagnosis
- Methodology used for mutation testing
- Sites of metastases at start of treatment
- Body weight and height at start of treatment
- Eastern Cooperative Oncology Group (ECOG) performance score (PS) (if available) at start of treatment
- Date of start and end of first-line treatment
- First-line treatment administered
- Starting dose of EGFR-TKI (first-or second-line)
- Dose modification(s) and date(s) of EGFR-TKI
- ECOG PS (if available) at start of second-line treatment
- Type of mutations at start of second-line treatment
- Methodology (allele-specific, NGS, sequencing) and material (tissue/liquid biopsy) used for mutational testing
- Sites of metastases at start of second-line treatment
- Date of start and end of second-line treatment
- Second-line treatment administered

- Reason for discontinuation of each treatment (e.g. progressive disease (PD), adverse event (AE))
- Best response to first and second-line treatment (as documented)
- Date of death
- Bevacizumab use with TKI (Yes/No)

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®).

Erlotinib (Tarceva®):
Patients were treated with erlotinib (Tarceva®) 25mg or 100mg or 150mg tablet once daily as indicated in the approved labels of erlotinib (Tarceva®).

Gefitinib (IRESSA®):
Patients were treated with gefitinib (IRESSA®): 250mg tablet once daily as indicated in the approved labels of gefitinib (IRESSA®):

Osimertinib (Tagrisso®):
Patients were/are treated with osimertinib 80 mg or 40 mg tablets once daily as indicated in the approved labels of osimertinib.

The Summaries of Product Characteristics on afatinib, erlotinib, gefitinib and osimertinib are contained in the ISF.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Time on treatment with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI). This will be assessed as the time from start of EGFR-TKI treatment until the end of treatment or death date by any cause. In the sequencing cohort it 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.

Secondary outcomes
Overall response rate, overall survival, time on treatment until failure of second-line (TTF2, uncommon mutation cohort only), and subsequent therapies used. Methodology and material used for mutational testing.

[redacted]

9.3.3 Covariates

NA

9.4 DATA SOURCES

Data will be collected from patients' medical records and recorded in eCRFs or will be captured from electronic health records (EHR).

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 eCRFs 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

Uncommon mutation cohort:

In LUX-Lung trials (1200.22, 1200.32, 1200.34), EAP (1200.45, 1200.55, 1200.66, 1200.193) and NIS (1200.205), 267 TKI-naïve patients were treated for uncommon mutations.

- 46% had one of the more frequent afatinib-sensitive uncommon mutation (G719X, L861Q, or S768I),
- 29% had an insertion in exon 20,
- 12% had a de novo T790M,
- 13% had a complex or compound mutation, and
- 10% had other uncommon mutations.

For the current study, a sample size of about 250 is mainly driven by feasibility. We expect that this will result in approximately

- 110 patients with frequent uncommon mutations,
- 70 patients with exon20 insertions, and
- 35 patients with compound mutations.

Given the label (and availability) for first and third generation TKIs, we assume that the majority of patients with these uncommon mutations will have been treated with afatinib. At least 50% of enrolled patients must have been treated with afatinib. At least 50% must have been treated with an EGFR-TKI in first-line (see rationale).

Comparison of the different TKIs will be limited to descriptive statistics because of the limited numbers of patients expected to have been treated with TKI other than afatinib.

Sequencing cohort:

Based on previous data from the GioTag study and expecting a higher proportion of Asian patients, the median time on treatment from start of the first-line treatment until the end of the second-line treatment is projected to be 30 months.

Table 9.5:1 shows the expected (50^{th} percentile) width of the 95% confidence interval to be 13.7 months, with an 80% chance of observing a confidence interval of less than 16.2 months. This is based upon 200 patients with 10 percent random censoring. The width of the confidence interval would increase if the rate of censoring were higher.

Table 9.5:1 95% confidence interval width for median duration of treatment with 200 patients, 30 month underlying median duration, and increasing random censoring[1]

95% CI width

	10% censoring	20% censoring	30% censoring
50th percentile	13.7 months	15.9 months	18.8 months
80th percentile	16.2 months	18.9 months	22.5 months

[1]Calculated by simulation with 10,000 iterations

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

The two cohorts will be analysed separately

- Uncommon mutations
- Sequencing of osimertinib after afatinib

The primary endpoint for both cohorts is time on treatment. Kaplan-Meier estimates will be calculated. In addition, the median will be tabulated along with the two-sided 95% confidence interval, using Greenwood's variance estimate.

[redacted]

The following additional endpoints will be analyzed similarly to the primary endpoint.

- overall survival
- time on treatment until failure of second-line (uncommon cohort only)

Patients who were not known to have discontinued treatment will be censored on the date they were last verified to have been on treatment.

A second round of data collection for additional follow-up may be performed in case a substantial proportion of patients had not discontinued treatment before the estimated median time on treatment at the time of the primary data collection.

[redacted]

Best overall response will be tabulated, as will the following:

- demographics
- disease characteristics
- methodology and material used for mutation classification
- anti-cancer drugs used prior to, or after EGFR-TKI (uncommon cohort only).

These endpoints will be analyzed descriptively.

Within the sequencing cohort, the proportion of patients with different types of resistance mutations observed at the time of discontinuation of osimertinib will be categorized and tabulated.

In this study, data will be gathered retrospectively from patients treated within the conditions of the approved marketing authorization of afatinib. Drug exposure during pregnancy, ADRs with causality to Gilotrif (serious or non-serious) and all fatal AEs will be reported to PV on the NIS AE form - excluding deaths to PD of the underlying malignancy. Safety data will be reviewed and analysed as part routine global pharmacovigilance procedures. All adverse events/reactions collected for the study per protocol will be summarised in the final study report.

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.

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:
In general, having a clearer focus on Asian countries reflects the higher incidence of EGFR mutations in this group.
1. a) Uncommon mutation cohort: There are no limitations coming from the site selection.

1. b) Sequencing cohort: 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 2 to 3 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.

2. Patient population:
2. a) Uncommon mutation cohort: Firstly, there is a bias as only patients that were tested for uncommon mutations and were treated with an EGFR-TKI could be enrolled into this NIS. Because of that bias, the results of the study will not be generalizable to all patients harbouring an uncommon mutation.

This study has no comparator group limiting the interpretability of the results as they cannot be put into perspective. The planned analyses by EGFR-TKI used includes no formal testing for statistical significance.

2. b) Sequencing cohort:
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 still 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 has only been approved recently and most patients that were prescribed with osimertinib are still on first-line treatment.

3. Retrospective data collection:
Other limitations are due to the retrospective nature of the study, which might lead to inconsistent or missing data.
Moreover, some endpoints, such as overall survival, could be not achievable as the retrospective window could be too narrow to catch events and most of patients would be censored.

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

Selection 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. Furthermore, with at least 60% Asian patients to be enrolled, the study population will reflect the higher incidence of EGFR mutation in Asian population.

Sequencing cohort: To overcome feasibility limitation driven by availability of osimertinib, patients who have received osimertinib treatment within an EAP/CUP are eligible, increasing the pool of eligible sites and potential patients.
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®).

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.

Immortal bias:
Sequencing cohort: 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.

Bias through drug availability:
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.

Testing bias:
Only patients that were tested for uncommon / T790M mutations and were treated with an EGFR-TKI /osimertinib in second line could be enrolled into this NIS. Because of that bias, the results of the study will not be generalizable to all patients harbouring an uncommon mutation or being treated with afatinib in first line.

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 CRO and BI SOPs and, for Japan, 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 and, for Japan, 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 give 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 (e.g. 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 Adverse Event of Special Interest (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

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.

Drug exposure during pregnancy, ADRs with causality to Gi(l)otrif (serious or non-serious) and all fatal AEs will be reported to PV on the NIS AE form/Pregnancy Monitoring Form - excluding deaths to PD of the underlying malignancy. Safety data will be reviewed and analysed as part routine global pharmacovigilance procedures. All adverse events/reactions collected for the study per protocol will be summarised in the final study report.

The following must be reported on the NIS AE Form and/or Pregnancy Monitoring Form for Studies in case such AE/drug exposure during pregnancy information is identified in the course of the review of the individual records:

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®) *Exemption applies	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.
The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Exemption

*Death due to disease progression of the underlying malignancy is a study endpoint and the natural course of the disease. As such it is exempted from reporting as an SAE. Progression of the subject's underlying malignancy will be recorded on the appropriate pages of the eCRF only and will not be reported on the NIS AE Form.
However, when there is evidence suggesting a causal relationship between Gi(l)otrif and the progression of the underlying malignancy, the event must be reported as an SAE on the NIS AE Form and on the eCRF.

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 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.

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.

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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 Study Master File (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 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
UpSwinG: Real World study on TKI activity in Uncommon mutations and Sequencing Giotrif®

EU PAS Register® number:
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.
Study reference number (if applicable): BI 1200-0316

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 Progress report(s)	☐	☒	☐	NA
1.1.4 Interim 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.

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An agency of the European Union

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
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: These items are not applicable to 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, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1 and 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☒	☐	NA
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	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.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9

Section 4: Source and study populations	Yes	No	N/A	Section Number
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 categorised according to time windows?	☒	☐	☐	9
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	NA
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	NA

Comments:

Item 5.5 and 5.6: The exposure is not categorized based on biological mechanism of action and there is no comparator in this study.

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, use of validation sub-study)	☐	☐	☒	NA

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

Comments:

Item 6.3: The data related to study outcomes 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 address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.12
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.12
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.12

Comments:

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Section 8: Effect measure 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)	☐	☒	☐	NA

Comments:

Item 8.1: No effect modifiers are 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
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
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
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)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
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), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	NA
9.3.3 Covariates and other characteristics?	☐	☐	☒	NA
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	NA

Comments:

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 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.7
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	NA
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	N.A.
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Item 10.4: No stratified analysis is planned for this study. Item 10.5: The study is descriptive in nature with no treatment comparisons. Therefore the issue of confounding is not relevant.

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

Comments:

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

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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 uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.1 and 9.2

Comments:

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

Section 13: Ethical/data protection 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:

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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:

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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:

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Name of the main author of the protocol: [redacted]

Date: 21/May/2019 [redacted]

Signature: _____

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

APPROVAL / SIGNATURE PAGE

Document Number: c28110847 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03

Title: UpSwinG: Real World study on TKI activity in Uncommon mutations and Sequencing Giotrif

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine	[redacted]	21 Jul 2020 16:30 CEST
Approval [redacted] Safety Evaluation Therapeutic Area		21 Jul 2020 16:36 CEST
Approval [redacted] of Global Epidemiology		21 Jul 2020 17:10 CEST
Verification-Paper Signature Completion		24 Jul 2020 15:12 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed