Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	c09038525-01
BI Study Number:	1200.270
BI Investigational Product:	Gi(l)otrif® (afatinib)
Title:	RealGiDo: Real-world data on Gi(l)otrif® dose adjustment in first-line treatment, TKI-naïve, advanced non-small cell lung cancer patients with EGFR activating mutations
Brief lay title:	Real World Data on Gi(l)otrif® dose adjustment
Protocol version identifier:	1.0
Date of last version of protocol:	01 March 2016
PASS:	No
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.
Active substance:	afatinib Antineoplastic agents, tyrosine kinase inhibitors ATC code: L01XE13
Medicinal product:	Gi(l)otrif® 50mg, 40mg, 30mg, 20mg tablet
Product reference:	20mg: EU/1/13/879/001, EU/1/13/879/002, EU/1/13/879/003 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
Procedure number:	EMEA/H/C/002280
Joint PASS:	No
Research question and objectives:	Primary objective: To assess the effects of Gi(l)otrif® dose modification on the frequency and severity of adverse drug reactions, time on treatment and time to progression with Gi(l)otrif® in real-world setting and compare with data from Lux-Lung 3 trial in a descriptive manner. Secondary objective: To obtain information on frequency and reasons for a modified starting dose of Gi(l)otrif® in real-world setting

Countries of study:	Austria, Canada, France, Germany, Italy, Japan, Korea, Mexico, Poland, Singapore, Spain, Taiwan, US
Author:	[redacted] Phone: [redacted] Fax: [redacted] E-mail: [redacted]
Marketing authorisation holder:	Boehringer Ingelheim International GmbH Binger Strasse 173 D-55216 Ingelheim am Rhein Germany
Date:	01 March 2016

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ASCO	American Society of Clinical Oncology
AUC	Area under the Curve
BI	Boehringer Ingelheim
CA	Competent Authority
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRO	Clinical Research Organization
eCRF	Electronic Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
Del19	EGFR Exon 19 Deletion
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EGFRm+	Epidermal Growth Factor Receptor Mutation Positive
ErbB	Erythroblastic Leukemia Viral Oncogene Homolog
EU	European Union
FDA	Food Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
ICH GCP	International Conference on Harmonisation guideline for Good Clinical Practice
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
L858R	L858R mutation at EGFR exon 21
LUX-Lung 3	BI Trial No.1200.32
MAH	Marketing Authorization Holder
NIS	Non-Interventional Study
NISed	Non-Interventional Study based on existing data
NSCLC	Non-Small Cell Lung Cancer
OPU	Operative Unit
OS	Overall Survival
PFS	Progression Free Survival
PK	Pharmacokinetics

PRO	Patients Reported Outcome
RDC	Remote Data Capture
RWD	Real World Data
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SD	Standard Deviation
SDV	Source Data Verification
SEAP	Statistical and Epidemiological Analysis Plan
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCM	Trial Clinical Monitor
TKI	Tyrosine Kinase Inhibitor
TMF	Trial Master File

3. RESPONSIBLE PARTIES

Boehringer Ingelheim (BI) has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to

- Manage the study in accordance with applicable regulations and internal standard operating procedures (SOPs),
- Direct the study team in the preparation, conduct, and reporting of the study,
- Ensure appropriate training and information of Local Clinical Monitors (CMLs), Clinical Research Associate (CRAs), and investigators of participating countries.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

The organization of the study in the participating countries will be done by the respective local BI-operative unit (OPU) or by a Contract Research Organization (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the study. In each local BI OPU participating in this study, a CML will be appointed responsible for coordinating the activities required in order to manage the study in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU. On-site monitoring will be performed by BI or a CRO appointed by BI.

An Investigator Site File (ISF) containing all relevant study related documentation will be maintained according to local regulations and BI SOPs at each study site. A copy of the ISF documents will also be kept as an electronic Trial Master File (TMF) at BI according to BI SOPs. Documents related to participating investigators and other important participants, especially their curricula vitae, will be filed in the TMF.

The coordinating investigator who will sign the report of this non-interventional study has been appointed by BI. The coordinating investigator has experience in lung cancer studies.

Co-ordinating investigator:

[redacted]

Phone: [redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Gi(l)otrif®			
Name of active ingredient: afatinib Antineoplastic agents, tyrosine kinase inhibitors ATC code: L01XE13			
Protocol date: 01 March 2016	**Study number:** 1200.270	**Version/Revision:** 1.0	**Version/Revision date:**
Title of study:	RealGiDo: Real-world data on Gi(l)otrif® dose adjustment in first-line treatment, TKI-naïve, advanced non-small cell lung cancer patients with EGFR activating mutations		
Rationale and background:	Post-hoc analyses from LUX-Lung 3 suggest that tolerability-guided dose adjustment of afatinib is an effective measure to reduce treatment-related AEs without affecting therapeutic efficacy. The objective of this non-interventional study (NIS): Real-World Data will help to understand if dose modifications are done similar as in LUX-Lung 3 trial and if the outcome on safety and effectiveness are as in trial settings. Furthermore, data on modified starting doses, the underlying reasons and effects on safety and outcome will be collected.		
Research question and objectives:	Primary objective: To assess the effects of Gi(l)otrif® dose modification on the frequency and severity of adverse drug reactions, time on treatment and time to progression with Gi(l)otrif® in real-world setting and compare with data from LUX-Lung 3 trial in a descriptive manner. Secondary objective: To obtain information on frequency and reasons for a modified starting dose of Gi(l)otrif® in real-world setting.		
Study design:	Non-interventional, multi-country, multi-site study based on existing data from medical records of patients treated with Gi(l)otrif® as part of the routine treatment according to the approved label.		
Population:	Sites in countries with launch dates prior to 1st Jan 2015 and known to prescribe Gi(l)otrif® on a regular basis will be chosen. In/-Exclusion criteria:		

	1. EGFR mutated (common mutations), TKI-naïve advanced NSCLC treated with Gi(l)otrif® as the first-line treatment for NSCLC within the approved label will be included 2. Patients treated within clinical trials are excluded 3. Patients still on treatment with Gi(l)otrif® will be excluded unless treatment period is ≥ 6 months
Variables:	Primary outcomes: Safety outcomes: Percentage of subjects with adverse drug reactions by severity class Effectiveness outcomes: Time on treatment with Gi(l)otrif® Time to progression with Gi(l)otrif®
Data sources:	NIS based on existing data from medical records of patients.
Study size:	At least 200 patients. ≥ 200 patients are planned based on feasibility aspects and assumptions.
Data analysis:	Safety data will be analysed in a descriptive manner. Incidence and severity of adverse drug reactions will be summarized and displayed. For patients who have dose modifications, frequency and severity of the most common AEs pre- and post-dose modification will be summarized and displayed. For effectiveness analysis, both time on treatment and time to progression will be estimated using Kaplan-Meier method, and the median along with two-sided 95% CI will be displayed (use the Greenwood's formula for estimation of standard errors). Log-rank test will be applied to compare between patients with and without dose modifications.
Milestones:	Start of data collection in May 2016 End of data collection in December 2016 Final report of study results expected in March 2017

5. AMENDMENTS AND UPDATES

Not applicable.

6. MILESTONES

Milestone	Planned Date
Registration in the European Union (EU) Post-Authorization Studies (PAS) register	EU PAS register number not yet assigned as the study is not yet registered in the EU PAS Register. The study will be registered shortly before the start of data collection.
Start of data collection	31 May 2016
End of data collection	31 Dec 2016
Final report of study results:	31 Mar 2017

7. RATIONALE AND BACKGROUND

The first marketing approval of afatinib was granted on 12 Jul 2013 in the USA (trade name Gilotrif®) for the indication of first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. It was approved in the European Union 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). [redacted]

The approval of Giotrif® was based on the results observed in the pivotal trial LUX-Lung 3 study. The LUX-Lung 3 study investigated the efficacy of chemotherapy compared with afatinib, a selective, orally bioavailable ErbB family blocker that irreversibly blocks signaling from epidermal growth factor receptor (EGFR/ErbB1), human epidermal growth factor receptor 2 (HER2/ErbB2), and ErbB4 and has wide-spectrum preclinical activity against EGFR mutations. A total of 1,269 patients were screened, and 345 were randomly assigned to treatment (afatinib or chemotherapy). Median progression-free survival (PFS) was 11.1 months for afatinib and 6.9 months for chemotherapy (hazard ratio [HR], 0.58; 95% CI, 0.43 to 0.78; P=.001). Median PFS among those with exon 19 deletions and L858R EGFR mutations (n=308) was 13.6 months for afatinib and 6.9 months for chemotherapy (HR, 0.47; 95% CI, 0.34 to 0.65; P=.001). The most common treatment related adverse events were diarrhea, rash/acne, and stomatitis for afatinib and nausea, fatigue, and decreased appetite for chemotherapy. Patients reported outcomes (PROs) favored afatinib, with better control of cough, dyspnea, and pain (P13-07382).

Afatinib 40 mg/day (oral) is approved for the treatment of patients with advanced EGFRm+ NSCLC. Dose adjustments are recommended based on pre-defined tolerability criteria. A post-hoc analyses of the effects of afatinib dose reduction on adverse events (AEs), pharmacokinetics (PK) and PFS in the phase III LUX-Lung 3 trial showed that dose reductions occurred in 53% (122/229) of patients; the majority (86%) within the first 6 months of treatment. In patients who dose reduced, decreases in the incidences of drug-related all grade (grade ≥ 3) AEs were 99.2% (20.5%) to 46.7% (4.1%) for diarrhea, 88.5% (26.2%) to 38.5% (3.3%) for rash/acne, 77.0% (12.3%) to 27.9% (0%) for stomatitis, and 44.3% (16.4%) to 36.9% (4.9%) for nail effects. Dose reductions tended to be more common in female patients, older patients, patients of Eastern Asian ethnicity, and patients with lower body weight. Dose reduction was more likely in patients with higher plasma concentrations of afatinib. On Day 43, patients who dose reduced to 30 mg ≥ 4 days previously (n=38) had geometric mean plasma afatinib concentrations of 24.4 ng/mL, vs 23.7 ng/mL in patients who remained on the 40 mg dose (n=126). Median PFS was 11.3 months in patients who dose reduced during the first 6 months of treatment, vs 11.0 months in patients who did not (HR=1.25 [95% CI, 0.91–1.72]). [ASCO 2015, Yang et al, # 8073] (P15-05676).

Post-hoc analyses from LUX-Lung 3 suggest that tolerability-guided dose adjustment of afatinib is an effective measure to reduce treatment-related AEs without affecting therapeutic efficacy:

- The frequency and severity of treatment-related AEs was lower following dose reduction
- Tolerability-guided dose modification reduced the inter-patient variability of afatinib exposure, while maintaining efficacious plasma levels
- Efficacy outcomes were similar in patients who dose reduced due to AEs versus those who did not

This real-world data (RWD) study will help to understand if dose modifications are done similar as in LUX-Lung 3 trial and if the outcome on safety and effectiveness are as in trial settings.

8. RESEARCH QUESTION AND OBJECTIVES

Research objective:
Data from real-world will help to understand if dose modifications are done similar as in LUX-Lung 3 trial and if the outcome on safety and effectiveness are as in trial settings. Furthermore, data on modified starting doses, the underlying reasons and effects on safety and outcome are needed.

Primary objective:
To assess the effects of Gi(l)otrif® dose modification on the frequency and severity of adverse drug reactions (ADRs), time on treatment and time to progression with Gi(l)otrif® in real-world setting and compare with data from LUX-Lung 3 trial in a descriptive manner.

Secondary objective:
To obtain information on frequency and reasons for a modified starting dose of Gi(l)otrif® in real-world setting.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional, multi-country, multi-site study based on existing data from medical records of patients treated with Gi(l)otrif® as part of the routine treatment according to the approved label.

Key study outcomes are:

- Effects of Gi(l)otrif® dose reduction on frequency of ADRs, and time on treatment, time to progression
- Proportion of patients starting with modified Gi(l)otrif® dose and the underlying reason(s)

Data on diagnosis, gender, date of birth, ethnicity, body weight and height, Eastern Cooperative Oncology Group performance score (ECOG) (R14-0080), EGFR mutational subgroup (Del19/L858R), starting dose of Gi(l)otrif®, start date of Gi(l)otrif® treatment, dose modifications with date, ADRs, concomitant medications (limited to medication for management of diarrhea, skin effects, mucositis/stomatitis as dichotomous variables (e.g. received anti-diarrhea medication yes/no), reason for dose modification of Gi(l)otrif®, treatment duration of Gi(l)otrif®, time to progression and type of progression (clinical, radiographic or both clinical/radiographic progression) will be collected from patients medical records by investigators.

9.2 SETTING

The NIS will be conducted in about 25-30 sites globally which are experienced in lung cancer treatment. An average of 8-10 patients per site (with a maximum of up to 15 patients per site) is expected.

Patient participation in this NIS is voluntary. Patients were treated and are treated according to the standard of care independent of patient's consent to participate in this NIS.

9.2.1 Selection of study population

Site selection:

Sites in countries with launch dates prior to 1st Jan 2015 and known to prescribe Gi(l)otrif® on a regular basis will be chosen. Asian and Non-Asian countries will be included.

Inclusion criteria:

All consecutive patients will be included if all the following criteria are present:

- Age ≥ 18 years

- Patients with EGFR mutation (common mutations), TKI-naïve advanced NSCLC, treated with Gi(l)otrif® as the first-line treatment for NSCLC within the approved label
- Signed and dated written informed consent per regulations. (Exemption of a written informed consent for retrospective observational studies in some countries per local regulations and legal requirements.)

Exclusion criteria:

Patient won't be included if any of the following criteria is present:

- Any contraindication to Gi(l)otrif® as specified in label.
- Patients with uncommon mutations are excluded as uncommon mutations are not within label in all participating countries (e.g. USA).
- Patients still on treatment with Gi(l)otrif® will be excluded unless treatment period is ≥ 6 months.
- Patients treated with Gi(l)otrif® within an interventional trial.

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

Patients treated with Gi(l)otrif® in interventional trials are excluded to ensure the non-interventional setting of this study. The threshold of ≥ 6 months treatment with Gi(l)otrif® for patients being still on treatment was chosen to avoid early censoring and enable collection of mature data on ADRs and treatment duration. However, patients who stopped Gi(l)otrif® < 6 months will be included to avoid bias. All patients fulfilling inclusion and exclusion criteria from a site will be entered to avoid bias. The maximum of 15 patients per site was chosen to avoid bias by high proportion of patients coming from one 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.

9.2.2 Details of study procedures

The study procedures will consist of:

- Start of data collection:
  Data of eligible and included patients will be collected after the site initiation visit (site initiation visit will be done in a virtual meeting). Data source is from existing data from patients' medical records.

- End of data collection:

After all data of eligible and included patients are collected, source data verification (SDV) will be completed and site close out visit will be performed. Sites will be visited once after data collection for SDV and closing visit.

9.3 VARIABLES

Data will be documented from the date of first dose of Gi(l)otrif® treatment until the date of last dose of Gi(l)otrif® treatment or end of data collection whichever occurs first.

During the data collection period, the following data will be collected from medical records in an eCRF by investigators during the study:

- Informed consent
- Diagnosis
- Demographics (gender, date of birth, ethnicity)
- Body weight and height at start of Gi(l)otrif® treatment
- ECOG performance score at start of Gi(l)otrif® treatment
- EGFR mutational subgroup (Del19/L858R)
- Starting dose of Gi(l)otrif®
- Start date of Gi(l)otrif® treatment
- End date of Gi(l)otrif® treatment
- Gi(l)otrif® dose modification(s) and date(s)
- ADRs
- Concomitant medications (limited to medication for management of diarrhea, skin effects, mucositis/stomatitis as dichotomous variables (e.g. received anti-diarrhea medication yes/no))
- Reason for dose modification(s)
- Date of progression
- Type of progression:
  a. clinical
  b. radiographic
  c. both clinical/radiographic progression

9.3.1 Exposures

Patients were/are treated with Gi(l)otrif® 50mg, 40mg, 30mg, 20mg tablet once daily as indicated in the approved labels of Gi(l)otrif®.
The recommended starting dose of Gi(l)otrif® is 40mg once daily. A modified starting dose of Gi(l)otrif® per objective would be considered as any other dose different than 40mg once daily.

The Summaries of Product Characteristics on Gi(l)otrif® is contained in the NIS ISF in the "Summary of Product Characteristics" section.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Safety outcomes:
- Percentage of subjects with adverse drug reactions (ADRs) by severity class

Effectiveness outcomes:
- Time on treatment with Gi(l)otrif®
- Time to progression with Gi(l)otrif®

9.3.2.2 Secondary outcomes

- Percentage of subjects with a modified starting dose of Gi(l)otrif®
- Reasons of modifying starting dose

9.3.2.3 Further outcomes

n.a

9.3.3 Covariates

n.a

9.4 DATA SOURCES

NIS based on existing data from patients' medical records. Data will be collected in the eCRF. SDV will be performed on about 30% of included patients.

9.5 STUDY SIZE

The post-hoc analysis of LUX-Lung 3 providing the rationale for this study was based on 229 patients with 53% patients experiencing dose reduction. With a sample size of 200 we would be in the same range as in the LUX-Lung 3 analysis which provided robust data. It will be sufficient to analyse the effects of dose modification on patients' safety and effectiveness and to compare it with data from LUX-Lung 3 trial descriptively.
Based on feedback from physicians we expect 25-30% patients starting with a lower dose. There will be around 50 patients starting with a modified dose, and around half of them with further de-/-escalation. This is a sufficient sample size to get some impression on the reasons of a modified starting dose in real-world setting.

9.6 DATA MANAGEMENT

Patients' data will be gathered in Remote Data Capture (RDC) system.
The data management procedures to ensure the quality of the data will be described in detail in the Statistical and Epidemiological Analysis Plan (SEAP) available in TMF.

9.7 DATA ANALYSIS

9.7.1 Main analysis

All collected data will be analysed separately for patients starting with 40mg and ≤ 30mg. Although due to anticipated low sample size in patients starting with ≤ 30mg, it will be mainly for exploratory purpose. Baseline demographics will be analysed with descriptive statistics (N, median, mean, 25%, 75% percentile, SD) and compared descriptively between patients who have dose modifications within the first 6 months of Gi(l)otrif® treatment and those who do not. All the demographics, safety and efficacy data from this study in real-world setting will be compared with data from LUX-Lung 3 trial in descriptive manner.

Analysis of Safety:
Safety analysis will include all patients treated with Gi(l)otrif® and be descriptive in nature. Incidence and severity of ADRs according to Common Terminology Criteria for Adverse Events (CTCAE) criteria (version 4.0) (R15-5988) when available will be summarized and displayed in number/percentage. For patients who had Gi(l)otrif® dose modifications within the first 6 months of Gi(l)otrif® treatment, frequency and severity of the common ADRs pre- and post-dose modification will be analysed (≥ 40mg vs < 40mg; and ≥ 30mg vs < 30mg). Missing or incomplete ADR dates will be imputed according to BI internal SOPs.

Analysis of Effectiveness:
Effectiveness analysis will include all patients treated with Gi(l)otrif®. Time on treatment is from the date of first dose of Gi(l)otrif® treatment to the date of last dose of Gi(l)otrif® treatment. Time to progression is from the date of first dose of Gi(l)otrif® treatment to the earliest date of documented progression (clinical, radiographic or both clinical/radiographic progression) or death. Time on treatment and time to progression will be estimated using Kaplan-Meier method, and the median along with two-sided 95% CI will be displayed (use the Greenwood's formula for estimation of standard errors). Log-rank test will be applied to compare between patients with and without dose modifications. Time on treatment and time to progression will be compared between patients who dose reduced to < 40 mg within the first 6 months of Gi(l)otrif® treatment and those who remained on Gi(l)otrif® 40 mg once daily. This is in analogy to the analysis made on LUX-Lung 3 where a cut-off of 6 months was used as most dose reductions occur during this time.

In the analyses of the two time-to-event endpoints, missing or incomplete data are managed by standard survival analysis techniques. For patients still on treatment, time on treatment will be censored at the date of data collection. For patients still on treatment and without progression, time to progression will be censored at the date of data collection. For patients stopped treatment and without progression/death or progression/death date missing, time to

progression will be censored on the last contact date.

[redacted]

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. An additional inspection/quality assurance check of this NIS can be performed in case of any deviation.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The generalization and consequently the external validity of the study results, may be limited by the participation in the study of only sites that prescribe Gi(l)otrif® on a regular basis to ensure sufficient patient recruitment. Patients treated by investigators with less experience might experience more side effects during their treatment with Gi(l)otrif®.
Methodological efforts have been taken to minimize selection bias: these efforts include the recommendation to include consecutive patients meeting each of the inclusion criteria and none of the exclusion criteria. In addition, this possible selection bias may be limited by the retrospective aspect of the data collection, data that have been already collected at the time of the study. Linked to this aspect is then the limitation due to data availability. Indeed, no additional data will be collected for the study purpose. So if the data is not available in the patient files, then this will be considered as missing data.
In addition, to reduce error in data collection, a standard study eCRF will be used, ensuring a measure of consistency among the collectors.
Another limitation is coming from the diverse handling of data collection from deceased patients which is allowed without informed consent in some countries but not in all.
However, no country-based analyses will be done. Given the median overall survival (31.6 months in LUX-Lung 3) and that time from launch of Gi(l)otrif to data collection in the participating countries is shorter than the median overall survival (OS) the majority of the patients are expected to be alive.

External validity is provided by the global approach of this study and the broad inclusion criteria but limited to patients treated within the label and at the selected, experienced sites. Internal validity will be given by source data verification.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRB) / Independent Ethics Committee (IEC) 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 NIS.

9.10.2 Records

eCRFs for individual patients will be provided by the sponsor (BI) via RDC system.

9.10.2.1 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.

9.10.2.2 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. Food and Drug Administration (FDA)). The CRA / on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

9.10.2.3 Storage of records

Study Site: The site must retain the source documents and essential documents for a period defined by regulations and the site's contract with the sponsor.
Sponsor: The sponsor must retain the essential documents according to the sponsor's SOP.

9.10.3 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 confidentiality will be ensured by using patient identification code numbers.

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.

9.10.4 Patient completion

The collection of the data of patients will continue until end of data collection or withdrawal of consent which occurs first.
At the earliest of the above criteria, the Patient Completion information should be completed in the eCRF.

9.10.5 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.

When the study is completed, the investigator should inform the head of the study site of the completion in writing, and the head of study site should prompt inform IRB and sponsor of the completion in writing (For Japan).

The EC/Competent Authority (CA) in each participating country, as required, needs to be notified about the end of the study or early termination of the study.

9.10.6 Protocol Violations

There are no protocol waivers. All protocol violations must be reported to the sponsor immediately.

9.10.7 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.

9.11 SUBJECTS

Please refer to Section 9.2.1 (Selection of study population).

9.11.1 Cases

n.a

9.11.2 Controls

n.a

9.12 BIAS

Methodological efforts have been taken to minimize selection bias: these efforts include the recommendation to include consecutive patients meeting each of the inclusion criteria and none of the exclusion criteria. In addition, this possible selection bias may be limited by the retrospective aspect of the data collection, data that have been already collected at the time of the study.

10. PROTECTION OF HUMAN SUBJECTS

10.1 INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline for GCP (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI SOPs. 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 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 trial are described in the investigator contract. As a general rule, no trial 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, retrospective observational studies can be exempt from a written informed consent per local regulations and legal requirements, IRB / IEC often grants a waiver of consent for retrospective chart review studies. In order to avoid bias by exclusion of subjects that cannot be given informed consent for any reason like death, missing contact information etc., exempt from a written informed consent should be asked for such situations.

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 trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML / CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG 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 (e.g. 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
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

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

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

Adverse Event of Special Interest (AESI)

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

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

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

Collection of AEs

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

The following must be collected by the investigator in the eCRF from signing the informed consent onwards until the end of the study:

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

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

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 adverse events should be classified and recorded according to the CTCAE criteria (version 4.0) (R15-5988) in the eCRF.

Pregnancy

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

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

Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline

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

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

Information required

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

Reporting of related AEs associated with any other BI drug

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

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

Expedited reporting of serious adverse events (SAE), e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

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

13. REFERENCES

13.1 PUBLISHED REFERENCES

P13-07382 Sequist LV, Yang JCH, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M
Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations.
J Clin Oncol 31 (27), 3327 - 3334 (2013)

P15-05676 Yang JCH, Ahn MJ, Dickgreber NJ, Halmos B, Hirsh V, Hochmair MJ, Levy BP, Marinis F de, Mok T, O'Byrne K, Okamoto I, Schuler MH, Sebastian M, Shah RNH, Tan EH, Yamamoto N, Marten A, Massey D, Wind S, Carbone DP;
Influence of dose adjustment on afatinib safety and efficacy in patients with advanced EGFR mutation-positive (EGFRm+) non-small cell lung cancer (NSCLC).
51st Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, 29 May - 2 Jun 2015
J Clin Oncol 33 (15) (Suppl), Abstr 8073 (2015)

R14-0080 Eastern Cooperative Oncology Group (ECOG)
ECOG performance status (revised: July 27, 2006).
http://ecog.dfci.harvard.edu/general/perf_stat.html (access date: 7 January 2014); Eastern Cooperative Oncology Group (ECOG) (2006)

R15-5988 Common terminology criteria for adverse events (CTCAE): version4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010, 5x7, 196 pages).
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (access date: 30 November 2015) (2010)

[redacted]

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

The stand-alone documents for this non-interventional study are:

- Informed Consent Form
- Statistical and Epidemiological Analysis Plan (SEAP)

The above documents will be archived in the Trial Master File in their original English master version.

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

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 page number(s) 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). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
RealGiDo: Real-world data on Gi(l)otrif® dose adjustment in first-line treatment, TKI-naïve, advanced non-small cell lung cancer patients with EGFR activating mutations

Study reference number:
1200.270

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	11
1.1.2 End of data collection[2]	☒	☐	☐	11
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	11
1.1.6 Final report of study results.	☒	☐	☐	11

Comments:

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
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)	☒	☐	☐	12,13
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	15,16
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	13,18

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	14
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	19

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15,16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	11
4.2.2 Age and sex?	☒	☐	☐	15
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	16
4.2.5 Co-morbidity?	☒	☐	☐	16
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	16

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	17

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	19

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	18,19
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	17
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	17,18
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	17,18
8.1.3 Covariates?	☐	☐	☒	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	17,18
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	17,18
8.2.3 Covariates? (e.g. age, sex, clinical and drug use				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	18,19

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	19
10.3 Are descriptive analyses included?	☒	☐	☐	19
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	19
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	20
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	21
11.3 Are methods of quality assurance described?	☒	☐	☐	21
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒ ☐	☐ ☒	☐ ☐	23
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	15
12.3 Does the protocol address other limitations?	☒	☐	☐	20

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	24
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	21,24

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	10

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☒	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	30

Comments:

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

Date: 26/2/2016

Signature: [redacted]

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: c09038525 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol

Title: 1200.270 clinical trial protocol

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Trial Clinical Monitor	[redacted]	01 Mar 2016 15:53 CET
Approval-[redacted] Safety Evaluation Therapeutic Area		01 Mar 2016 16:00 CET
Approval-Therapeutic Area[redacted]		01 Mar 2016 16:06 CET
Approval-Team Member Medicine		02 Mar 2016 09:30 CET
Approval-On behalf of[redacted] or[redacted] or[redacted]		02 Mar 2016 16:15 CET
Approval-Other		02 Mar 2016 19:09 CET
Verification-Paper Signature Completion		03 Mar 2016 15:26 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**