Post Authorisation Safety Study (PASS) Information

Title	**Safety and Effectiveness of Ramucirumab in Patients with Advanced Gastric Cancer in the European Union and North America: A Prospective Observational Registry (I4T-MC-JVDD)**
Protocol version identifier	2.0
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EU PAS Register No:	ENCEPP/SDPP/9400
Active substance	Ramucirumab (ATC code: L01XC)
Medicinal product(s):	Cyramza®
Product reference:	H0002829
Procedure number:	MEA 001
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 and effectiveness of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer.
Countries of study	This study will be conducted in the European Union and North America. 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.
AR	adverse reaction
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	ethical review board
EU	European Union
GEJ	gastro-oesophageal junction
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
HCC	hepatocellular carcinoma
HER2	human epidermal growth factor receptor 2
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
MAA	marketing authorisation application
MAH	marketing authorisation holder

mBC	metastatic breast cancer
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	non-small cell lung cancer
OS	overall survival
PASS	post authorisation safety study
PBRER	Periodic Benefit Risk Evaluation Report
PFS	progression-free survival
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
UK	United Kingdom
US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor

3. Responsible Parties

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4. Abstract

Title: Safety and Effectiveness of Ramucirumab in Patients with Advanced Gastric Cancer in the European Union and North America: A Prospective Observational Registry (I4T-MC-JVDD)

Version: 2.0. **Date:** April 2015

Rationale and background: Ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds vascular endothelial growth factor (VEGF) receptor 2.

To date, 6 Phase 3 trials evaluating the safety and efficacy of ramucirumab have been completed and the data have been unblinded and analysed. In these Phase 3 trials, a total of 2748 patients (safety population) have been treated with ramucirumab, either as a single agent or in combination with other antineoplastic agents in diverse tumour types, including gastric/gastro-oesophageal junction (GEJ) cancer, hepatocellular carcinoma, non-small cell lung cancer, metastatic colorectal cancer, and metastatic breast cancer.

The safety profile of single-agent ramucirumab in the pivotal Phase 3 REGARD trial was acceptable, with an adverse event (AE) profile that was similar to placebo. The safety profile of ramucirumab in combination with paclitaxel in the pivotal Phase 3 RAINBOW trial demonstrated that the combination was well tolerated in patients with gastric cancer, with manageable AEs. Thus, ramucirumab as a single agent or in combination with paclitaxel demonstrated a clinically acceptable safety profile in patients with advanced gastric or GEJ adenocarcinoma.

In order to evaluate the safety and effectiveness of ramucirumab in gastric or GEJ adenocarcinoma under real-world disease conditions, Lilly proposed a prospective observational cohort non-comparative study / registry in the European Union (EU) and North America. The safety profile of ramucirumab will be further described in the subgroups of special interest, including elderly patients, patients with cardiac comorbidities, and patients with hepatic or renal impairment. Patient enrolment into this study will depend upon ramucirumab approval status and reimbursement ability in respective countries.

Research question and objectives: The overall study objective is to evaluate the safety and effectiveness of ramucirumab under real-world disease conditions in the EU and North America, and specifically:

- **Primary objective:**
  To describe the safety of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions in the EU and North America.
- **Secondary objectives:**
  To describe the safety profile in the following subgroups:
  - Elderly patients
  - Patients with cardiac comorbidities

- Patients with hepatic impairment
- Patients with renal impairment

To describe the effectiveness of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions in the EU and North America.

Study design: This is a prospective, non-interventional, non-comparative, observational cohort study / registry in the EU and North America. The study design will reflect real-life clinical management of patients with advanced gastric cancer or GEJ adenocarcinoma. Type and frequency of actual patient visits and all evaluations will be done as for routine clinical practice.

Population: This study will include a cohort of approximately 600 adult patients with advanced gastric or GEJ adenocarcinoma whose disease has progressed after prior chemotherapy and who are treated with ramucirumab alone or in combination therapy as second-line therapy under real-world disease conditions.

Variables / Outcomes:

- ***Study treatment exposure:*** Ramucirumab treatment alone or in combination with chemotherapy.
- ***Patient, disease, and clinical characteristics***
- ***Safety:*** Adverse events will be collected, coded, and categorized using the Medical Dictionary for Regulatory Activities (MedDRA).
- ***Effectiveness:*** The measures include overall survival (OS) and progression-free survival (PFS).

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

Study size: Taking into account the rarity of gastric cancer in the EU and North America, this study plans to enrol approximately 600 patients treated with ramucirumab alone or in combination therapy. For the primary objective of this study, the sample size was determined based on the probability of observing at least 1 event for infrequent events and the width of confidence intervals (CIs) around event incidence for more common events. The sample size was also based on feasibility considerations including, but not restricted to, the low incidence and prevalence of the study population in the real world setting and predicted ramucirumab market uptake for monotherapy and combination therapy.

Data analysis: For the primary objective (that is, safety), data analyses will be conducted in all patients (that is, patients treated with ramucirumab alone or in combination therapy pooled together) and also will be stratified on the basis of whether patients received ramucirumab as monotherapy, combination therapy with paclitaxel, or combination therapy with anticancer agents other than paclitaxel. For the secondary objective (that is, effectiveness), data analyses will be stratified on the basis of whether patients received ramucirumab as monotherapy, combination therapy with paclitaxel, or combination therapy with anticancer agents other than paclitaxel.

A descriptive analysis will be conducted to evaluate the safety of ramucirumab. Categorical measures will be summarised as counts and percentages, while continuous measures will be summarised using mean, median, standard deviation, and range.

Safety analyses will be performed for at least the following subgroups:

- Elderly patients
- Patients with cardiac comorbidities
- Patients with hepatic impairment
- Patients with renal impairment

For effectiveness outcomes, OS and PFS, Kaplan-Meier estimates (including curves) will be generated. The median and survival rates at given time points (for example, 3 months, 6 months, 9 months, 12 months) will be computed together with their 95% CIs using the Kaplan-Meier method. Best tumour response, treatment patterns, healthcare resource utilisation, and supportive care will be summarised descriptively.

5. Amendments and Updates

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
2.0	22 April 2015	Section 4 (Abstract) Section 6 (Milestones) Section 7 (Rationale and Background) Section 8 (Research Questions and Objectives) Section 9 (Research Methods) Section 11 (Management and Reporting of Adverse Events/ Adverse Reactions) Section 12 (Plans for Disseminating and Communicating Study Results) Section 13 (References)	The majority of sections were revised to provide supplemental information and further clarification regarding: o safety profile in patients with comorbidities such as cardiac, renal and hepatic comorbidities for which only limited data or no data are available from clinical trials (including objectives), o laboratory data to be collected and documented, o strategies for overcoming a situation that the number of patients with comorbidities will be too small, o periodic reporting, o data sources.	Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur's PASS protocol/results/ interim PASS results/ DUS protocol Assessment Report was adopted by PRAC on 26 March 2015 (before the start of data collection).

6. Milestones

Milestone	Planned date
Start of patient enrolment	Enrolment will start after placement of ramucirumab on the market in the first of participating study countries; estimated Q4 2015. The start of patient enrolment may change, subject to the uptake of ramucirumab.
End of data collection	Patient recruitment will end within 5 years after study initiation; estimated Q4 2020 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 ramucirumab and patient participation.
Study progress report 1	The planned date for the first study progress report may change, subject to change in the start date of patient recruitment. Study progress reports will be included annually in the ramucirumab Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR) commencing 1 year after the expected first patient visit (that is, the first study update will be included in the Q4 2016 PBRER/PSUR and no more frequently than annually thereafter).
Interim report 1	An interim analysis is planned when the targeted sample size reaches 300 (that is, half of the targeted study size).
Registration in the EU PAS register	Subject to the final protocol approval date, estimated Q3 2015.
Final report of study results	One year from the end of data collection, estimated Q4 2021. The planned date for the final report may change, subject to the changes in the start or end of patient recruitment proposed above.

7. Rationale and Background

Ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds vascular endothelial growth factor (VEGF) receptor 2. Cumulatively, as of 31 December 2014, ramucirumab or ramucirumab/placebo has been administered either as a single agent or in combination with various antineoplastic agents to approximately 7222 patients with different oncologic conditions in Phase 1/1b, Phase 2, and Phase 3 clinical trials. Based upon actual exposure data from completed clinical trials and the enrolment/randomisation schemes for ongoing trials, an estimated 4122 patients have received ramucirumab, with 991 patients receiving single-agent ramucirumab and 3131 patients receiving ramucirumab in combination with other antineoplastic agents. This is in contrast to the available data provided, which included only 236 ramucirumab patients (REGARD trial), at the time of the prior submission for the post authorisation safety study (PASS) protocol versions (dated August 2014 and December 2014, respectively).

To date, 6 Phase 3 trials evaluating the safety and efficacy of ramucirumab have been completed and the data have been unblinded and analysed. In these Phase 3 trials, a total of 2748 patients (safety population) have been treated with ramucirumab, either as a single agent or in combination with other antineoplastic agents in diverse tumour types, including 563 patients with gastric or gastro-oesophageal (GEJ) cancer, 317 patients with hepatocellular carcinoma (HCC), 627 patients with non-small cell lung cancer (NSCLC), 529 patients with metastatic colorectal cancer (mCRC), and 752 with metastatic breast cancer (mBC).

The safety profile of single-agent ramucirumab in the pivotal Phase 3 REGARD trial was acceptable, with an adverse event (AE) profile that was similar to placebo. The safety profile of ramucirumab in combination with paclitaxel in the pivotal Phase 3 RAINBOW trial demonstrated that the combination was well tolerated in patients with gastric cancer, with manageable AEs. Thus, ramucirumab as a single agent or in combination with paclitaxel demonstrated a clinically acceptable safety profile in patients with advanced gastric or GEJ adenocarcinoma.

During the initial Committee for Medicinal Products for Human Use (CHMP) review of the marketing authorisation application (MAA) for ramucirumab in the treatment of gastric cancer, the Pharmacovigilance Risk Assessment Committee (PRAC) requested a PASS to be conducted to characterise the safety and effectiveness of ramucirumab in patients with gastric cancer under real-world disease conditions. The safety profile of ramucirumab will be further described in the subgroups of special interest, including elderly patients, patients with cardiac comorbidities, and patients with hepatic or renal impairment. Lilly proposed a prospective, non-interventional, non-comparative observational cohort study/registry in the European Union (EU) and North America. Patient enrolment into this study will depend upon ramucirumab approval and reimbursement status in respective countries.

8. Research Question and Objectives

The overall study objective is to evaluate the safety and effectiveness of ramucirumab in gastric or GEJ adenocarcinoma under real-world disease conditions in the EU and North America, and specifically:

Primary Objective:

- To describe the safety profile of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions in the EU and North America.

Secondary Objectives:

- To describe the safety profile in the following subgroups:
    - Elderly patients
    - Patients with cardiac comorbidities
    - Patients with hepatic impairment
    - Patients with renal impairment
- To describe the effectiveness of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions in the EU and North America.

9. Research Methods

9.1. Study Design

This is a prospective, non-interventional, non-comparative, observational cohort study / registry in the EU and North America. The study design will reflect real-life clinical management of patients with advanced gastric cancer or GEJ adenocarcinoma. Type and frequency of actual patient visits and all evaluations will be done as for routine clinical practice.

9.2. Setting

9.2.1. Definition of the Disease

Locally advanced and unresectable or metastatic gastric or GEJ adenocarcinoma that has progressed after prior chemotherapy.

9.2.2. Study Population

This study will include a cohort of approximately 600 adult patients from the EU and North America with advanced gastric cancer or GEJ adenocarcinoma whose disease has progressed after prior chemotherapy and who are treated with ramucirumab alone or in combination therapy as second-line therapy under real-world disease conditions. The decision to initiate use of ramucirumab is made independently by the participant and their health care provider and is not mandated by the study design or protocol.

9.2.2.1. Inclusion Criteria

[1] Adult patients (age ≥ 18 years at enrolment) with advanced gastric cancer or GEJ adenocarcinoma whose disease has progressed after prior chemotherapy.

[2] Patients who initiate ramucirumab treatment either as a single agent or in combination with chemotherapy.

[3] Patients who have been fully informed and have given written 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 more than 1 line of chemotherapy for advanced gastric cancer or GEJ adenocarcinoma.

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

9.2.3. Duration of the Study

Patients will be followed for 12 months, until death, or loss to follow-up/withdrew consent, whichever occurs first, after initiation of ramucirumab treatment. Given that median overall survival (OS) time for patients with gastric cancer receiving second-line therapy is approximately 5 to 9 months, the available follow-up time will allow for the evaluation of long-

term safety and effectiveness. Of note, the median treatment duration for patients receiving ramucirumab observed in clinical trials is approximately 2 to 5 months.

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

9.2.4. Site Recruitment and Physician Selection

Physicians with a recognized competency in oncology who treat advanced gastric cancer or GEJ adenocarcinoma and treat with ramucirumab after prior chemotherapy will be prospectively identified as sites for potential inclusion in the study in each participating country.

A reasonable number of sites in the EU and North America will be utilised to reach the targeted patient number.

The country selection will be based on multiple factors, including number of sites with a recognized 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, suburban), practice setting (hospital-based, academic setting, private practice), estimated eligible patient availability, and staffing availability.

Site selection criteria will also include projected availability of eligible patients within the 5 years enrolment period and the availability of physician (and other site staff) time to complete the case report forms to the extent possible representativeness of sites reflective of the treatment patterns within each country. Selection criteria and basic site information (for example, patient volume, physician specialty, practice setting) will be collected via a site qualification survey.

9.2.5. Patient Identification

The physician should refer to the ramucirumab Summary of Product Characteristics (SmPC) (EU) and United States Prescribing Information (USPI) (United States) 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

Elderly population will be defined as patients aged ≥65 years. Other cut-off points (that is, 70 and 75 years of age) will be included in the analysis if subgroup sample size allows. The presence of cardiac comorbidity in the study population will be identified based on medical history, including, but not limited, to angina, myocardial infarction, congestive heart failure (CHF), and arrhythmia. Hepatic or renal impairment will be evaluated based on medical history and/or blood chemistry data (see Section 9.3.4 for additional details), if available.

9.3. Variables

9.3.1. Study Treatment

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

- Treatment (ramucirumab alone or in combination with chemotherapy), reason for treatment choice and chemotherapy regimen (if administered in combination)
- Dates of administration
- Pre-medications administered, if any
- Dosage and administration details (for example, infusion rate, duration)
- 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, blood pressure, ethnicity, smoking status, alcohol use, unintentional weight loss ≥10% over the 3 months prior to ramucirumab initiation
- Medical history
- Cancer diagnosis and characteristics, such as date of initial diagnosis, initial and current stage, histology, grading, sites of metastases, and human epidermal growth factor receptor 2 (HER2) status
- Prior anti-cancer treatment for gastric/GEJ adenocarcinoma: type of therapy (for example, surgery, radiation, adjuvant, neoadjuvant as well as chemotherapy, biologic), overall response, and ongoing complications from prior anti-cancer treatment
- Prior medications other than anti-cancer therapy, received within 14 days prior to initiation of ramucirumab which could potentially exacerbate ramucirumab-related toxicities (for example, chronic non-steroidal anti-inflammatory drugs and anticoagulants).

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
- Blood pressure
- Supportive care and procedure information (see Section 9.3.7)
- Laboratory:

- Haematology profile (including neutrophils and platelets)
- Coagulation profile (including partial thromboplastin time /activated partial thromboplastin time)
- Serum chemistry profile (including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and serum creatinine)
- Urinalysis (including urine protein)

9.3.4. Treatment Discontinuation and Post-discontinuation

The following information will be collected, if available:

- The date and main reason for ramucirumab and chemotherapy discontinuation
- Post discontinuation systemic anti-cancer therapy.

9.3.5. Safety Outcomes

- Regardless of the relatedness to ramucirumab, adverse events (including serious adverse events [SAEs]) from first administration of ramucirumab up to and including 90 days after last ramucirumab administration and any associated corrective medications, transfusions or supportive care will be recorded.
- Post 90 days after last ramucirumab infusion only AEs (including SAEs) related to ramucirumab will be recorded.

9.3.6. Effectiveness Outcomes

- Overall survival will be calculated from the date of first administration of ramucirumab to the date of death due to any cause.
  - After discontinuation from therapy, patient's survival status (dead, alive, lost to follow-up, withdrew from the study) up to 12 months from start of ramucirumab will be collected.
  - Date of death, date of withdrawal, or date of patient last known alive will also be collected.
- Progression-free survival (PFS) will be calculated from the date of first administration of ramucirumab to the date of disease progression or death due to any cause, whichever occurs first.
  - Disease progression will be determined by the physician based on normal clinical practice.
  - Date of progression will be collected.
- Best tumour response
  - Tumour response will be determined by the physician based on normal clinical practice.
  - Method of determination and frequency of assessment will be collected.

9.3.7. Supportive Care

The following supportive care will be collected, if available:

- Hospitalisations (related to advanced gastric/GEJ adenocarcinoma management and/or AEs) including:
    - Type of hospitalisation (for example, intensive care unit, standard ward, palliative units, day hospital, outpatient, emergency)
    - Admission and discharge dates
    - Main reason for hospitalisation at admission (that is, AE or disease related)
- Concomitant medications use and type (for example, granulocyte colony-stimulating factors, erythropoietin)
- Transfusions and type (for example, packed red blood cells, platelets, fresh frozen plasma, whole blood)
- Radiation therapy

9.4. Data Sources

For information recorded per routine clinical practice (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. All data reported on the electronic case report form (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 gastric cancer in the EU and North America, this study plans to enrol approximately 600 patients treated with ramucirumab as monotherapy or in combination therapy.

For the primary objective of this study, the sample size was determined based both on the probability of observing at least 1 event for infrequent events and the width of confidence intervals (CIs) around event incidence for more common events. The sample size was also based on feasibility considerations including, but not restricted to, the low incidence and prevalence of gastric cancer in the EU and North America under the real world setting and predicted ramucirumab market uptake for monotherapy and combination therapy.

Additionally, safety analyses are planned for the following subgroups: elderly patients, patients with cardiac comorbidities, patients with hepatic impairment, and patients with renal impairment.

It has been reported that approximately 77% and 61% of gastric cancer patients were diagnosed at ≥65 years of age in the United Kingdom (UK) and United States (US), respectively (Howlader

et al. 2014; Cancer Research UK 2015). Therefore, it is expected that at least half of patients to be enrolled into this study will consist of elderly patients.

The prevalence of hepatic and renal impairment increases with age, but these patients will represent a small subset of the overall study population. Considering the expected median age of the study population and the prevalence of these diseases in the real world setting (Ayodele et al. 2010; Blachier et al. 2013; van Gestel et al. 2013), it is estimated that at least 30 patients (5% conservative estimate of prevalence) will fall into each of these subgroups.

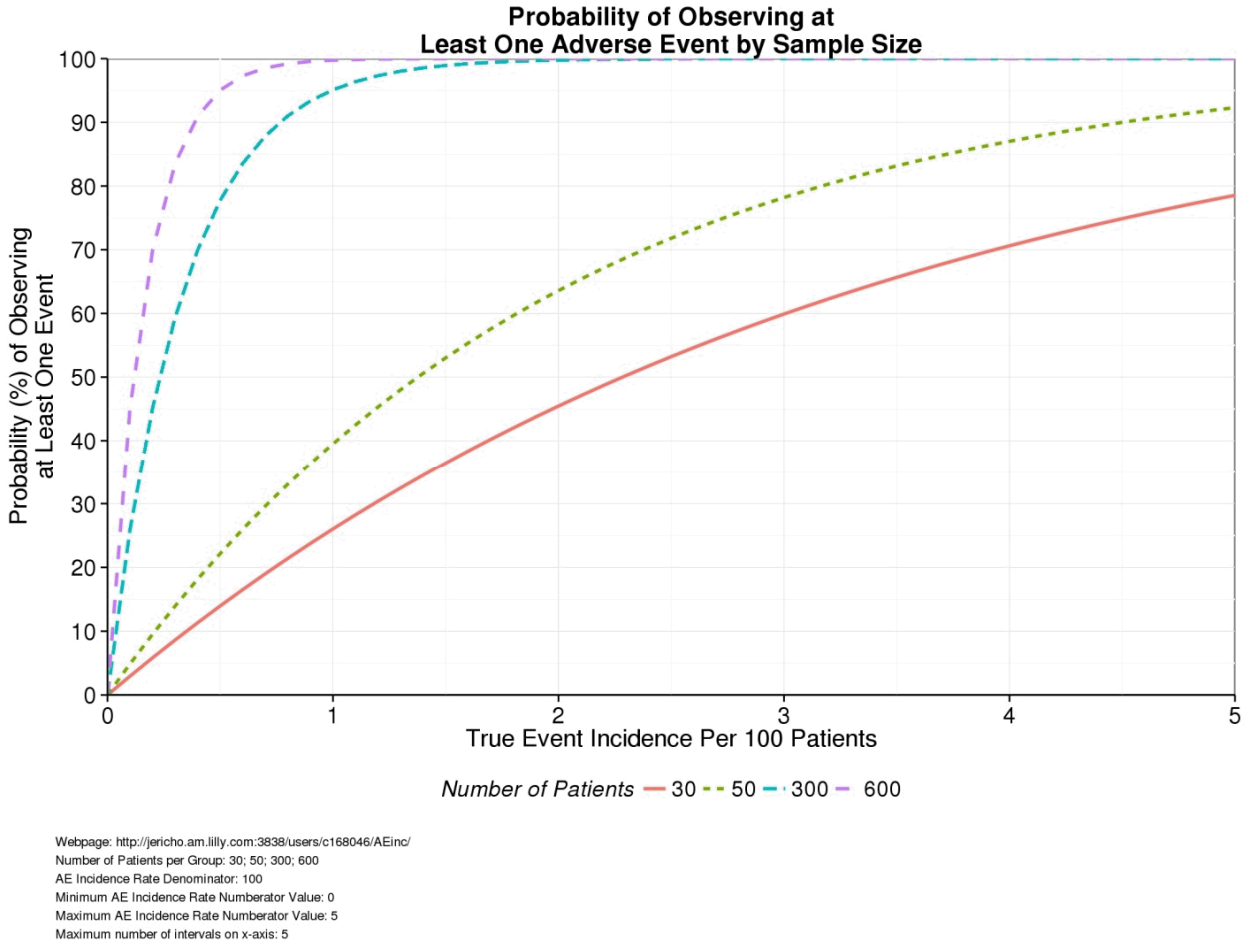
To date, in addition to gastric cancer, ramucirumab has now been studied in a number of additional tumour types, including NSCLC, mCRC, mBC, and HCC, and the safety data available from these trials represent a sizable number of ramucirumab-treated patients who fall within the subpopulations of interest (that is, elderly patients and patients with hepatic or renal impairment). The clinical study reports for each of these studies have been submitted to the CHMP. Therefore, no further strategies on oversampling patients for the aforementioned subgroups will be introduced in this observational study.

Due to the inclusion/exclusion criteria of these trials, only a limited number of patients with cardiac comorbidities have been studied. This patient population is expected to be relatively common in real-life settings. A recent study in New Zealand found that the prevalence of comorbid conditions in gastric cancer patients was higher compared to other cancers for most conditions. The prevalence of cardiac comorbidity among gastric cancer patients (n=705) was about 28% (including cardiac arrhythmias: 13.5%; CHF: 8.2%; and angina: 6.4%) (Sarfati et al. 2013). In a cross-sectional study of 94 Italian patients who underwent curative gastrectomy, the prevalence of cardiac disease was found to be 13.8% (Pisanu et al. 2007). Smith and colleagues (2007) reported that the prevalence of comorbid CHF was 7.8% of the total number of gastric cancer patients. Altogether, it is estimated that at least 60 patients (10% conservative estimate of prevalence) with cardiac comorbidity will be enrolled in this study.

Due to the naturalistic enrolment in this observational study, increasing the overall sample size will have a minimal impact on these subgroup sample sizes. To overcome the situation of insufficient enrolment in patients with cardiac comorbidity, patient recruitment will be carefully monitored over the course of the study and reviewed at the interim analysis. Oversampling strategies may be implemented at a later stage to meet the enrolment goal (that is, 60 patients) as needed. Actions may include implementation of temporary or permanent caps on enrolment of patients without cardiac comorbidity to ensure adequate numbers of patients with cardiac comorbidity are enrolled.

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 30 to 600. For example, for a sample size of 300 patients and a true event incidence of 1%, the probability of observing at least 1 event is 95%. For patients with cardiac comorbidity with an expected sample size of 60, the probability to observe a safety event is expected to be >90% if the event occurs in approximately 5/100 patients. Table 9.1 presents the 95% CIs for a range of incidences that could potentially be observed in this study. The range of incidences in Table 9.1 is based on the observed incidences

of the AEs of special interest from REGARD (from <1% [for example, infusion-related reaction, cardiac failure] to 16% [for example, hypertension] for all grades in the ramucirumab treatment arm) and RAINBOW (from 1.2% [gastrointestinal perforation] to 41.9% [for example, bleeding/haemorrhage events] for all grades in the ramucirumab plus paclitaxel arm). Thus, Table 9.1 shows that the width of the 95% CI decreases as sample size increases; samples greater than 200 patients enable the estimation of the detection of the AE rate with a good degree of precision. The increase in sample size from 600 to 1000 patients does not significantly improve the precision of the detection rate for AEs. Smaller samples will increase 95% CI width but still carry a reasonable probability of detection as shown in Figure 9.1. For instance, with a sample size of 50 patients, an observed AE rate (estimated AE proportion) of 15% implies that the true AE rate falls in the range between 5.1 and 24.9 with probability of 95%.



Abbreviations: AE = adverse event.

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

Table 9.1. Ninety-Five Percent Confidence Intervals for Event Incidences

Sample Size	Observed Event Incidence						
	5%	10%	15%	20%	30%	40%	45%
1000	[3.7; 6.4]	[8.1; 11.9]	[12.8; 17.2]	[17.5; 22.5]	[27.2; 32.8]	[37; 43.0]	[41.9; 48.1]
900	[3.6; 6.4]	[8.0; 12.0]	[12.7; 17.3]	[17.4; 22.6]	[27.0; 33.0]	[36.8; 43.2]	[41.8; 48.3]
800	[3.5; 6.5]	[7.9; 12.1]	[12.5; 17.5]	[17.2; 22.8]	[26.8; 33.2]	[36.6; 43.4]	[41.6; 48.5]
700	[3.4; 6.6]	[7.8; 12.2]	[12.4; 17.7]	[17.0; 23.0]	[26.6; 33.4]	[36.4; 43.6]	[41.3; 48.7]
600	[3.3; 6.7]	[7.6; 12.4]	[12.1; 17.9]	[16.8; 23.2]	[26.3; 33.7]	[36.1; 43.9]	[41.0; 49.0]
500	[3.1; 6.9]	[7.4; 12.6]	[11.9; 18.1]	[16.5; 23.5]	[26.0; 34.0]	[35.7; 44.3]	[40.6; 49.4]
400	[2.9; 7.1]	[7.1; 12.9]	[11.5; 18.5]	[16.1; 23.9]	[25.5; 34.5]	[35.2; 44.8]	[40.1; 49.9]
300	[2.5; 7.5]	[6.6; 13.4]	[11.0; 19.0]	[15.5; 24.5]	[24.8; 35.2]	[34.5; 45.5]	[39.4; 50.6]
200	[2.0; 8.0]	[5.8; 14.2]	[10.1; 20.0]	[14.5; 25.5]	[23.7; 36.4]	[33.2; 46.8]	[38.1; 51.9]
100	[0.7; 9.3]	[4.1; 15.9]	[8.0; 22.0]	[12.2; 27.8]	[21.0; 39.0]	[30.4; 49.6]	[35.3; 54.8]
50	[0.0; 11.0]	[1.7; 18.3]	[5.1; 24.9]	[8.9; 31.1]	[17.3; 42.7]	[26.4; 53.6]	[31.2; 58.8]
30	[0.0; 12.8]	[0.0; 20.7]	[2.2; 27.8]	[5.7; 34.3]	[13.6; 46.4]	[22.5; 57.5]	[27.2; 62.8]

Note: The 95% confidence intervals are calculated based on exact binominal models.

9.6. Data Management

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 programs 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 programs will be stored and archived according to the vendor's procedures. These datasets and analysis programs will be transferred to 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 for routine clinical practice.

The physician will review the eligibility criteria (that is, patients with advanced gastric cancer or GEJ adenocarcinoma whose disease has progressed after prior chemotherapy and for whom a treatment decision of ramucirumab as subsequent therapy has been made) and will ask the patient to confirm his/her willingness to participate by signing the informed consent form.

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 to be collected and entered in the clinical database:

- Site address
- Type of centre (academic/non-academic, public or private practice)

9.6.2.2. Patient Data

Information collected (as described in Section 9.3) as part of routine clinical practice 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 on-line 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 account with a username and password. 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. All participating sites will have access to the data entered by the individual site on their own enrolled patients through the EDC system.

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. Lost to Follow-Up Patients

The participating physician 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 willing to participate.

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 informed consent forms (ICFs), 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.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the study and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 12 years after completing participation in the study. Documents to be archived include the patient enrolment log and the signed ICF. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the study sponsor.

9.7. Data Analysis

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

9.7.1. Analysis Population

This population includes all patients who have given informed consent and received at least one dose of ramucirumab alone or in combination therapy as second-line therapy. Both safety and effectiveness analyses will be based on this population.

9.7.2. Primary Analyses

For the primary objective (that is, safety), data analyses will be conducted in all patients (that is, patients treated with ramucirumab alone or in combination therapy pooled together) and also will be stratified on the basis of whether patients received ramucirumab as monotherapy, combination therapy with paclitaxel, or combination therapy with anticancer agents other than paclitaxel.

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

The primary focus of AE reporting will be based on the AEs reported between the date of first dose of study treatment and 90 days after last dose of study drug. The AEs will be summarised by Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class and preferred term. Deaths from any cause will also be summarised. The AEs reported 91 days post treatment discontinuation will be summarised separately.

9.7.3. Secondary Analyses

Similar safety analyses (as described in 9.7.2) will be performed for the following subgroups:

- Elderly patients
- Patients with cardiac comorbidities
- Patients with hepatic impairment
- Patients with renal impairment

A descriptive analysis will be conducted to evaluate the effectiveness of ramucirumab. Data analyses will be stratified on the basis of whether patients received ramucirumab as monotherapy, combination therapy with paclitaxel, or combination therapy with anticancer agents other than paclitaxel.

For OS and PFS, Kaplan-Meier estimates (including curves) will be generated. The median and survival rates at given time points (for example, 3 months, 6 months, 9 months, 12 months) will be computed together with their 95% CIs using the Kaplan-Meier method.

The real-world treatment patterns in gastric cancer patients treated with ramucirumab will be summarised, including dosage and administration details, treatment modification and reasons (for example, delay, reduction, or discontinuation), and treatment regimen (for example, ramucirumab monotherapy, combination with paclitaxel, combination with other chemotherapy). Other effectiveness measures such as best tumour response, healthcare resource utilisation, and supportive care (for example, transfusions, concomitant medications) during the study period will be summarised. The number of hospitalisations, cumulative length of hospitalisation, and reason for hospitalisation will be summarised as well.

9.7.4. Interim Analysis and Periodic Study Updates

An interim safety analysis is planned when approximately half the targeted sample size have been enrolled in the study. Details will be specified in the SAP. Additionally, study updates (for example, number of patients enrolled, number of patients in each subgroup of interest) will be included annually in the ramucirumab PBRER/PSUR commencing 1 year after the expected first patient visit (that is, the first study update will be included in the Q4 2016 PBRER/PSUR and subsequent updates will be included no more frequently than annually thereafter).

9.8. Quality Control

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

Information recorded as part of routine clinical practice will be transcribed to an eCRF. Computerized 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. In addition, data collection and validation procedures will be detailed in appropriate operational documents.

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, non-comparative, observational cohort study / registry in the EU and North America. Taking into account the rarity of gastric cancer in the EU and North America, this study plans to enrol approximately 600 patients treated with ramucirumab alone or in combination therapy.

Follow-up bias: A low loss to follow-up rate is expected, in part due to the ability to follow up directly with patients at the hospital. Maintaining a low rate of loss to follow-up will lower the risk of bias that could result, for example, if patients with AEs were less likely to return to the study physician for follow up.

Overcoming the situation of insufficient enrolment of patients of cardiac comorbidity: As discussed in Section 9.5, due to the naturalistic enrolment in this observational study, increasing the overall sample size will have a minimal impact on sample sizes of subgroups of interest. Recruitment of patients dependent on market factors: Market uptake of new products such as ramucirumab is unpredictable and has the potential to impact the feasibility of meeting the recruitment targets, overall, and within each of the subgroups of interest. Although patients with cardiac comorbidity are expected to be relatively common in real-life settings, 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 oversampling subgroups of interest, and/or initiation of additional sites within participating countries may also be triggered. 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 oversampling will be scrutinised by comparing patient characteristics to the overall patient population.

Robust data quality of clinical variables 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 at 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 for Good Pharmacovigilance Practices (GVPs) and Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE 2008), the Declaration of Helsinki [WWW] and its amendments, and any applicable national guidelines.

10.1. Subject Consent to Release Information

This is an observational research program 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 practice in the provision of care to patients with advanced gastric/GEJ adenocarcinoma. The patient will provide authorisation for the uses and disclosures 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 all AEs they become aware of that occur in temporal association with Lilly drug under evaluation (that is, ramucirumab) as defined in this protocol.

Adverse events, including SAEs from the first administration of Lilly drug under evaluation (that is ramucirumab) up to and including 90 days after the last ramucirumab administration, will be recorded and reported. Starting at 91 days since the last ramucirumab administration, only AEs including SAEs related to ramucirumab will be recorded and reported.

Additionally, the study physician or other study personnel will record via eCRF the following information for Lilly drug under evaluation as defined in this protocol, regardless of whether there is an associated serious or non-serious AE:

- pregnancy exposures
- breast-feeding exposures
- overdoses
- misuse
- abuse
- off-label use
- medication error
- lack of drug effect
- suspected transmission of infectious agent

Study personnel are requested to report adverse reactions (ARs) in temporal association with Lilly drugs not under evaluation and with any **non**-Lilly drugs to the appropriate party (for example, regulators or Lilly) as they would in normal practice as required by applicable laws, regulations, and practices.

11.1. Serious Adverse Events

Study site personnel will record and report to Lilly or its designee any SAEs occurring in temporal association with the Lilly drug 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 forms. An SAE is any AE from this study 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 inpatient 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.

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

Study site personnel will report to Lilly or its designee any **non-serious** events occurring in temporal association with the Lilly drug under evaluation within 30 days of awareness of the event via the study eCRFs.

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.

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, number of patients in each subgroup) will be included in the ramucirumab PBRER/PSUR, as described in Section 9.7.4. Additionally, the study findings may be presented at a scientific congress and submitted to a peer-reviewed journal.

13. References

Ayodele OE, Alebiosu CO. Burden of chronic kidney disease: an international perspective. *Adv Chronic Kidney Dis.* 2010;17(3):215-224.

Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol*. 2013;58(3):593-608.

Cancer Research UK website. Stomach cancer incidence statistics report. 2015. Available at: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/stomach/incidence/#gastricc. Accessed March 30, 2015.

Declaration of Helsinki 59th World Medical Association General Assembly, Seoul, October 2008. Available at: http://www.wma.net/en/30publications/10policies/b3/17c.pdf. Accessed April 17, 2015.

Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, D, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.

ISPE. Guidelines for good pharmacoepidemiology practices (GPP). *Pharmacoepidemiol Drug Safety*. 2008;17:200-208.

Pisanu A, Montisci A, Piu S, Uccheddu A. Curative surgery for gastric cancer in the elderly: treatment decisions, surgical morbidity, mortality, prognosis and quality of life. *Tumori.* 2007;93(5):478-484.

Sarfati D, Gurney J, Lim BT, Bagheri N, Simpson A, Koea J, Dennett E. Identifying important comorbidity among cancer populations using administrative data: Prevalence and impact on survival. *Asia Pac J Clin Oncol.* 2013 Dec 19. doi: 10.1111/ajco.12130. [Epub ahead of print]

Smith JK, McPhee JT, Hill JS, Whalen GF, Sullivan ME, Litwin DE, Anderson FA, Tseng JF. National outcomes after gastric resection for neoplasm. *Arch Surg.* 2007;142(4):387-393.

van Gestel YR, Lemmens VE, de Hingh IH, Steevens J, Rutten HJ, Nieuwenhuijzen GA, van Dam RM, Siersema PD. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients. *Ann Surg Oncol.* 2013;20(2):371-380.

Annex 1. List of Standalone Documents

None.

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]	☒	☐	☐	15
1.1.3 Study progress report(s)	☒	☐	☐	
1.1.4 Interim progress report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 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 is a hypothesis generating study, thus no formal hypothesis(-es) are to be tested.

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?	☒	☐	☐	21 - 22
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)	☒	☐	☐	27 - 28

Comments:

Section 4: 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?	☒	☐	☐	18 - 19
4.2.2 Age and sex?	☒	☐	☐	18
4.2.3 Country of origin?	☒	☐	☐	18
4.2.4 Disease/indication?	☒	☐	☐	18
4.2.5 Co-morbidity?	☒	☐	☐	19
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)	☒	☐	☐	18

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	18
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)	☒	☐	☐	18
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	18-19
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

As this is a prospective cohort study, the exposure will be prospectively ascertained.

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?	☒	☐	☐	20 - 22
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)	☒	☐	☐	20 - 22

Comments:

As this is a prospective cohort study, the endpoints will be prospectively ascertained.

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)	☒	☐	☐	20
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: 8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	18

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
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.)	☒	☐	☐	19-22
8.1.3 Covariates?	☒	☐	☐	20-22
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)	☒	☐	☐	18-19
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	19 - 22
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	20-22
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	27
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	22-25

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?	☒	☐	☐	27 - 28

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.3 Are descriptive analyses included?	☒	☐	☐	27 - 28
10.4 Are stratified analyses included?	☒	☐	☐	27 - 28
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	29
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

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?	☒	☐	☐	26
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	25-27
11.3 Are methods of quality assurance described?	☒	☐	☐	28-29
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	28-29
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	31

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	29-30
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)	☒	☐	☐	29
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	29

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.3 Does the protocol address other limitations?	☒	☐	☐	29-30

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?	☒	☐	☐	31
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	31

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?	☒	☐	☐	29-30

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)?	☒	☐	☐	34
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	34

Comments:

Name of the main author of the protocol: Yu-Jing Huang, PhD

Date: 20 April 2015

Signature: Yu-Jing Huang

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