Post Authorisation Safety Study (PASS) Information

Title	**Prospective International Observational Cohort Study Assessing Safety Outcomes Among Squamous Non-Small Cell Lung Cancer Patients Treated with Necitumumab in Combination with Gemcitabine and Cisplatin in Comparison to Patients Treated with Cisplatin-Based Doublets (I4X-MC-B002)**
Protocol version identifier	Version 1
Date of last version	Approval date can be found at the bottom of the page.
EU PAS Register No:	ENCEPP/SDPP/12595
Active substance	Necitumumab (ATC Code: L01XC22)
Medicinal product(s):	Portrazza®
Product reference:	EU/1/15/1084/001
Procedure number:	EMEA/H/C/003886/MEA/002
Marketing authorisation holder(s)	Eli Lilly Nederland B.V., Grootslag 1-5 NL-3991 RA Houten, The Netherlands
Joint PASS	No
Research question and objectives	To evaluate the safety of necitumumab administered in combination with gemcitabine and cisplatin in comparison to cisplatin doublets for treatment of adult patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) who have not received prior chemotherapy for this condition.
Countries of study	This study will be conducted in the European Union (EU). Factors such as drug placement on the market, uptake, and physician willingness to participate will determine the countries selected.
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2. List of Abbreviations

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ATE	arterial thromboembolism
BMI	body mass index
CI	confidence interval
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	ethical review board
EU	European Union
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
Hb	haemoglobin
IEC	independent ethics committee
IgG1	immunoglobulin G subclass 1
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
KRAS	Kirsten rat sarcoma viral oncogene homolog
LMWH	low molecular weight heparin
MAH	marketing authorisation holder

MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NSCLC	non-small cell lung cancer
PASS	post-authorisation safety study
PBRER	Periodic Benefit Risk Evaluation Report
PRAC	Pharmacovigilance Risk Assessment Committee
PS	performance status
PSUR	Periodic Safety Update Report
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event
UFH	unfractionated heparin
US	United States
USPI	United States Prescribing Information
VTE	venous thromboembolism

3. Responsible Parties

Sponsor: Eli Lilly and Company

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4. Abstract

Title: Prospective International Observational Cohort Study Assessing Safety Outcomes Among Squamous Non-Small Cell Lung Cancer Patients Treated with Necitumumab in Combination with Gemcitabine and Cisplatin in Comparison to Patients Treated with Cisplatin-Based Doublets

Rationale and background: Necitumumab is a recombinant, human immunoglobulin G subclass 1 (IgG1) monoclonal antibody that binds with high affinity and specificity to the epidermal growth factor receptor (EGFR) and blocks the ligand-binding site, blocking activation by all known ligands and inhibiting relevant biological consequences in vitro.

To date, two Phase 3 trials evaluating the safety and efficacy of necitumumab have been completed and the data have been unblinded and analysed. The pivotal Phase 3 SQUIRE trial (N = 1093) was conducted in squamous non-small cell lung cancer (NSCLC) patients including 538 patients receiving necitumumab in combination with gemcitabine and cisplatin. SQUIRE has shown a favourable benefit-risk profile for necitumumab in combination with gemcitabine and cisplatin in treating adult patients with locally advanced or metastatic squamous NSCLC who have not received prior chemotherapy for this condition. The other Phase 3 trial, INSPIRE, was conducted in non-squamous NSCLC population in combination with pemetrexed and cisplatin.

In order to further evaluate the safety of necitumumab in combination with gemcitabine and cisplatin in squamous NSCLC under real-world conditions, Lilly proposed a prospective observational cohort comparative study in the European Union (EU). Patient enrolment into this study will depend upon necitumumab approval and reimbursement status in respective countries.

Research question and objectives: The overall study objective is to evaluate the safety of necitumumab administered in combination with gemcitabine and cisplatin in comparison to cisplatin doublets, for treatment of adult patients with locally advanced or metastatic squamous NSCLC who have not received prior chemotherapy for this condition. Patients will be evaluated under real-world conditions in EU countries.

Primary objective: To characterise and compare the incidence of select adverse events (AEs) in locally advanced or metastatic squamous NSCLC patients receiving treatment of necitumumab in combination with gemcitabine and cisplatin or patients treated with cisplatin-based doublets under real-world conditions. The safety outcomes of interest include thromboembolic events (including venous thromboembolism [VTE] and arterial thromboembolism [ATE]), cardiorespiratory disorders (including life-threatening ventricular arrhythmia, cardiac arrest, and cardiorespiratory arrest), and severe electrolyte disturbances (including Grade ≥3 hypomagnesaemia and hypokalaemia).

Secondary objectives:

- To characterise the real-world use of thromboprophylaxis
- To characterise the real-world management of hypomagnesaemia
- To characterise and compare the incidence of other treatment-emergent AEs (TEAEs) of interest (see Section 9.3.5) under real-world conditions
- To review and summarise electrocardiograms (ECGs) as obtained in the target population
- To evaluate EGFR protein expression status as well as EGFR and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation status
- To characterise supportive care and hospitalisation(s) and reasons for hospitalisation(s) of the target population.

Study design: This is a prospective, non-interventional, comparative, observational cohort study conducted in the EU. The study design will reflect real-life clinical management of patients with locally advanced or metastatic squamous NSCLC who have not received prior chemotherapy for this condition. The type and frequency of actual patient visits and all evaluations will be performed as per routine clinical practise. Physicians will be asked to record data for study endpoint assessments every 3 months (± 15 days) from the start of the study treatments.

Population: This study will include 2 cohorts of a total of approximately 1000 adult patients with locally advanced or metastatic squamous NSCLC who have not received prior chemotherapy for this condition: Cohort 1 will consist of approximately 667 patients receiving necitumumab in combination with gemcitabine and cisplatin treatment; Cohort 2 will consist of approximately 333 patients receiving cisplatin-based doublets without necitumumab.

Variables/Outcomes:

- ***Study treatment exposure:*** Necitumumab in combination with gemcitabine and cisplatin, or cisplatin-based doublets without necitumumab
- ***Patient, disease, and clinical characteristics***
- ***Safety****:* AEs will be collected, coded, and categorised using the Medical Dictionary for Regulatory Activities (MedDRA).
- ***Supportive care and hospitalisation(s).***

Data sources: Data will be requested for transcription to electronic case report forms (eCRFs).

Study size: Taking into account the rarity of squamous NSCLC in the EU, this study plans to enrol approximately 1000 patients, including 667 patients treated with necitumumab in combination with gemcitabine and cisplatin, and 333 patients treated with comparator cisplatin-based doublets. The sample size is calculated based on the probability of observing at least 1 event for less common events in a single cohort and the width of confidence intervals (CIs) around incidence differences between the 2 cohorts that could potentially be observed in this study. The sample size is also based on feasibility considerations including, but not restricted to,

the low incidence and prevalence of the disease in the real-world setting and predicted necitumumab market uptake.

Data analysis: For the primary and secondary objectives, data analyses will be conducted in all eligible patients (all patients who have given informed consent and received at least 1 dose of necitumumab in combination with gemcitabine and cisplatin or 1 dose of cisplatin-based doublet) in both cohorts. In addition, for the secondary objective of characterising use of thromboprophylaxis, the data analyses will include both the primary cohort and the subgroup who receives thromboprophylaxis during chemotherapy.

Descriptive analyses (including standard univariate analyses) will be conducted to evaluate demographic and clinical characteristics and crude incidence proportion and rate of AEs. Categorical measures will be summarised as counts and percentages, while continuous measures will be summarised using mean, median, standard deviation, and range.

Propensity score stratification will be performed to adjust for baseline differences in potential confounding factors to compare the risk of AEs of interest in patients receiving necitumumab in combination with gemcitabine and cisplatin to those receiving other cisplatin-based doublets.

Milestones: This study will have the following milestones:

- Enrolment will start after placement of necitumumab on the market in the first of participating study countries; estimated to be Q2 2017. The start of patient enrolment may change, subject to the uptake of necitumumab.
- Patient recruitment will end within 5 years after study initiation and data will be collected for the enrolled patients; end of data collection estimated to be Q12 2023 or after the targeted number of participating patients has been reached and their data collection completed, whichever is earlier. The end of data collection may change, subject to the uptake of necitumumab and patient participation.
- Study progress reports will be included in the necitumumab Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR) starting at the first patient visit. The inclusion of the study in the PBRER/PSUR will depend on the first patient visit.
- An interim analysis is planned when the target sample size reaches 334 patients enrolled in the necitumumab combination cohort with gemcitabine and cisplatin (that is, half of the target study size of this cohort).
- Registration in the EU Post-Authorisation Study (PAS) Register is subject to the final protocol approval date, estimated to be Q2 2017.
- Final report of study results is estimated to be Q1 2024 or 1 year after the end of data collection. The final study report will be submitted with a PBRER/PSUR. If there is important new safety information affecting the benefit-risk of necitumumab, the study report and corresponding documents will be submitted earlier in accordance with the regulations. The planned date for the final report may change, subject to the changes in the start or end of patient recruitment proposed above.

5. Amendments and Updates

Not applicable.

Amendment or update no.	Date	Section of study protocol	Amendment or update	Reason

Abbreviation: NA = not applicable; no. = number.

6. Milestones

Milestone	Planned date
Start of patient enrolment	Enrolment will start after placement of necitumumab on the market in the first of participating study countries; estimated to be Q2 2017. The start of patient enrolment may change, subject to the uptake of necitumumab.
End of data collection	Patient recruitment will end within 5 years after study initiation and data will be collected for the enrolled patients; end of data collection estimated to be Q1 2023 or after the targeted number of participating patients has been reached and their data collection completed, whichever is earlier. The end of data collection may change, subject to the uptake of necitumumab and patient participation.
Study progress reports	Study progress reports will be included in the necitumumab PBRER/PSUR starting at the expected first patient visit. The inclusion of the study in the PBRER/PSUR will depend on the first patient visit.
Interim report	An interim analysis is planned when the target sample size reaches 334 patients enrolled for the necitumumab in combination with gemcitabine and cisplatin cohort (that is, half of the target study size of this cohort).
Registration in the EU PAS Register	Subject to the final protocol approval date; estimated to be Q2 2017.
Final report of study results	Estimated to be Q1 2024 or 1 year after the end of data collection. The final study report will be submitted with a PBRER/PSUR. If there is important new safety information affecting the benefit-risk of necitumumab, the study report and corresponding documents will be submitted earlier in accordance with the regulations. The planned date for the final report may change, subject to the changes in the start or end of patient recruitment proposed above.

Abbreviations: EU = European Union; PAS = post-authorisation study; PBRER = Periodic Benefit Risk Evaluation Report; PSUR = Periodic Safety Update Report; Q = quartile.

7. Rationale and Background

Necitumumab is a recombinant, human immunoglobulin G subclass 1 (IgG1) monoclonal antibody that binds with high affinity and specificity to the epidermal growth factor receptor (EGFR) and blocks the ligand-binding site, blocking activation by all known ligands and inhibiting relevant biological consequences in vitro. Necitumumab in combination with gemcitabine and cisplatin chemotherapy was approved by the European Commission on 15 February 2016 for the treatment of adult patients with locally advanced or metastatic EGFR expressing squamous non-small cell lung cancer (NSCLC) who have not received prior chemotherapy for this condition (Portrazza Summary of Product Characteristics [SmPC] 2016).

In the last decade, major improvements have been achieved in the treatment of patients with non-squamous NSCLC, including the approvals of pemetrexed and bevacizumab for this histological subtype; however, development of new treatment options offering survival benefits for patients with squamous NSCLC disease lags behind. The intended purpose of giving necitumumab in combination with gemcitabine and cisplatin is to improve overall survival in the treatment of patients with locally advanced or metastatic squamous NSCLC who have not received prior chemotherapy for this condition. This combination has shown a favourable benefit-risk profile, as demonstrated by the necitumumab clinical trial programme.

Necitumumab is associated with a number of important identified risks including venous thromboembolism (VTE), hypersensitivity/infusion-related reactions, arterial thromboembolism (ATE), severe hypomagnesaemia, and severe skin reactions. Important potential risks include cardiorespiratory disorders. Information is currently considered missing in such areas as activity in biomarker-defined tumour subtypes (EGFR protein expression status and EGFR and Kirsten rat sarcoma viral oncogene homolog [KRAS] mutation status).

During the review by the Committee for Medicinal Products for Human Use (CHMP) of the marketing authorisation application for necitumumab in the treatment of squamous NSCLC in Q4 2015, the Pharmacovigilance Risk Assessment Committee (PRAC) requested a post-authorisation safety study (PASS) to be conducted to characterise the safety of necitumumab in patients with squamous NSCLC under real-world disease conditions. Eli Lilly and Company (hereafter Lilly) proposed a prospective, non-interventional, comparative, observational cohort study in the European Union (EU). Patient enrolment into this study will depend upon necitumumab approval status and reimbursement ability in respective countries.

8. Research Question and Objectives

The overall study objective is to evaluate the safety of necitumumab administered in combination with gemcitabine and cisplatin in comparison to cisplatin doublets, for treatment of adult patients with locally advanced or metastatic squamous NSCLC who have not received prior chemotherapy for this condition. Patients will be evaluated under real-world conditions in EU countries.

8.1. Primary Objective

To characterise and compare the incidence of select adverse events (AEs) in locally advanced or metastatic squamous NSCLC patients receiving treatment of necitumumab in combination with gemcitabine and cisplatin or patients treated with cisplatin-based doublets under real-world conditions. The safety outcomes of interest include:

- **Thromboembolic events:**
  - Venous thromboembolism (VTE): This will include incidental and symptomatic pulmonary embolism and deep vein thrombosis (DVT), including fatal cases as assessed by an adjudication committee.
  - Arterial thromboembolism (ATE): This will include myocardial infarction (MI), stroke, and systemic ATE, including fatal cases as assessed by an adjudication committee.
- **Cardiorespiratory disorders:** This will include life-threatening ventricular arrhythmia, cardiac arrest, and cardiorespiratory arrest, including fatal cases as assessed by an adjudication committee.
- **Severe electrolyte disturbances (Grade ≥3):** This will include hypomagnesaemia and hypokalaemia.

8.2. Secondary Objectives

- To characterise the real-world use of thromboprophylaxis
- To characterise the real-world management of hypomagnesaemia
- To characterise and compare the incidence of other treatment-emergent AEs (TEAEs) of interest (see Section 9.3.5) under real-world conditions
- To review and summarise electrocardiograms (ECGs) as obtained in the target population
- To evaluate EGFR protein expression status as well as EGFR and KRAS mutation status
- To characterise supportive care and hospitalisation(s) and reasons for hospitalisation(s) of the target population.

9. Research Methods

9.1. Study Design

This is a prospective, non-interventional, comparative, observational cohort study conducted in the EU. The study design will reflect real-life clinical management of patients with locally advanced or metastatic squamous NSCLC (see disease definition below). Type and frequency of actual patient visits and all evaluations will be performed as per routine clinical practise. Physicians will be asked to record data for study endpoint assessments at least every 3 months (± 15 days) from the start of treatment.

9.2. Setting

9.2.1. Definition of the Disease

Locally advanced or metastatic squamous NSCLC in patients who have not received prior chemotherapy for this condition.

9.2.2. Study Population

This study will include adult patients with locally advanced or metastatic squamous NSCLC who receive either necitumumab in combination with gemcitabine and cisplatin treatment (Cohort 1), or a cisplatin-based chemotherapy without necitumumab (Cohort 2) under real-world conditions. Per the necitumumab SmPC, after receipt of up to 6 cycles of necitumumab in combination with gemcitabine and cisplatin treatment, necitumumab as monotherapy can be administered in patients whose disease has not progressed, until disease progression or unacceptable toxicity.

Platinum-based doublets are a standard of care for advanced NSCLC in Europe (Besse et al. 2014). Given that carboplatin is associated with a different safety profile compared to cisplatin (Ardizzoni et al. 2007) and that the primary objective of this study is to evaluate specific AEs of necitumumab in combination with gemcitabine and cisplatin, cisplatin-based doublets are considered a more relevant comparator group than carboplatin-based therapies. Since there is no guideline for a single 'standard' platinum-based doublet for the treatment of NSCLC (Besse et al. 2014), patients receiving cisplatin-based doublets, that is, Cohort 2, will be analysed as a whole, although, if enough patients are enrolled under chemotherapy regimens other than gemcitabine and cisplatin, subgroup analyses may be performed on specific chemotherapy regimens.

The decision to initiate use of necitumumab in combination with gemcitabine and cisplatin or cisplatin-based doublets is made independently by the participant and their health care provider and is not mandated by the study design or protocol. The study will be conducted in Europe; however, if the number of patients available for follow-up is less than the desired sample size, consideration will be given to extending the site/patient enrolment to North America.

9.2.2.1. Inclusion Criteria

[1] Adult patients (age ≥18 years at enrolment) with locally advanced or metastatic squamous NSCLC who have not received prior chemotherapy for this condition. Prior adjuvant therapies, neoadjuvant therapies, or biologics are not considered as prior chemotherapies.

[2] Patients who initiate necitumumab in combination with gemcitabine and cisplatin or patients who initiate cisplatin-based doublets, independently from entry in study

[3] Patients who have been fully informed and have given written informed consent to the use of the needed information to be part of the observational study.

9.2.2.2. Exclusion Criteria

[4] Patients who have received prior chemotherapy for locally advanced or metastatic squamous NSCLC

[5] Patients who initiate treatment of necitumumab alone or necitumumab in combination with medications other than gemcitabine and cisplatin for locally advanced or metastatic squamous NSCLC

[6] Patients concurrently participating in any study including administration of any investigational drug (including necitumumab) or procedure (including survival follow-up).

9.2.3. Duration of the Study

As this is an observational study, type and frequency of actual patient visits and all evaluations will be done as per routine clinical practise. Since no visits are mandated as part of this study, baseline and follow-up data collection will be performed as described in Section 9.4.

The objective of the study is to characterise the occurrence of AEs of interest among adult patients with advanced squamous NSCLC receiving necitumumab in combination with gemcitabine and cisplatin and compare these to patients receiving cisplatin-based doublet therapies under real-world conditions. Given that 4 cycles of first-line platinum-based chemotherapy is recommended for most patients, and a maximum of 6 cycles when maintenance treatment is considered (Reck et al. 2014), and that each cycle of cisplatin is 3 to 4 weeks, the maximum duration of exposure to chemotherapy (with or without necitumumab) is 24 weeks or approximately 6 months.

The median treatment duration for patients receiving necitumumab in combination with gemcitabine and cisplatin observed in the SQUIRE study was 6 cycles or approximately 4 months. Patients in the necitumumab arm who had at least stable disease could continue to receive necitumumab monotherapy. In the SQUIRE study, the median duration of monotherapy was 4 cycles or approximately 3 months. Thus, the planned observation period of 9 months in this study from treatment onset will allow for several months of follow-up.

9.2.4. Site Recruitment and Physician Selection

Physicians with a recognised competency in oncology who treat locally advanced or metastatic squamous NSCLC patients and prescribe anti-cancer treatments will be prospectively identified for potential inclusion in the study in each participating country. An updated curriculum vitae for each physician will be collected and reviewed as part of the feasibility process.

A reasonable number of sites in countries representative of the EU will be utilised to reach the targeted patient number. If the number of patients available for follow-up is less than the desired sample size, consideration will be given to extending the site/patient enrolment to North America. The country selection will be based on multiple factors, including number of sites with a recognised competency in oncology per capita and favourable regulatory and ethical environment to conduct observational studies. Selection of study sites will be determined at the country level and will include criteria such as physician speciality, geographical location (for example, rural, urban, or suburban), practise setting (hospital-based, academic, or private practise), estimated eligible patient availability, and staffing availability, to maximise the generalisability of data.

Site selection criteria will also include projected availability of eligible patients within the 5-year enrolment period and the availability of physician (and other site staff) time to complete the case report forms (CRFs) to the extent possible representative of sites reflective of the treatment patterns within each country. The patient recruitment per site and the market uptake of necitumumab will be closely monitored before and during the study. Selection criteria and basic site information (for example, patient volume, physician specialty, and practise setting) will be collected via a site qualification survey.

9.2.5. Patient Identification

The physician should refer to the drug SmPC (EU) (and United States Prescribing Information [USPI] if enrolment extends to the US) for treating patients.

All patients presenting during the enrolment period will be assessed for eligibility according to the defined inclusion/exclusion criteria, and all eligible patients will be offered the opportunity to participate in the study. Each study physician will include patients until the targeted number of patients per country is reached.

9.2.5.1. Patients of Special Interest

Patients using thromboprophylaxis during the study chemotherapy will be identified based on their use of concomitant medication, including, but not limited to unfractionated heparin (UFH), low molecular weight heparins (LMWHs), aspirin or vitamin K antagonists, or other direct oral anticoagulants.

9.2.6. Steering Committee

A Steering Committee will be constituted in order to ensure the appropriate conduct of the observational study. Members will include external experts with strong expertise in oncology, vascular medicine, cardiology and observational studies, as well as representatives of the MAH.

9.3. Variables

9.3.1. Study Treatment

The following information regarding study treatment administration will be collected, if available:

- Treatment (necitumumab in combination with gemcitabine and cisplatin, necitumumab as monotherapy after necitumumab in combination with gemcitabine and cisplatin, and specific cisplatin-based doublet)
- Dates of administration
- Pre-medications administered, if any
- Dosage and administration details
- Reason for dose reductions and dose delays
- Reason for treatment discontinuation (Section 9.3.4).

9.3.2. Demographics and Baseline Characteristics

The following information will be collected prior to start of treatment, if available:

- Demographic and baseline (pre-treatment) characteristics such as age, gender, weight, height, ethnicity, and smoking status
- Medical history
- Cancer diagnosis and characteristics, such as date of initial diagnosis, date and diagnosis of locally advanced or metastatic disease, initial and current stage, histology, sites of metastases, and EGFR protein expression status and EGFR/KRAS mutation status
- Prior anti-cancer treatment for squamous NSCLC: type of therapy (for example, surgery, radiation, adjuvant, neoadjuvant, as well as biologic).

9.3.3. Information to be Collected at Baseline and during Treatment

The following information will be collected at baseline and during treatment, if available:

- Eastern Cooperative Oncology Group (ECOG) performance status (PS)
- Smoking status
- Weight and height
- Concomitant medications
- Supportive care and procedure information (see Section 9.3.7)
- Thromboprophylaxis or anticoagulant use
- Magnesium replacement or supplementation (type, administration route, and dose and duration of treatment)
- Electrocardiogram (digital 12-lead ECG at baseline and during treatment)
- Laboratory:
    - Haematology profile (such as haemoglobin, leukocytes, neutrophils, and platelets)
    - Serum electrolyte profile (such as serum magnesium, potassium, and calcium)
    - Serum chemistry profile (such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and serum creatinine)

9.3.4. Treatment Discontinuation and Post-Discontinuation

The following information will be collected, if available:

- The date and main reason for discontinuation of any study drug
- Post-discontinuation systemic anti-cancer therapy
- After discontinuation from therapy, patient's survival status (dead, alive, lost to follow-up, or withdrew from the study) up to 9 months from the therapy initiation will be collected.

9.3.5. Safety Outcomes

All serious adverse events (SAEs) and the non-serious protocol-defined AEs specified below will be collected after initiation of study treatment for the duration of 9 months.

The following non-serious protocol-defined AEs should be collected, irrespective of causality and severity/seriousness:

- Thromboembolic events
    - VTE (such as DVT or superficial thrombosis or incidental and symptomatic pulmonary embolism)
    - ATE (such as MI or cerebrovascular accident/stroke)
- Cardiorespiratory disorders (such as life-threatening ventricular arrhythmia, cardiac arrest, or cardio-respiratory arrest)
- Electrolyte disturbances (hypomagnesaemia, hypokalaemia, or hypocalcaemia)
- Skin reactions (such as rash, dermatitis acneiform, acne, dry skin, pruritus, skin fissures, erythema, or severe reactions such as toxic epidermal necrolysis or Steven-Johnson syndrome)
- Eye disorders (such as conjunctivitis, blepharitis, or keratitis)
- Hypersensitivity/infusion-related reactions (such as drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, or infusion-related reaction)
- Interstitial lung disease (such as acute respiratory distress syndrome, interstitial lung disease, pneumonitis, or pulmonary fibrosis)
- Major and minor bleeding.

The AEs listed above were identified based on safety data known for other monoclonal anti-EGFR antibodies and/or clinical experience with necitumumab; furthermore, they are identified as primary or secondary objectives in the study protocol. As such, they were determined to be protocol-defined AEs.

9.3.6. Adjudication Committee

An independent adjudication committee consisting of external experts with strong expertise in cardiology and vascular medicine will assess any fatal cases, as well as all cases reported as having thromboembolic event by a blinded review. The adjudication committee will consist of members with expertise in oncology and cardiovascular medicine. A separate charter will be developed to explain the adjudication process in detail.

9.3.7. Supportive Care and Hospitalisations

The following supportive care will be collected, if available:

- Concomitant medications use and type (for example, thromboprophylaxis and magnesium repletion)
- If available, any additional available investigations conducted in patients who experienced thromboembolism (VTE or ATE)
- Transfusions and type (for example, packed red blood cells, platelets, fresh frozen plasma, and whole blood)
- Radiation therapy
- Hospitalisation(s) including:
    - Main reason for hospitalisation at admission
    - Duration of hospitalisation.

9.4. Data Sources

For information recorded per routine clinical practise (as described in Section 9.3), data will be requested for transcription to an electronic data capture (EDC) system. To ensure accurate, complete, and reliable data, the study physician will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the data entered by the site into the provided EDC system for this study. The sites/physicians will report AEs, pre-existing conditions, and medical history events using verbatim terms. These terms will be mapped to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA®). The participating sites will report the Common Terminology Criteria for Adverse Events (CTCAE) term and CTCAE grade for SAEs and non-serious protocol-defined AEs (Section 9.3.5). The World Health Organisation (WHO) Drug Dictionary will be used for coding of medications.

All data reported on the eCRF must be derived from and be consistent with the source documents, or the discrepancies must be explained.

9.5. Study Size

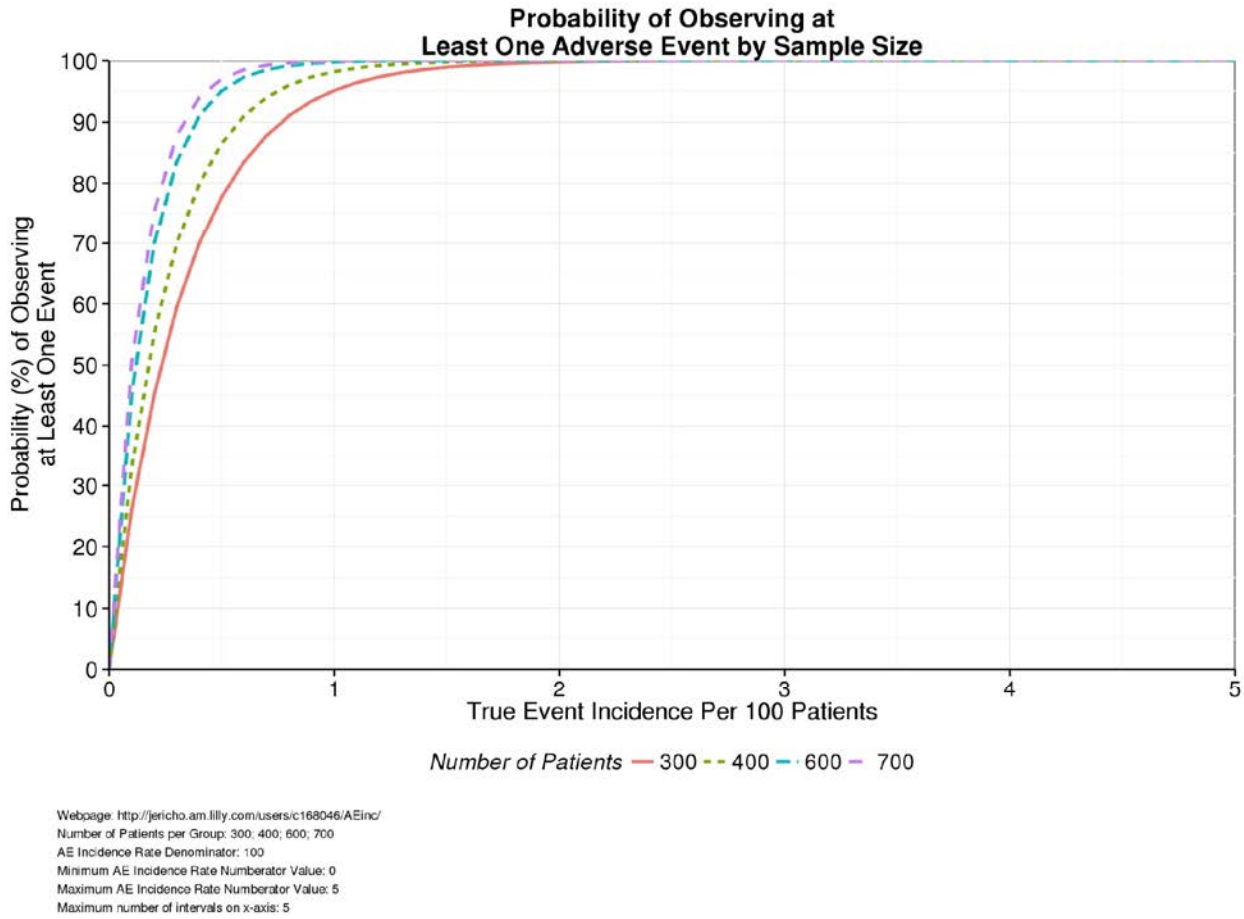
Taking into account the rarity of squamous NSCLC in the EU and North America, this study plans to enrol approximately 1000 patients, including 667 patients treated with necitumumab in combination with gemcitabine and cisplatin (Cohort 1) and 333 patients treated with comparator cisplatin-based doublet therapies (Cohort 2). The size of the necitumumab in combination with gemcitabine and cisplatin cohort is larger than that in the pivotal Phase 3 SQUIRE trial, which included 538 patients treated with necitumumab in combination with gemcitabine and cisplatin.

For the primary objective of this study, the sample size was based on the probability of observing at least 1 event for the less common events in a single cohort and the width of CIs around incidence differences between the 2 cohorts that could potentially be observed in this study. The sample size is also based on feasibility considerations including, but not restricted to, the low incidence and prevalence of squamous NSCLC in the EU and North America in a real-world setting and predicted necitumumab market uptake.

Figure 9.1 shows the probability of observing at least 1 event for a range of true incidences from 0% to 5% for tentative samples ranging from 300 to 700 in an arm. The range of incidences in Figure 9.1 is based on the observed incidences of the less common AEs of interest from SQUIRE (from <1% [for example, cardiorespiratory disorder in gemcitabine and cisplatin arm] to 4.4% [for example, severe hypokalaemia in the necitumumab in combination with gemcitabine and cisplatin arm]). As shown in Figure 9.1, for a true event incidence of 1% and a sample size of 300 patients , the probability of observing at least 1 event is 95%; when the sample size increases to 600, the probability to observe a safety event is expected to be >99%. Based on Figure 9.1, a total of 667 patients in Cohort 1 (necitumumab in combination with gemcitabine and cisplatin) and 333 patients in Cohort 2 (cisplatin-based doublets) will be sufficient to observe at least 1 AE of interest in either cohort.

Since the primary objective of the study is to characterise the safety in the necitumumab-containing cohort, a 2:1 patient allocation (rather than 1:1) was chosen to allow for better precision of the estimate in the necitumumab-containing cohort; this will enable further exploration of secondary endpoints in patients experiencing select AEs. Table 9.1 presents the 95% CIs for a range of incidence differences that could potentially be observed in this study. Under the proposed sample size scenario, the incidence difference estimate will be observed with a precision ≤5.5%.

To enrol the planned number of patients in each cohort and to maximise generalisability, sampling strategies will be implemented. Actions may include implementation of temporary or permanent caps in enrolment to ensure the balance of enrolment rate of patients in the 2 cohorts regarding geography/region and time period during which patients are enrolled.



Abbreviation: AE = adverse event.

Figure 9.1. The probability of observing at least 1 adverse event by sample size.

Table 9.1. Difference and Width of 95% Confidence Intervals for Observed Event Incidences

	Observed Incidence Rates			
	Cohort 1			
Cohort 2	**5%**	**10%**	**15%**	**20%**
Cohort 1: Cohort 2 = 2:1 (N = 1000; 667 patients in Cohort 1 and 333 patients in Cohort 2)				
5%	0 ±3.1%	5% ±3.5%	10%±3.8%	15%±4.1%
10%	-5%±3.8%	0±4.2%	5%±4.4%	10%±4.7%
15%	-10%±4.4%	-5%±4.7%	0±4.9%	5%±5.1%
20%	-15%±4.8%	-10%±5.1%	-5%±5.3%	0±5.5%

9.6. Data Management

Patient data are recorded on data forms. Study personnel are responsible for the integrity of the data (that is, accuracy, completeness, legibility, and timeliness) reported to Lilly.

All patients who provide consent to release information and who fulfil the study population definition criteria and study entry criteria will be included in the analyses. For those patients who are lost to follow-up, or who withdraw from the study, the analyses will include all data up to the point of their last data collection.

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. High data quality standards will be maintained, and processes and procedures will be utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

Datasets and analytic programmes will be kept on a secure server and archived according to Lilly's record retention procedures. If the study is conducted by a third party, the datasets and analytic programmes will be stored and archived according to the vendor's procedures. These datasets and analysis programmes will be transferred to the Lilly data repository via a secure transfer system.

9.6.1. Data Collection Schedule

As this is an observational study, type and frequency of actual patient visits and all evaluations will be done as per routine clinical practise.

The physician will review the eligibility criteria (that is, adult patients with locally advanced or metastatic squamous NSCLC who have not received prior chemotherapy for the locally advanced or metastatic squamous NSCLC, and for whom a treatment decision of necitumumab in combination with gemcitabine and cisplatin or cisplatin-based doublets without necitumumab has been made) and will ask the patient to confirm his/her willingness to participate by providing consent to release information.

If a patient is lost to follow-up, an effort should be made to contact him or her and inquire about his/her health status.

9.6.2. Data to Be Collected

9.6.2.1. Site/Physician Questionnaire

Before starting recruitment, each participating physician will complete a site questionnaire. The following information is to be collected and entered in the clinical database:

- Site address
- Type of centre (academic/non-academic, public, or private practise)
- Years of medical practise in treating lung cancer patients.

9.6.2.2. Patient Data

Information collected (as described in Section 9.3) as part of routine clinical practise will be transcribed to an eCRF. All data will be collected and entered directly into the EDC system. All participating sites will have access to the data entered regarding the individual site's own

enrolled patients. All sites will be fully trained on using the online data capture system, including eCRF completion guidelines and help files. Sites will be responsible for entering extracted patient data into a secure internet-based EDC database via the eCRF. Study physicians and site personnel will be able to access their accounts with usernames and passwords. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. The eCRF should be reviewed, electronically signed, and dated by the study physician. All changes or corrections to eCRFs should be documented in an audit trail, and an adequate explanation is required.

9.6.2.3. Missing Data

The eCRF will be designed to require certain items to be completed prior to advancing to the next item, thereby minimising missing data for required items. Select items may not be applicable to all patients and will be recorded appropriately in the eCRF.

9.6.2.4. Patient Withdrawal

Patients may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a patient is withdrawn prior to completing the study follow-up period, any known reason for withdrawal should be documented in the database. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient (Note: once a patient withdraws consent, the sponsor cannot use any data beyond the date of withdrawal; thus, no information should be collected from patients after withdrawal).

9.6.2.5. Patients Lost to Follow-Up

The participating physician or site personnel shall make every effort to contact the patients who are lost to follow-up in order to confirm survival and identify the reason for not being willing to participate within legal and ethical boundaries. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the patient will not be considered lost to follow-up.

All available information in the patient's file through the date of last contact or visit should be entered in the eCRF for the lost to follow-up patients. The statistical analysis plan (SAP) will specify how such patients will be considered for purposes of endpoint assessment.

9.6.3. File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or the study sponsor, the physician agrees to keep records, including the identity of all participating patients, all original signed consent-to-release information, copies of all eCRFs, SAE forms, source documents, and adequate documentation of relevant correspondence. The records should be retained by the physician according to local regulations or as specified in the study contract, whichever is longer.

9.7. Data Analysis

All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified, missing data will not be imputed or "carried forward." Details of the data analyses will be defined in the SAP.

Analysis population includes all patients who have given informed consent and received at least 1 dose of necitumumab in combination with gemcitabine and cisplatin or 1 dose of cisplatin-based doublet. The analyses of both primary and the majority of secondary objectives will be based on this population. The secondary objective to characterise the real-world use of thromboprophylaxis will be conducted among both the entire study population and the subgroup who receives thromboprophylaxis.

9.7.1. Primary Analyses

Primary analysis will focus on clinically important AEs: VTEs (incidental and symptomatic pulmonary embolism, DVT upper and lower, intra-abdominal thrombosis); ATEs (MI, stroke, transient ischaemic attack, systemic embolism); cardiorespiratory disorders; and electrolyte disturbances (magnesium, calcium, potassium). Data analyses will be conducted on all eligible patients in the 2 cohorts and will be based upon assessments from the adjudicated review where applicable. Results from the participating physicians' review will also be presented.

The primary focus of AE reporting will be based on the AEs reported between the date of first dose of study treatment and over the duration of 9 months. The AEs will be summarised by MedDRA System Organ Class and preferred term. Fatal cases will be assessed by an adjudication committee and will be summarised.

The analyses will be conducted overall and by treatment period (chemotherapy treatment phase in both cohorts, and if applicable, monotherapy necitumumab phase in Cohort 1, and follow-up phase in both cohorts).

Categorical measures will be summarised for each cohort as counts and percentages, and continuous measures will be summarised using mean, median, standard deviation, and range.

To compare the select AE incidence and calculate the 95% CIs in the 2 cohorts, propensity score stratification will be performed to adjust for baseline differences in potential confounding factors.

Propensity Score Model

Propensity score for each patient is defined by the predicted probability of being in a necitumumab-containing cohort, given their baseline characteristics (Schneeweiss et al. 2009). No post-baseline or outcome information will be used in this part of the analyses. By using only pre-treatment characteristics in the propensity score modelling, the comparison groups can be formed independently of any outcome information. The propensity score will be estimated using logistic regression, with cohort (the necitumumab in combination with gemcitabine and cisplatin cohort or other cisplatin-based doublets cohort) as the outcome variable. The logistic regression propensity model will include the following terms as independent variables: pre-identified baseline characteristics such as age, sex, ECOG PS, and so on, and other factors specific to a particular AE, such as prior history of VTE or ATE. The interaction term or nonlinear terms for continuous variables will also be considered.

Removal of Non-Overlapping Regions of the Propensity Score Distributions

The estimated propensity scores for each patient will then be grouped into 5 strata based on quintiles of the propensity score distribution. The frequencies of patients from each cohort will be summarised by strata to insure sufficient number of patients from each cohort for comparisons. Boxplots may be utilised to summarise the distribution of propensity scores across strata. Prior to forming the propensity score strata, patients in non-overlapping regions of the propensity score distributions will be removed from the primary analysis (Austin and Mamdani 2006; Imbens 2015).

If the degree of overlap is poor, additional steps can be performed. For example, a) if there is not a sufficient number of patients assigned to either cohort within any particular quintile, patients with corresponding propensity scores may be deleted from the future outcome analysis and explained separately; or b) patients with extreme predicted probabilities (<5% and >95%) may be deleted from the future outcome analysis; or c) limit to a descriptive analysis which shows the vast differences in populations in the 2 cohorts.

Baseline characteristics and outcomes of patients excluded from the analysis will be summarised relative to the set of patients included in the analysis. This will allow for more appropriate interpretation regarding the generalisability of the results.

Balance Assessment

The within-stratum balance in all the baseline variables between cohorts will be assessed and if the balance is not achieved, the need for additional variables, interactions, or non-linear terms, or a reduction in terms, may be assessed by examining baseline data relationships with potential confounders and cohort (though not with outcome of interest). However, the propensity score model will be finalised prior to initiating the analysis of the study outcome measure.

For balance assessment, first, a 2-way ANOVA (analysis of variance [or an appropriate model for non-continuous covariate]) with each covariate as the dependent variable and a model including cohort, propensity score strata, and the interaction of cohort and propensity score strata will be conducted. This approach detects differences in mean covariate values between the cohorts that are both consistent across strata (cohort $p<0.05$) and consistent for each strata (interaction $p>0.2$).

In addition, the absolute standardised differences, defined as the absolute difference in means between the 2 groups divided by a measure of the standard deviation of the variable, will be computed within strata. As a rule of thumb, absolute standardised differences >0.10 indicate an imbalance that might require further investigation (Austin and Mamdani 2006). For continuous covariates, the absolute standardised difference is defined as:

$$d = \frac{\left|\bar{x}_{treatment} - \bar{x}_{control}\right|}{\sqrt{\frac{s^2_{treatment} + s^2_{control}}{2}}}$$

where $\bar{x}_{treatment}$ and $\bar{x}_{control}$ denote the sample mean of the covariate in treated and untreated subjects, and $s^2_{treatment}$ and $s^2_{control}$ are the sample standard deviations of the covariate in the treated and untreated subjects, respectively (Flury and Riedwyl 1986). For dichotomous covariates, the absolute standardised difference is defined as:

$$d = \frac{|\hat{p}_T - \hat{p}_C|}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T) + \hat{p}_C(1-\hat{p}_C)}{2}}}$$

where $\hat{p}_T$ and $\hat{p}_C$ denote the prevalence of the dichotomous covariate in treated and untreated subjects, respectively. The standardised difference is typically defined without the use of absolute values.

As opposed to significance testing and standardised differences, which assess differences in means, within-strata box plots (or histograms) will be used to investigate the similarity in the full distributions of key covariates between the treatment cohorts. This assessment of the distributions will allow for detection of violations of the positivity assumptions.

Final Analysis with Propensity Score Stratification

After the propensity score strata are finalised and the balance are achieved, the primary comparison of incidence of select AEs between patients in Cohort 1 and Cohort 2 will be assessed by a propensity score stratified analysis. The estimated propensity scores will be grouped into strata as described above. Cohort differences in the incidence rate of select AEs will be computed within each of the strata and then averaged equally across strata (equal weighting is equivalent to weighting by the total number of patients per strata) for the overall cohort difference estimate (Rosenbaum and Rubin 1984). This will be accomplished using a generalised linear model with incidence (0/1) of an AE as dependent variable and strata (as a class variable), cohort, the interaction of strata and cohort, select key covariates, and the interactions between strata and the key covariates as independent variables (the additional covariates will account for residual imbalance within strata for key variables anticipated to be related to outcome (D'Agostino and D'Agostino 2007; Imbens 2015). As a sensitivity analysis, a non-parametric propensity score stratified bootstrap resampling (Faries et al. 2010) may be conducted. Two-sided 95% CIs will be reported. Summary statistics will include a description of the results by strata in addition to the overall analysis above. If interactions between cohort and strata are observed, the follow-up analyses to understand differences in the populations between strata and factors leading to differential effects will be performed.

More detailed analyses methods will be specified in the SAP.

Additional analyses will be performed to examine possible risk factors (at baseline and on-treatment) for VTEs and ATEs. The following risk factors will be considered; these risk factors were defined based on literature review.

Risk factors for ATEs include:

- Age ≥65
- Hypertension
- History of ATE
- History of arteriosclerosis
- History of hyperlipidaemia/hypercholesterolaemia
- History of diabetes mellitus
- Hematologic lab values:
    - platelets ≥350000/μL
    - leucocytes >11000/μL
    - haemoglobin (Hb) <10g/dL
- Body mass index (BMI) ≥35kg/m²
- Smoking history: ever smokers.

Risk factors for VTEs include:

- Age ≥65
- Relevant medical history for VTE
- ECOG PS 2
- Hematologic lab values:
    - platelets ≥350000/μL
    - leucocytes >11000/μL
    - Hb <10g/dL
- BMI ≥35kg/m²
- Current smoking status: smokers
- Khorana risk score (Khorana et al. 2008; Lyman et al. 2013):
    - High risk (score ≥3).

The full list of risk factors will be defined in the SAP.

Risk factors will be summarised for each cohort and the relationship between thromboembolic events and risk factors will be explored. In addition, a multivariate logistic regression model may be constructed by selecting variables among all the potential variables listed above using stepwise selection method. Additional details will be included in the SAP.

To address unmeasured confounding, effort will be made to collect information regarding potential confounding variables. Sensitivity analysis to assess the potential impact of unmeasured confounding will be addressed in the SAP.

Though many analyses will be conducted as part of this research, the primary approach will not adjust for multiplicity.

9.7.2. Secondary Analyses

Similar safety analyses (as described in Section 9.7.1) will be performed for other TEAEs of interest, such as severe skin reactions and hypersensitivity/infusion-related reactions under real-world conditions.

The real-world supportive care patterns will be summarised descriptively for each cohort. To characterise use of thromboprophylaxis, the analysis will summarise rate and type of thromboprophylaxis (for example, UFH, LMWHs, aspirin, or vitamin K antagonists), characteristics of patients receiving thromboprophylaxis (for example, demographic characteristics, medical history, cancer characteristics, comorbidities, and hospitalisation), rate of thromboembolic events among those who use thromboprophylaxis, and rate of AEs associated with thromboprophylaxis including bleeding.

To characterise management of hypomagnesaemia, the analysis will summarise rate and type and timing of magnesium repletion. ECG as obtained during treatment in each cohort will be reviewed and the results will be summarised. Patients' EGFR protein expression status or EGFR and KRAS mutation status will be summarised, as tested and reported during their routine care. The number and type of hospitalisations, duration of stay, and reason for hospitalisation will be summarised as well.

Since this is an observational study, the decision on the type and frequency of supportive care and all evaluations is made independent of the study entry and not mandated by the study protocol.

9.7.3. Periodic Study Updates and Interim Analysis

Study updates (for example, number of patients enrolled and number of patients in each cohort of interest) will be included in the necitumumab PBRER/PSUR starting at the first patient visit. Additionally, an interim analysis is planned when approximately half of the targeted sample size of necitumumab in combination with gemcitabine and cisplatin cohort have been enrolled in the study and have been followed for 1 cycle to allow for review of the aggregate data. The interim analysis will allow for an administrative check of the data to examine the assumptions of the study design, patient demographics and clinical characteristics and assess the need for an amendment, if applicable. The interim analysis will allow for a timely descriptive analysis of the aggregated data, to identify trends. Findings will be reported per applicable guidelines.

9.8. Quality Control

9.8.1. Data Collection, Validation, and Quality Control at the Company Level

Information recorded as part of routine clinical practise will be transcribed to an eCRF. Computerised handling of the data by Lilly or the vendor may generate data queries to which the participating physician is obliged to respond by confirming or modifying the data questioned. To ensure accurate, complete, and reliable data, the MAH or its representatives will do the following:

- provide written or electronic instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the treating physicians and study coordinators. This training will give instruction on the protocol and the completion of the eCRFs.
- be available for consultation and be in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection. When errors are noted or suspected, queries will be generated.

In addition, data collection and validation procedures will be detailed in appropriate operational documents (on file with the MAH).

9.8.2. Data Quality Control at Site Level

Data quality control will be performed on active sites (which have enrolled at least 1 patient). Quality control will be performed by qualified designated personnel in each country.

9.9. Limitations of the Research Methods

This is a prospective, non-interventional, comparative, observational cohort study in the EU. Taking into account the rarity of squamous NSCLC in the EU, this study plans to enrol approximately 1000 patients, including 667 treated with necitumumab in combination with gemcitabine and cisplatin and 333 treated with cisplatin-based doublet therapy.

Non-randomisation information bias: Given the nature of this observational study, the patients participating in the study will not be randomised. The decision on the type of treatment is made based on physicians' clinical judgment independent of the study entry. The 2 treatment cohorts may be different on their observed covariates, which can introduce information bias in the outcome estimates. The propensity score analysis will be performed by calculating and matching on the probability of receiving a treatment given the observed covariates, thereby increasing the comparability of the 2 treatment groups and to reduce the bias.

Diagnostic suspicion bias: Since patient visits and all evaluations will be done as per routine clinical practise, physician's knowledge of the necitumumab pivotal trial results and SmPC special warnings about thromboembolic events and cardiorespiratory disorders may lead to more investigations in patients receiving necitumumab compared to patients in the comparator cohort. Therefore, there is a potential diagnostic suspicion (ascertainment) bias to observe more thromboembolic events and cardiorespiratory disorders among patients receiving necitumumab than those who received cisplatin-based doublet. Frequency of investigational tests will be included as a covariate in the multivariate analysis, to control for the potential imbalance and to reduce this bias.

Missing information of some outcomes: As the variables will be collected in the routine clinical practise setting, some of the secondary outcomes may be inconsistently captured during the study on all patients, such as ECG, EGFR protein expression status.

Recruitment of patients depends on market factors: Market uptake of new products such as necitumumab (Portrazza®) is unpredictable and has the potential to impact the feasibility of

meeting the Cohort 1 recruitment target. Continuous monitoring of patient recruitment at the site and country levels will allow strategies to be employed in response to any such challenges and to reduce or eliminate the potential impact of these factors. These include potentially initiating additional sites within participating countries. If the number of patients available for follow-up is still less than the desired sample size, consideration will be given to extending the site/patient enrolment to North America. All sites will be trained and clearly instructed that the treatment decision should be independent of enrolment into the study. Any selection bias that may arise from this expansion of sites will be scrutinised by comparing patient characteristics to the overall patient population.

Considering the rarity of squamous NSCLC and that carboplatin-based chemotherapies are the most commonly used first-line regimens in the US for NSCLC (Azzoli et al. 2007), if the number of patients available for follow-up is still less than the desired sample size after the site/patient enrolment extending to North America, consideration will be given to supplementing the prospective cohort study by extracting information from medical charts in Europe and North America to populate the eCRF as a contingent to ensure the delivery of the study on time.

Robust data quality of clinical variables, such as treatments, study outcomes and other clinical characteristics, is expected, as the information is directly collected by the physicians. In order to limit potential bias in patient selection, participating physicians will be asked to invite all patients to participate who meet the study criteria.

9.10. Other Aspects

9.10.1. Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (that is, substantial, significant) amendments will be approved by the relevant regulatory authorities and will usually require submission or notification to the relevant institutional review board (IRB)/ independent ethics committee (IEC) for approval or favourable opinion, if applicable. In such cases, the amendment will be implemented at the site only after approval or favourable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by each participating site and will be submitted to the relevant IRB/IEC or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to continued participation in the study.

10. Protection of Human Subjects

To ensure the quality and integrity of research, this study will be conducted under the Guidelines on Good Pharmacovigilance Practices (GVP) issued by the EMA (2016), the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE 2015), the Declaration of Helsinki (World Medical Association [WMA] 2016) and its amendments, and any applicable national guidelines.

10.1. Subject Consent to Release Information

This is an observational research programme and does not impose any form of intervention on the study physician. Hence, the assessment and treatment of patients is based solely on the study physician's routine or usual practise in the provision of care to patients with locally advanced or metastatic squamous NSCLC. The patient will provide authorisation for the use and disclosure of their personal health information. This consent covers the collection and release of data regarding treatment and its outcomes for the entire period of the study. The confidential nature of the patient information will be maintained.

10.2. Ethical Review and Regulatory Considerations

Observational studies will be submitted to ethical review boards (ERBs) for approval whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with applicable laws and regulations of the region, country, or countries where the study is being conducted.

11. Management and Reporting of Adverse Events/ Adverse Reactions

The study physician or other site personnel will record via eCRF any protocol-defined AEs, including all associated fatal outcomes, including the entire follow-up period. The protocol-defined AEs include all SAEs and the protocol-defined non-serious AEs specified in Section 9.3.5. All other AEs will not be actively collected, as they are considered observations that are predominant in a terminally ill cancer population treated with cytotoxic chemotherapy regimens. Furthermore, data from the clinical programme of necitumumab have generated a good understanding of those AEs; therefore, they are not included in the objectives of this study, and consequently they will not be collected.

Investigators and other study personnel are requested to report any suspected adverse reactions (SARs) with Lilly products not under evaluation in this protocol or SARs with non-Lilly products to the appropriate party (for example, regulators or the MAH) as they would in normal practise as required by applicable laws, regulations, and practises.

Investigators and other study personnel are not obligated to actively collect AEs or SAEs in patients once they have discontinued from the study. However, if the investigator learns of any SAE, including death, at any time after the patient has discontinued from the study, and the event is considered reasonably possibly related to the Lilly product under evaluation, the investigator must promptly notify Lilly.

The management and reporting of adverse reactions for this protocol will be in adherence to GVP Module VI (EMA 2014) and E2A Guidelines (International Conference on Harmonisation [ICH] 1994).

11.1. Serious Adverse Events

Study site personnel will report to Lilly or its designee any SAE occurring in temporal association with the Lilly drugs under evaluation within 24 hours of awareness of the event via a sponsor-approved method. Reports issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE that results in 1 of the following outcomes:

- death
    - death due to disease progression should not be reported as an SAE unless the physician deems it to be possibly related to the study drug
- initial or prolonged in-patient hospitalisation
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- or is considered significant by the physician for any other reason, such as important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered SAEs when, based upon appropriate medical judgment, they may jeopardise the patient.

11.2. Non-Serious Adverse Events Reporting Timing

The investigator or other study personnel will record any **non-serious** protocol-defined AE arising in temporal association with the Lilly product(s) under evaluation within 30 days of awareness of the event via electronic data entry. Lilly or its designee will execute the data extraction every 30 days for European sites to comply with regulatory reporting requirements.

11.3. Product Complaints

Lilly collects product complaints on products used in medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to concomitant drugs are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

Investigators are instructed to report product complaints as they would for products in the marketplace.

12. Plans for Disseminating and Communicating Study Results

The study will be registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Study progress updates (for example, number of patients enrolled and number of patients in each cohort) will be included in the necitumumab PBRER/PSUR, as described in Section 9.7.3. An interim analysis will be conducted as described in Section 9.7.3. The final report of the study results will be submitted as described in Section 6. Additionally, the study findings may be presented at a scientific congress and submitted to a peer-reviewed journal.

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Annex 1. List of Stand Alone Documents

Not applicable.

Annex 2. ENCePP Checklist for Study Protocols

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]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☒	☐	☐	15
1.1.4 Interim progress report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

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)	☒	☐	☐	16
2.1.2 The objective(s) of the study?	☒	☐	☐	17
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	18
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This study will compare the two study cohorts qualitatively, instead of conducting formal hypothesis(-es) tests.

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	☒	☐	☐	18

[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 3: Study Design	**Yes**	**No**	**N/A**	**Page Number(s)**
design)				
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	17
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)	☒	☐	☐	28, 30, 32

Comments:

Section 9.2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	18
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	19
4.2.2 Age and sex?	☒	☐	☐	19
4.2.3 Country of origin?	☒	☐	☐	18
4.2.4 Disease/indication?	☒	☐	☐	18, 19
4.2.5 Co-morbidity?	☐	☐	☒	
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)	☒	☐	☐	19

Comments:

The study population is not defined in terms of co-morbidities. Medical history/comorbidities of eligible patients will be collected in the study.

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)	☒	☐	☐	20-21
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)	☐	☐	☒	34
5.3 Is exposure classified according to time windows? (e.g.	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
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?	☐	☐	☒	

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?	☒	☐	☐	22-23
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)	☒	☐	☐	32-33

Comments:

The safety outcomes will be collected by the physicians. An independent adjudication committee will assess fatal cases and cases reported as having thromboembolic events by a blinded review.

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)	☒	☐	☐	29-31
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	31

Comments:

Section 9.4: 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-	☒	☐	☐	23, 26-27

Section 9.4: Data sources	Yes	No	N/A	Page Number(s)
face interview, etc.)				
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.)	☒	☐	☐	23, 26-27
8.1.3 Covariates?	☒	☐	☐	23, 26-27
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)	☒	☐	☐	21
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	22
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	21-23
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	23
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	23
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	23
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?	☒	☐	☐	23-26

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?	☒	☐	☐	28-32

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.3 Are descriptive analyses included?	☒	☐	☐	28-32
10.4 Are stratified analyses included?	☒	☐	☐	28, 30
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	28-32
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	32

Comments:

Details of the data analysis will be defined in the SAP.

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?	☒	☐	☐	27
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	27
11.3 Are methods of quality assurance described?	☒	☐	☐	32-33
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	33-34
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	20

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	34
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)	☒	☐	☐	33
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	23-25, 33-34
12.3 Does the protocol address other limitations?	☒	☐	☐	33-34

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?	☒	☐	☐	35
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	35

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?	☒	☐	☐	14

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, 32, 38
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	38

Comments:

Name of the main author of the protocol: PPD

Date: XX November 2016

Signature: _____

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