Retrospective Observational Comparative Safety Study Information

Title	Safety Profile of Pemetrexed+Carboplatin AUC5 and Pemetrexed+Carboplatin AUC6 for Patients with Non-Small Cell Lung Cancer
Version identifier	1.0
Date of last version	Not applicable
EU PAS Register No:	ENCEPP/SDPP/9318
Active substance	Pemetrexed L01BA04 Carboplatin L01XA02
Medicinal product(s):	Alimta Paraplatin and generic forms of Carboplatin
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s)	Eli Lilly and Company
Joint PASS	Not applicable
Research question and objectives	To describe the safety profiles among NSCLC patients treated with Pem/Carbo AUC5 and the Pem/Carbo AUC6
Country(-ies) of study	United States of America
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Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly and Company
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2. List of Abbreviations

Term	Definition
AUC	area under the curve
CI	Confidence interval
EMR	Electronic medical records
FDA	(United States) Food and Drug Administration
GFR	Glomerular filtration rate
HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
IR	Incidence rate
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
Pem/Carbo	Pemetrexed + Carboplatin chemotherapy
RWE	Real-world evidence
SCLC	Small cell lung cancer
US	United States

3. Responsible Parties

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4. Abstract

Title: Safety Profile of Pemetrexed+Carboplatin AUC5 and Pemetrexed+Carboplatin AUC6 for Patients with Non-Small Cell Lung Cancer

Version: 1.0. **Date:** 20 November 2014

Rationale and background: Pemetrexed in combination with carboplatin chemotherapy (Pem/Carbo) is widely recognized and endorsed by local and regional treatment guidelines (e.g., NCCN 2015) and is broadly used in clinical practice to treat patients with nonsquamous NSCLC in various countries around the world. There is a lack of information summarizing the safety profile of patients treated with this combination in real-world settings, which is in need by health care professional (HCPs).

Research question and objectives: The purpose of this study is to evaluate the safety profiles of NSCLC patients treated with Pem/Carbo AUC5 and Pem/Carbo AUC6.

Study design: A retrospective cohort study is proposed. The study will use information from a United States (US) database that contains oncology clinics electronic medical records (EMR), combined with medical claims and pharmacy data, to assess the incidence of haematological and non-haematological safety outcomes among NSCLC patients treated with Pem/Carbo AUC5 relative to Pem/Carbo AUC6.

Population: The study population are the NSCLC patients with evidence of initiating Pem/Carbo AUC5 or Pem/Carbo AUC6 on or after the date of NSCLC diagnosis. During 04 February 2004 (the date that Pemetrexed was first approved by FDA in the US) and 31 May 2014 (30 days before the last date that the data are available in the database), among all patients with only 1 primary tumour type and valid age information, those who meet the following criteria will be included in the study:

1) Patients were diagnosed with lung cancer as a primary cancer (at least one ICD-9-CM code in 162.2, 162.3, 162.4, 162.5, 162.8, or162.9, or a TUMOR TYPE value of "Lung Cancer"), **excluding** those who had a small cell histology (ICD-O-3 code 8002, 8041-8045, or a cancer subtype recorded as "SCLC" [small cell lung cancer] in the IMS Oncology EMR); ***and***
2) Patients initiated the Pem/Carbo AUC5 or Pem/Carbo AUC6 after the lung cancer diagnosis. The date of Pem/Carbo AUC5 or Pem/Carbo AUC6 initiation is the index date, **excluding** those who started on Pemetrexed/Carboplatin/Bevacizumab and then switched to Pem/Carbo AUC5 or Pem/Carbo AUC6 and those who started on Pem/Carbo AUC5 or Pem/Carbo AUC6 and then switched to Pemetrexed/Carboplatin/Bevacizumab; ***and***
3) Patients must be 18 years of age or older on the index date, have valid gender and weight information, at least one non-missing serum creatinine test result during the period from 7 days prior to the index date until 7 days after the index date, and valid dose record for the index carboplatin prescription; ***and***

4) Patient's oncology practice must be stable between the index date and end of record in the database, or 30 June 2014, whichever first.

Variables

Exposure variable is Pem/Carbo AUC5 or Pem/Carbo AUC6. Carboplatin AUC value is calculated based on recorded Carboplatin dose, patient's gender, age, weight, and serum creatinine concentration.

Patient characteristics include patients' demographic characteristics (age and gender) and comorbidity conditions identified before the index date. The comorbidity conditions to be considered include: Diabetes, diabetes with chronic complications, cardiovascular disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, hemiplegia or paraplegia, renal disease, and moderate or severe liver disease.

Other medications include medications prescribed or administered, including systemic anti-cancer treatments and all other medications by drug class, recorded up to 3 months prior to the index date (index date not included), and concomitant medications during the Pem/Carbo on-treatment period will be reported.

Study outcomes are the safety endpoint events that occurred on or after the index date. The haematological outcomes to be assessed include: Neutropenia, Leukopenia, Thrombocytopenia, Anemia, and Febrile neutropenia. The non-haematological outcomes include: Alopecia, Anorexia, Constipation, Diarrhea, Fatigue, Mucositis/stomatitis, Nausea, Rash, Vomiting, Peripheral sensory neuropathy, and Renal failure.

Data sources: The present study will use a US-based oncology clinics based electronic medical record and medical claim database: IMS Oncology Database.

Study size: A feasibility assessment to determine the sample size and study power has been conducted. With a 95% confidence interval (CI) and around 80% power, to detect a statistically significant risk ratio ≥ 2, when the ratio of Pem/Carbo AUC5 arm: Pem/Carbo AUC6 arm is 3:1, 344 Pem/Carbo AUC5 patients and 115 Pem/Carbo AUC6 patients will be required given 10% or more of the unexposed group having the study outcome.

Data analysis: The primary analysis of this protocol is to describe the incident safety outcomes after index date in patients who were administered at least 1 Pem/Carbo AUC5 or Pem/Carbo AUC6 treatment. If data allow, incidence rates, rate difference, and hazard ratios (HRs) will be estimated among the comparable Pem/Carbo AUC5 patients and Pem/Carbo AUC6 patients with the application of the propensity score stratification method.

5. Amendments and updates

Not applicable.

6. Milestones

Milestone	Planned date
Start of data analysis	20 April 2015
End of data analysis	31 September 2015
Final report of study results	31 December 2015

7. Rationale and background

Alimta (pemetrexed) was first approved by FDA on 04 February 2004 for treatment of malignant pleural mesothelioma. In the same year, the European Commission approved Alimta for 2 indications: malignant pleural mesothelioma, and second-line treatment for patients with NSCLC. In 2008, both the European health authorities and FDA approved the use of Alimta in combination with cisplatin in the first-line treatment of NSCLC. Most recently, in 2009, Alimta as a single agent was approved by FDA as maintenance therapy for nonsquamous NSCLC after "platinum-based" first-line chemotherapy.

Pemetrexed in combination with carboplatin chemotherapy (Pem/Carbo) is widely recognized and endorsed by local and regional treatment guidelines (e.g., NCCN 2015), and is broadly used in clinical practice to treat patients with nonsquamous NSCLC in various countries around the world. A summarizing of the existing scientific evidence about the safety profile of the Pem/Carbo combination is needed to answer frequently occurring questions arising from HCPs.

A recent meta-analysis of clinical trial data reported a better safety profile among non-squamous NSCLC patients treated with Pem/Carbo AUC5 than Pem/Carbo AUC6 patients in general. However, there is still a lack of information about the safety profile of these 2 treatment regimens in real-world settings.

The proposed real-world experience (RWE) study will complement the clinical trial meta-analysis by evaluating the same clinical parameters and safety outcomes as the meta-analysis, and also by providing additional subgroup analyses using a US-based database of oncology clinics electronic medical record and medical claims. Notably, this RWE study does not include any clinical trial data included in the clinical trial meta-analysis.

Lilly intends to disseminate its findings from this study by including the results in a manuscript submitted to an appropriate journal and/or through poster or podium presentations, as appropriate. In addition, Lilly intends to make the results available to HCPs who may request such information on an unsolicited basis in a manner that is acceptable under applicable local regulations. The results of this study effort will not be used to establish recommendations for clinicians on 1 dose of carboplatin over another.

8. Research question and objectives

The purpose of this study is to evaluate the safety profiles of NSCLC patients treated with Pem/Carbo AUC5 and Pem/Carbo AUC6.

The primary objectives include:

1) To describe demographic and clinical characteristics of the NSCLC patients treated with Pem/Carbo AUC5 or Pem/Carbo AUC6;
2) To estimate the crude incidence proportions and incidence rates of the safety outcomes among the NSCLC patients treated with Pem/Carbo AUC5 or Pem/Carbo AUC6;
3) If data allow, to estimate the incidence rate, rate difference, and HR of safety outcomes among the NSCLC patients treated with Pem/Carbo AUC5 or Pem/Carbo AUC6, adjusted for patients' demographic and clinical characteristics.

If data allow, the secondary objectives include conducing subgroup analysis to further examine the safety profiles of the NSCLC patients treated with the 2 regimens in those who were below 70 and who were 70 years or older.

9. Research methods

9.1. Study design

This will be a retrospective cohort study design using IMS Oncology, a US oncology clinic database including electronic medical records, inpatient/outpatient medical claims, and pharmacy claims. The 2 exposure groups will be patients with evidence of Pemetrexed (ATC L01BA04) and Carboplatin (ATC L01XA02) (Pem/Carbo) AUC5 or Pem/Carbo AUC6 treatment after the NSCLC diagnosis. The index date will be the date of the first evidence of Pem/Carbo AUC5 or Pem/Carbo AUC6 treatment after the NSCLC diagnosis. Carboplatin dose is calculated using Calvert Formula (Annex 3). For each patient, the baseline period will be defined as the period from the first record in the database until the index date. For each study endpoint, the follow-up begins on the date of the first qualifying treatment initiation and continues until the occurrence of the study end point, end of on-treatment period (defined as 30 days after the last dose of the study medicine before treatment discontinuation, see Section 9.3.1), an administration/prescription record indicating a switch from the study medicines to another carboplatin AUC value in combination with pemetrexed, the last record in the database, or 30 June 2014, whichever comes first. The study contains descriptive analysis to present the frequencies and proportions for the patient characteristics and study endpoints, as well as adjusted comparative analysis to present HRs and incidence rate difference of the study endpoints, with the null hypothesis that there is no difference between the 2 exposure groups. While there is no a priori hypothesis about the confounders to be included or the difference in safety profile occurrence among the 2 exposure groups, some patient characteristics may be adjusted for, such as age and gender.

9.2. Setting

During 04 February 2004 to 31 May 2014, among all IMS Oncology patients with only 1 primary tumour type and valid age information, those who meet the following criteria will be included in the study:

1) Patients were diagnosed with lung cancer as a primary cancer (at least one ICD-9-CM code in 162.2, 162.3, 162.4, 162.5, 162.8, or162.9, or a TUMOR TYPE value of "Lung Cancer"), **excluding** those who had a small cell histology (ICD-O-3 code 8002, 8041-8045, or a cancer subtype recorded as "SCLC" in the IMS Oncology EMR); ***and***
2) Patients initiated the Pem/Carbo AUC5 or Pem/Carbo AUC6 on or after the lung cancer diagnosis. The date of Pem/Carbo AUC5 or Pem/Carbo AUC6 initiation is the index date, **excluding** those who started on Pemetrexed/Carboplatin/Bevacizumab and then switched to Pem/Carbo AUC5 or Pem/Carbo AUC6 and those who started on Pem/Carbo AUC5 or Pem/Carbo AUC6 and then switched to Pemetrexed/Carboplatin/Bevacizumab; ***and***
3) Patients must be 18 years of age or older on the index date, have valid gender and value weight information after the index date, at least 1 non-missing serum creatinine test result during the period from 7 days prior to the index date until 7 days after the index date, and valid dose record for the index carboplatin prescription; ***and***

4) Patient's oncology practice must be stable between the index date and end of record in the database, or 30 June 2014, whichever comes first.

9.3. Variables

9.3.1. Exposure

The exposure variable is Pem/Carbo AUC5 or Pem/Carbo AUC6 treatment after the diagnosis of NSCLC. The Carboplatin AUC value is determined by recorded index Carboplatin dose and glomerular filtration rate (GFR) using Calvert Formula. Creatinine clearance, calculated based on gender, age, weight, and serum creatinine, is used as surrogate for GFR (see Annex 3). The on-treatment period begins on the day of the first dose of the study treatment and continues to 30 days after the treatment discontinuation. Treatment discontinuation is defined as a gap in continuous study medication coverage exceeding 42 days (2 cycles), or an administration record indicating a switch from the study medication to another treatment, whichever comes first. The administration of Pemetrexed and Carboplatin and patients' gender, age, weight, and serum creatinine will be abstracted from the electronic medical records.

9.3.2. Patient Characteristics

Baseline characteristics include patients' demographic characteristics (age and gender) and comorbidity conditions identified on or before the index date, and patients' medication use up to 3 months prior to the index date. The comorbidity conditions to be considered include: Diabetes, diabetes with chronic complications, cardiovascular disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, hemiplegia or paraplegia, renal disease, and moderate or severe liver disease. Comorbidities were selected and modified based on Charlson's comorbidity index (Charlson et al. 1987; Deyo et al. 1992; Simon et al. 2012). Given that the study cohort are all cancer patients, cancer characteristics will be described separately. The comorbidity conditions will be identified through ICD-9-CM diagnosis codes suggested by Deyo et al. 1992. Medications prescribed or administered recorded up to 3 months prior to the index date (index date not included) will be reported. All systemic anti-cancer treatments and all other medications will be identified.

Concomitant medications during the Pem/Carbo AUC5 or Pem/Carbo AUC6 on-treatment period will also be reported.

9.3.3. Study Outcomes

The study outcomes are the safety endpoint events that occurred on or after the index date during the on-treatment period. EMR, in-patient, and outpatient claims will be used to identify the events of interest. The safety endpoints to be assessed include haematological outcomes including neutropenia, leukopenia, thrombocytopenia, anaemia, and febrile neutropenia and non-haematological outcomes including alopecia, anorexia, constipation, diarrhoea, fatigue, mucositis/stomatitis, nausea, rash, vomiting, peripheral sensory neuropathy, and renal failure.

The safety outcomes will be identified through ICD-9-CM diagnosis codes recorded in the EMR and medical claims.

For each safety endpoint, the observation period begins when Pem/Carbo AUC5 or Pem/Carbo AUC6 treatments are first administered to the patient (index date) and last until the end of follow-up (defined in Section 9.1).

9.4. Data sources

IMS Oncology is a private-practice database of longitudinal, patient-level EMR, hospital charge data, and medical and pharmacy claims collected from physicians and other healthcare providers across the 50 states in the US. The IMS pharmacy claims database, established in 2001, includes claims (National Council for Prescription Drug Programs Version 5.2) for more than 2 billion prescriptions dispensed annually. The IMS medical claims database, established in 1999, includes more than one billion annual claims (CMS 1500 forms) containing diagnosis and visit information and represents activity of more than 865,000 physicians per month. The IMS CDM database contains patient hospital-visit records for approximately 9 million in-patient and 96 million out-patient visits annually.

Especially, the IMS Oncology EMR data consist primarily of medium and large community-based oncology practices. Each practice utilizes an Electronic Medical Record system capturing detailed, patient-level clinical data which is then de-identified, assigned a synthetic ID, and integrated into the warehouse. IMS receives data-feeds from Medical Oncology Practices and Comprehensive Cancer Centers in the US. More than 500,000 cancer patients are in this dataset, representing 344 locations from 37 states. This encompasses about 550 treating providers. Approximately 60,000 patients are observed in this database every month. Detailed clinical data are available for these EMR patients. Data attributes include but are not limited to: Diagnosis (and includes non-oncology as well as oncology diagnoses), Cancer Staging, TNM Values, Patient Demographics, Lab Results and Vitals, Injectables and Oral Medications including chemo and hormonal drugs, Dosing, and Drug Regimens and Treatment Intervals. Facility information (type, State) is also included. In addition, for a small subset of patients, available patient social history (e.g., smoking, alcohol use), and blood transfusion data at an administration level are provided. The data time period is from January 2000 to June 2014, although the data are more robust from 2004 onward.

9.5. Study size

Feasibility assessments were conducted to determine the sample size based on IMS Oncology data between 04 February 2004 and 31 December 2012. The feasibility study showed that there were 345 eligible patients receiving Pem/Carbo AUC5 and 115 eligible patients receiving Pem/Carbo AUC6 treatment. Study power was calculated using Epi Info 7. Sample size for the retrospective cohort study was estimated to detect a statistically significant risk ratio ≥ 2 based on the assumption of proportion of the safety outcomes in the unexposed group or reference group (Pem/Carbo AUC5) with around 80% power, at 95% two-sided CI. Based on the feasibility counts, the available samples size will have 80% power to detect a statistically significant risk ratio ≥ 2 if 10% or more of the Pem/Carbo AUC5 group have the study outcome.

The risk ratio value of 2 was selected based on the suggestion from OMOP: "You need a relative risk >2 to have confidence in result…detecting effects smaller than 2 will incur higher risk of false positives" (FDA Science Board Subcommittee, Review of the FDA/CDER Pharmacovigilance Program, May 6, 2011).

Table 9. Power and Sample Size Estimation of Primary Retrospective Cohort Study, with 2-sided Confidence Level of 95% ($\alpha = 0.05$).

% Outcome in Unexposed Group	*Power = 1- β (type II error)*							
	Pem/Carbo AUC5				Pem/Carbo AUC6			
	60	70	80	90	60	70	80	90
Unexposed: Exposed Ratio = 3:1								
1	2,419	3,048	3,876	5,188	807	1,016	1,292	1,730
5	460	579	736	986	154	193	246	329
10	215	271	**344**	460	72	91	**115**	154
15	133	168	213	285	45	56	71	95
20	92	116	148	198	31	39	50	66
25	68	85	108	145	23	29	36	49

9.6. Data management

SAS ® Proprietary Software 9.2 will be utilized for data management; the relevant comments such as *proc datasets, proc format, proc sql*, etc. will be used to access the raw data, manage the analytical dataset, and process the integrated analytical datasets.

Datasets and analytic programs will be kept on a secure server and archived per Lilly record retention procedures.

9.7. Data analysis

All data programming and analysis will be carried out using SAS (version 9.2). Analyses will be conducted in the NSCLC patients treated with Pem/Carbo AUC5 or Pen/Carbo AUC6, excluding SCLC patients, in IMS Oncology between 04 February 2004 and 30 June 2014. Specific objectives will be addressed as described below.

Aim 1: To describe baseline demographic and clinical characteristics of the NSCLC patients treated with Pem/Carbo AUC5 or Pem/Carbo AUC6

For each group, the demographic characteristics, cancer characteristics, comorbidities during pre-index period, and other systemic cancer treatments and other medications during 3 months prior to the index will be assessed using descriptive statistics. Concomitant medications during the on-treatment period will also be summarized for each group. The demographic and clinical characteristics will be summarized using counts and frequencies with 95% CI for categorical variables and mean/standard deviation/median/min/max for continuous variables. The statistical significance of differences in patient demographic and clinical characteristics, and prior and

concomitant medications will be assessed using t-tests or chi-square tests as appropriate. If data allow, subgroup analyses will be performed separately for patients age 70 years or older.

Aim 2: To estimate the crude incidence rates of the safety outcomes among the NSCLC patients treated with Pem/Carbo AUC5 or Pem/Carbo AUC6

For the incidence estimation, only the first occurrence of the safety outcomes occurred on or after the index date will count. The incidence rate with 95% CIs will be estimated using the counts of the first occurrence of the events and the exposure follow-up time. The occurrence of the safety outcomes during the follow-up will be summarized as counts and frequencies with 95% CIs.

Aim 3: If data allow, to estimate the incidence rates, rate difference, and HR of treatment-emergent safety outcomes among the NSCLC patients treated with Pem/Carbo AUC5 or Pem/Carbo AUC6, adjusted for patients' demographic and clinical characteristics

If data are available, propensity score stratification will be used to adjust for differences in the distribution of baseline characteristics. Propensity score stratification, instead of propensity score matching, is used because there are 3 times as many Pem/Carbo AUC5 as Pem/Carbo AUC6 patients eligible for study inclusion and propensity score would have led to the exclusion of a substantial number of Pem/Carbo AUC5-treated patients, thereby not compromising generalizability.

Propensity score stratification will be performed in 2 steps, and the propensity score models will be assessed and finalized before the assessment of outcome data. First, for all eligible patients, unconditional logistic regression will be used to estimate the probability of initiating Pem/Carbo AUC6 treatment given their baseline demographic characteristics, baseline comorbidities, and medications used during 3 months prior to the index date. Patients will then be classified into strata determined by quintiles of the propensity score in the Pen/Carbo AUC6 cohort, to produce cohorts with similar baseline characteristics within each stratum. Adjusted estimates of the safety outcome incidence rates and rate differences will be calculated by taking a weighted average of the stratum-specific estimates where the weights equalled the number of Pem/Carbo AUC6 patients in each stratum divided by the total number of Pem/Carbo AUC6 patients. Because the strata will be constructed based on quintiles of the Pem/Carbo AUC6 cohort, the weights will be 0.2 for each stratum (Greenland et al. 1999, Sato and Matsuyama 2003, Stuart 2010).

Given that propensity score stratification has better generalizability while propensity score matching is more advantaged in terms of bias control, propensity score matching will be applied as a sensitivity analysis. Appropriate sensitivity analysis may also be conducted to evaluate the robustness of various assumptions, for example unmeasured confounding.

Cox regression models will be used to compare time-to-event between the Pem/Carbo AUC5 and Pem/Carbo AUC6 cohorts, with Pem/Carbo AUC5 serving as reference. Statistical significance will be determined using 95% CIs and two-tailed p-values ($p \leq 0.05$). Incidence rates and rate differences will be estimated.

If data allow, the Cox regression models will be applied to the subgroups defined by age (<70 years, ≥70 years) to assess the potential effect modification by age.

Number and proportion of missing data for each pertinent variable will be reported.

9.8. Quality control

The study will use an existing database, which have been used primarily for research, fully HIPAA compliant. The study programs for data management or statistical analyses will be validated by individual(s) outside the study team to ensure data integrity and accuracy. All study programs, log files, and output files will be stored on the secure sever, and archiving any statistical programming performed to generate the results. In addition, the diagnosis criteria for comorbidity and safety outcome endpoints would be adjudicated by 2 experienced clinicians to ensure the accuracy of the diagnosis and decrease the misclassification.

9.9. Limitations of the research methods

The current study adopts an existing propensity score stratification methodology to preserve the generalizability of the results to all eligible NSCLC patients treated with Pem/Carbo AUC6 and minimize biases due to the unequal distributions of important baseline characteristics between the 2 patient groups, given the non-randomization property of observational database. Since random assignment is impossible, this approach offers robust control for confounding because it enables tailoring of the covariates selection based on pre-treatment characteristics of the 2 treatment groups and the events of interest. If data allow, propensity score matching will be conducted as a sensitivity analysis. However, given the nature of the data, which will be addressed below, residual confounding could be a possibility.

While the EMR and medical claims data are extremely valuable for the efficient and effective examination of disease outcome and treatment patterns, these data are collected for the purpose of administration and payment, instead of pharmaco-epidemiology research. Therefore, there are limitations associated with the use of these data.

First, information about the medical conditions is to be collected using ICD-9 disease classification coding system in the EMR or medical claims; thus, the conditions captured will be the severe conditions that need medical attention, but not the less severe ones. Caution needs to be taken that the pattern of less severe conditions may not be reflected by the study results.

Second, some important information are not well populated in the EMR database, such as certain lab results and Eastern Cooperative Oncology Group performance status, to assess how a patient's disease is progressing and determine appropriate treatment and prognosis. However, the study does include a number of pre-treatment covariates in the propensity score method to balance and minimize the differences between the Pem/Carbo AUC5 and Pem/Carbo AUC6 cohorts.

Third, the presence or absence of disease may not be completely accurate, because the diagnostic code may be incorrectly coded or included as rule-out criteria rather than actual disease, especially in the medical claims.

According to the feasibility analysis, if a study endpoint occurs to more than 10% of each exposure group, then the study will be able to detect a statistically significant risk ratio ≥ 2 with around 80% power, at 95% two-sided CI.

9.10. Other aspects

None

10. Protection of human subjects

All information about this observational study and individual medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. This study will be conducted in accordance with applicable laws and regulations of the region, country, or countries where the study is being conducted, as appropriate.

11. Management and reporting of adverse events/adverse reactions

During the course of retrospective observational research, the proposed study will not involve chart validation to obtain extra information on adverse events. Thus, Lilly is not expecting to report any adverse events or reactions.

12. Plans for disseminating and communicating study results

Lilly intends to disseminate its findings from this study by including the results in a manuscript submitted to an appropriate journal and/or through poster or podium presentations, as appropriate. In addition, Lilly intends to make the results available to HCPs who may request such information on an unsolicited basis in a manner that is acceptable under applicable local regulations. The results of this study effort will not be used to establish recommendations for clinicians on one dose of carboplatin over another.

13. References

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Annex 1. List of stand-alone documents

Not applicable.

Annex 2. ENCePP Checklist 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:
Safety Profile of Pemetrexed+Carboplatin AUC5 and Pemetrexed+Carboplatin AUC6 for Patients with Non-Small Cell Lung Cancer

Study reference number:
ENCEPP/SDPP/9318

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]	☒	☐	☐	9
1.1.2 End of data collection[2]	☒	☐	☐	9
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	9

Comments:
The study is not an EU PAS.

[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)	☒	☐	☐	10
2.1.2 The objective(s) of the study?	☒	☐	☐	11
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	12
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	12
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	12

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)	☒	☐	☐	12
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	13
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)	☒	☐	☐	12

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	14
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	12
4.2.2 Age and sex?	☒	☐	☐	12
4.2.3 Country of origin?	☒	☐	☐	14
4.2.4 Disease/indication?	☒	☐	☐	12
4.2.5 Co-morbidity?	☒	☐	☐	13
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)	☒	☐	☐	12

Comments:

The investigated disease (NSCLC) and treatments (Pemetrexed/Carboplatin AUC5 and Pemetrexed/Carboplatin AUC6) do not have seasonality.

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)	☒	☐	☐	13
5.2 Does the protocol discuss the validity of exposure				

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐ 13	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	13
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	13
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

The study is focusing on the safety outcomes of two treatments: Pemetrexed/Carboplatin AUC5 and Pemetrexed/Carboplatin AUC6.

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?	☒	☐	☐	13
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)	☒	☐	☐	17

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)	☒	☐	☐	16
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	17

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.)	☒	☐	☐	13
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.)	☒	☐	☐	13
8.1.3 Covariates?	☒	☐	☐	13
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)	☒	☐	☐	13
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	13
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
	☒	☐	☐	13
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	12
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	14
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	12
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	14

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	14 -15

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	16
10.2 Is the choice of statistical techniques described?	☒	☐	☐	16
10.3 Are descriptive analyses included?	☒	☐	☐	15 -16
10.4 Are stratified analyses included?	☒	☐	☐	17
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	16-17
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	17

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?	☒	☐	☐	17
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	17
11.3 Are methods of quality assurance described?	☒	☐	☐	17
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	17
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	17

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	17
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)	☒	☐	☐	17
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	18
12.3 Does the protocol address other limitations?	☒	☐	☐	17

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?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	19
13.3 Have data protection requirements been described?	☒	☐	☐	19

Comments:

The study will use an existing database, which have been used primarily for research, fully HIPAA compliant. All records are de-identified and no individuals are identifiable through the data.

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?	☒	☐	☐	8

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?	☒	☐	☐	21

Comments:

This study is not required by any regulartory authorities.

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Annex 3. Additional Information

Calvert Formula for Calculation of Carboplatin Dose

Target AUC (mg/mL x min) = Carboplatin Dose (mg) / [GFR (mL/min) + 25]

GFR, Glomerular Filtration Rate. Please note that in this study calculated creatinine clearance is used as surrogate for GFR (as measured by 51Cr EDTA clearance). Creatinine clearance is calculated by using the Cockcroft-Gault formula.

Cockcroft-Gault Formula for Calculation of Creatinine Clearance

For serum creatinine concentration in mg/dL:

Creatinine clearance for males (mL/min) = $\frac{(140-age)\times(weight)^a}{(72)\times(serum\ creatinine)}$

Creatinine clearance for females (mL/min) = $\frac{(0.85)\times(140-age)\times(weight)^a}{(72)\times(serum\ creatinine)}$

For serum creatinine concentration in μmol/L:

Creatinine clearance for males (mL/min) = $\frac{(140-age)\times(weight)^a}{(0.81)\times(serum\ creatinine)}$

Creatinine clearance for females (mL/min) = $\frac{(0.85)\times(140-age)\times(weight)^a}{(0.81)\times(serum\ creatinine)}$

[a] Age in years, weight in kilograms.