European Medicines Agency
SCIENCE MEDICINES HEALTH

25 September 2014
EMA/CHMP/305462/2014
Committee for Medicinal Products for Human Use (CHMP)

# CHMP assessment report

## CYRAMZA

## International non-proprietary name: RAMUCIRUMAB

## Procedure No.: EMEA/H/C/002829/0000

**Note**

Assessment report as adopted by the CHMP with all information of a commercial confidential nature deleted.

# Product information

| | |
|---|---|
| Name of the medicinal product: | CYRAMZA |
| Applicant: | Eli Lilly Nederland B.V.<br>Grootslag 1-5<br>NL-3991 RA Houten<br>The Netherlands |
| Active substance: | RAMUCIRUMAB |
| International Nonproprietary Name/Common Name: | RAMUCIRUMAB |
| Pharmaco-therapeutic group (ATC Code): | Antineoplastic agents, monoclonal antibodies (LO1XC) |
| Therapeutic indication: | Cyramza in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy (see section 5.1).<br><br>Cyramza monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate (see section 5.1). |
| Pharmaceutical form: | Concentrate for solution for infusion |
| Strength: | 10 mg/ml |
| Route of administration: | Intravenous use |
| Packaging: | vial (glass) |
| Package sizes: | 1 vial  x 10 ml, 1 vial  x 50 ml and 2 vials x 10 ml |

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# List of abbreviations

| | |
|---|---|
| 5-FU | 5-fluorouracil |
| ADA | anti-drug antibody |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine transaminase |
| AST | aspartate transaminase |
| AUC0-∞ | Area under the concentration-time curve from zero to infinity |
| AUC0-$\tau$ | Area under the concentration-time curve over a dosing interval $\tau$ |
| BSC | best supportive care |
| CI | confidence interval |
| CL | Clearance calculated using mg/kg dose |
| Cmax | maximum observed serum concentration |
| Cmin | $C_{trough}$ serum concentration |
| CR | complete response |
| CRF | case report form |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DC101 | rat anti-mouse VEGFR-2 monoclonal antibody |
| ECG | electrocardiogram |
| ECOG PS | Eastern Cooperative Oncology Group performance status |
| ELISA | enzyme-linked immunosorbent assay |
| GCP | good clinical practice: |
| GI | gastrointestinal |
| GOJ | gastro-oesophageal junction |
| HEL | Human erythroleukemia cell line |
| HER2 | human epidermal growth factor receptor 2 |
| HL60 | Human promyelocytic leukemia cells |
| HR | hazard ratio |
| ICD | informed consent document |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IgG1 | immunoglobulin G, subclass 1 |
| INR | International Normalized Ratio |
| IRR | infusion-related reaction |
| ITT | intent to treat |
| IV | intravenous |
| MAb | monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| NCI-CTCAE | National Cancer Institute – Common Terminology Criteria for Adverse Events |
| NGNA | N-glycolylneuraminicacid |
| ORR | objective response rate |
| OS | overall survival |
| PAE-KDR | Porcine aortic endothelial cells |
| PD | progressive disease |
| PDT | post-discontinuation anticancer therapy |
| PFS | progression-free survival |
| PI | Principal Investigator |
| PK | pharmacokinetic(s) |
| PP | Per Protocol |
| PR | partial response |
| QoL | quality of life |
| RPLS | reversible posterior leukoencephalopathy syndrome |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | stable disease |
| sVEGFR-2 | soluble vascular endothelial growth factor receptor-2 |
| t1/2 | Terminal half-life |

| TE-ADA | treatment-emergent anti-drug antibody |
| TEAE | treatment-emergent adverse event |
| TE-SAE | treatment-emergent serious adverse event |
| tmax | time to Cmax |
| ULN | upper limit of normal |
| US | United States |
| VEGF | vascular endothelial growth factor |
| VEGFR-1 | vascular endothelial growth factor receptor-1 |
| VEGFR-2 | vascular endothelial growth factor receptor-2 |
| Vss | Volume of distribution at steady state calculated using mg/kg dose |
| Vz | Volume of distribution during the terminal elimination phase calculated using mg/kg dose |
| A-Gal | α-1,3,-galactose |

# 1. Background information on the procedure

## 1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 23 August 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Cyramza, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 November 2012.

Cyramza was designated as an orphan medicinal product EU/3/12/1004 on 4 July 2012. CYRAMZA was designated as an orphan medicinal product in the following indication: treatment of gastric cancer.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Cyramza as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The applicant applied for the following indication:
Cyramza as a single agent is indicated for the treatment of patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma after prior chemotherapy.

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ramucirumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

### Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

### Information relating to orphan market exclusivity

### Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### New active Substance status

The applicant requested the active substance RAMUCIRUMAB contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

*Scientific Advice*

The applicant received Scientific Advice from the CHMP on 20 May 2010, 19 April 2012 and 15 December 2011. The Scientific Advice pertained to insert quality and clinical aspects of the dossier.

*Licensing status*

CYRAMZA has been given a Marketing Authorisation in in the United States on 21 April 2014.

## 1.2. Manufacturers

**Manufacturer of the active substance**

ImClone Systems LLC
33 ImClone Drive,
Branchburg
New Jersey
NJ 08876
UNITED STATES

**Manufacturer responsible for batch release**

Lilly Pharma Fertigung und Distribution GmbH & Co. KG
Teichweg 3
D-35396 Giessen
Germany

## 1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:     Pieter de Graeff                Co-Rapporteur: Kolbeinn Gudmundsson

- The application was received by the EMA on 23 August 2013.

- The procedure started on 25 September 2013.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 December 2013.

- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 January 2014.

- During the meeting on 23 January 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 April 2014.

- The integrated inspection report of the GCP inspections carried out at three clinical investigator sites in India, Canada and USA between 12 February and 13 March 2014 was issued on 31 March 2014.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 June 2014.

- PRAC RMP Advice and assessment overview, adopted by PRAC on 12 June 2014.

- During the CHMP meeting on 26 June 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.

  The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 August 2014.

  The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 1 September 2014.

- During the CHMP meeting on 23 September 2014, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.

- During the meeting of 22-25 September 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Cyramza.

# 2. Scientific discussion

## 2.1. Introduction

Gastric cancer is the fourth most common cancer in the world and is a major cause of cancer-related death (Ferlay et al. 2010). There were approximately one million new cases of stomach cancer worldwide in 2008 (640,000 men, 348,000 women), with approximately 736,000 deaths (463,000 men, 273,000 women), making it the third-leading cause of cancer death globally in men and the fifth in women (Ferlay et al. 2010). The ratio of men to women is about 2:1. Gastric cancer incidence varies markedly by geographic region. In the European Union (EU), incidence and mortality for gastric cancer were estimated at 80,626 cases and 57,654 deaths, respectively, for 2012 (Steliarova-Foucher et al. 2012).

The 5-year survival rate for gastric cancer, regardless of stage at diagnosis, is 24% and the prognosis for patients diagnosed with advanced gastric cancer is approximately 1 year median survival (Winer et al. 2009; Price et al. 2012).

More than half of gastric adenocarcinomas are diagnosed at an advanced stage (locally advanced or metastatic) when resection is not possible, as the disease is typically asymptomatic in early stages (Fuchs and Mayer 1995). Disease-related symptoms, which are extensive and severe in advanced gastric cancer, include the following: fatigue, early satiety, nausea, vomiting, dyspepsia, anorexia, pain after eating, dysphagia, abdominal pain, diarrhoea or constipation, melena, hematemesis, weight loss, anaemia, and concomitant nutritional problems (Eckardt et al. 1990; Wanebo et al. 1993; Everett and Axon 1997; DeVita et al. 2008; American Cancer Society 2011; Cervantes et al. 2013).

Surgical resection is the only treatment modality that is potentially curative, though a large proportion of patients still relapse following resection and therefore combined modality approaches are standard for $\geq$ stage 1B disease.

Chemotherapy for locally advanced or metastatic disease includes combination chemotherapy with cisplatin and fluropyrimidines or other chemotherapy agents including docetaxel, carboplatin, oxaliplatin, epirubicin, paclitaxel, irinotecan or mytomicin. Two-drug cytotoxic regimens are preferred because of lower toxicity. Three-drug regimens are reserved for medically fit patients with good performance status. One of the dosings and schedules of paclitaxel as single agent is 80 mg/m2 IV on days 1, 2, 15 cycled

every 28 days (Hironaka et al., 2013). Trastuzumab can be added to chemotherapy for HER2-neu overexpressing adenocarcinoma (Bang et al., 2010).

VEGF Receptor 2 is the key mediator of VEGF induced angiogenesis. Ramucirumab is a human receptor-targeted antibody that specifically binds to VEGF Receptor 2 and blocks binding of VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand stimulated activation of VEGF Receptor 2 and its downstream signalling components, including p44/p42 mitogen-activated protein kinases, neutralizing ligand-induced proliferation and migration of human endothelial cells (SmPC, section 5.1; see Non-clinical aspects).

The applicant applied for a marketing authorisation for the following indication: Cyramza as a single agent is indicated for the treatment of patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma after prior chemotherapy.

The final indication following CHMP review of this application is: Cyramza in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy (see section 5.1).

Cyramza monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate (see section 5.1).

Ramucirumab therapy must be initiated and supervised by physicians experienced in oncology (see SmPC, section 4.2). Cyramza is administered as an intravenous infusion over approximately 60 minutes. It should not be administered as an intravenous bolus or push. To achieve the required infusion duration of approximately 60 minutes, the maximum infusion rate of 25 mg/minute should not be exceeded, instead the infusion duration should be increased. The patient should be monitored during infusion for signs of infusion-related reactions (see SmPC, section 4.4) and the availability of appropriate resuscitation equipment should be ensured.

The recommended dose of ramucirumab as a single agent is 8 mg/kg every 2 weeks.

The recommended dose of ramucirumab is 8 mg/kg on days 1 and 15 of a 28-day cycle, prior to paclitaxel infusion. The recommended dose of paclitaxel is 80 mg/m2 administered by intravenous infusion over approximately 60 minutes on days 1, 8 and 15 of a 28-day cycle.

## *2.2.  Quality aspects*

### 2.2.1.  Introduction

The drug substance of Cyramza is ramucirumab, a recombinant, human (IgG1) monoclonal antibody produced in a stably transfected NS0 mouse myeloma cell line. Ramucirumab binds specifically to the extracellular domain of the human vascular endothelial growth factor receptor-2 (VEGFR-2) inhibiting VEGF-stimulated activation of VEGFR-2 and p44/p42 mitogen-activated protein kinases, and neutralizing VEGF-induced mitogenesis of human endothelial cells. Ramucirumab does not involve Fc-region effector functions as a part of its mode of action. Cyramza is proposed for the treatment of patients with gastric cancer. Sterile 10 mg/ml solution of Cyramza is provided in Type I glass vials and diluted with 0.9% sodium chloride prior to i.v. injection.  Cyramza is subject to medical prescription and administered to patients in a hospital or outpatient setting by a medical professional. The proposed shelf-life is 36 months at 2°C - 8°C.

The other ingredients are histidine (buffer), histidine monohydrochloride (buffer), sodium chloride (isotonicity agent), glycine (isotonicity agent), polysorbate 80 (stabiliser) and water for injections. There are two drug product (DP) presentations, 500 mg/50 mL and 100 mg/10 mL filled in Type I glass vials, with a rubber stopper and aluminium seal with a plastic flip-off cap.

## 2.2.2. Active Substance
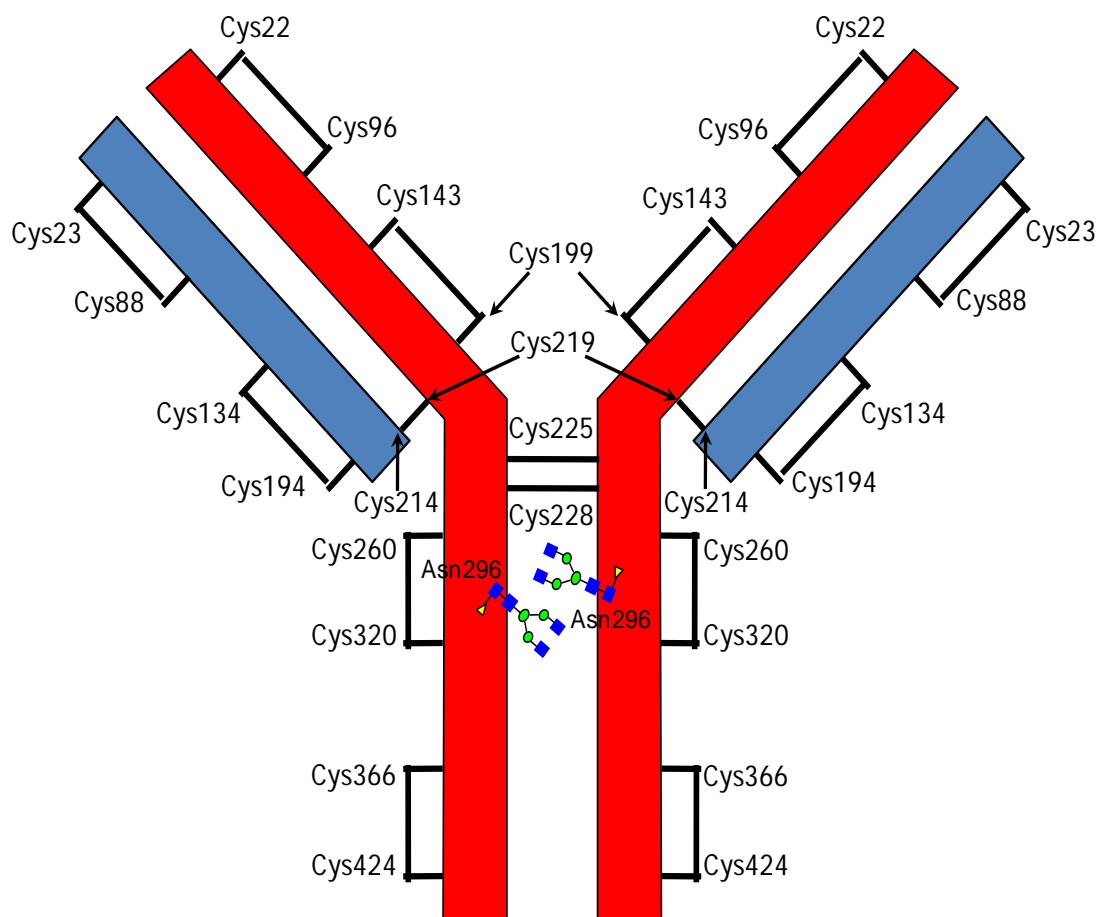


Schematic of Ramucirumab

Ramucirumab drug substance (DS) is a clear to slightly opalescent and colourless to slightly yellow liquid with pH 5.7 - 6.3. Ramucirumab is typical IgG1 molecule consisting of two κ -light chains (LC) and two γ1-heavy chains (HC). Each HC and LC contains 446 and 214 amino acids, respectively. The molecule has 16 disulfide bonds and two N-linked glycosylation sites at Asn296 of HC, no O-linked glycosylation has been observed. The molecular weight of glycosylated ramucirumab is 146756 Da.

The Applicant's claim that Ramucirumab is a new active substance (NAS) has been accepted since ramucirumab comprises a 'substance not previously authorised, i.e. a monoclonal antibody which is manufactured through rDNA technology with a novel amino acid sequence. Since the product comprises a novel amino acid sequence, the CHMP has accepted the NAS claim.

### Manufacture

Manufacture and control facilities for ramucirumab DS have been listed and an adequate overview of the DS manufacturing process at ImClone Systems LLC; 33 ImClone Drive; Branchburg, NJ 08876 USA has been provided.

## Cell Culture

Ramucirumab is produced in a fed-batch process using an NS0 cell line. The cell culture process involves three stages: (1) the seed train, (2) the inoculum train, and (3) the production stage. Following the production stage the cell culture fluid containing ramucirumab is separated from the cells by centrifugation and filtered. The resulting cell culture filtrate is then further purified (see below).

Cell culture and in-process controls (IPC) have been sufficiently described and are considered appropriate.

## Purification process

The purification process consists of a series of chromatography, viral inactivation and filtration and ultrafiltration/diafiltration steps.

Each step of the purification process has been adequately described, including description of the different buffers used, column regeneration, and storage conditions of both columns and product after each step. Suitable IPCs are in place, with acceptable limits.

## Control of materials

Ramucirumab is expressed from a NS0 (mouse) cell line. The expression plasmids and NS0 cell line source, history, generation as well as testing of the cell banks (accession cell bank (ACB), master cell bank (MCB), and the preparation of the working cell bank (WCB)) including methods and reagents used during cell culture and storage conditions have been described in detail following the principles in respective guidelines (ICH Q5B, Q5A and Q5D). Absence of adventitious agents has been sufficiently established. Genetic stability is extensively demonstrated.

Other raw materials are described and in general, appropriate information on raw materials is submitted.

## Control of critical steps and intermediates

This submission does not use a quality by design (QbD) approach; the manufacturing process development is based on a traditional approach which incorporates state of the art methods for investigation and classification of critical parameters.

In general, the procedure for classification of critical quality attributes (CQAs) and critical process parameters (CPPs) is deemed acceptable. The approach is described in detail; it is noted that it is aimed at identifying process parameters (PPs) which have a probable risk of impacting a CQA; these were included in preliminary design of experiments (DoEs) investigations. Experimental studies on selected parameters, for each unit operation, having potential to impact on CQAs were then performed using scale-down models to determine the process parameter criticality and to define the PARs.

The general approach of the Applicant was found appropriate. However, a number of factors were not sufficiently investigated, and gave rise to specific remarks mainly related to the effects on process parameters on impurity removal. Upon request, (additional) CPPs/cIPCs were set. The Applicant's strategy is now acceptable.

## Process validation and/or evaluation

Data have been presented for full-scale validation lots including results for all routine CPPs, CIPCs, and release tests. In addition, additional (non-routine) data have been presented for impurity removal and storage of intermediates.

Validation was performed in a traditional fashion; all validation lots were manufactured 'at-target', i.e. with PPs at the intended set point. The data provided sufficiently demonstrate that under these

conditions, the process is highly consistent and able to deliver a Drug Substance which complies with specifications.

The clearance of process related impurities was evaluated at selected process steps in the bulk drug substance manufacturing process. In conclusion, the validation exercise is deemed satisfactory.

Characterisation

Ramucirumab is a recombinant human mAb of IgG1 subclass with one Fc glycosylation site on Asn296N. Ramucirumab specifically binds to the extracellular domain of the human VEGFR2/KDR. The Applicant has characterised the primary, secondary and higher order structure, post-translational modifications, glycosylation, charged isoforms, purity and biological activity associated with ramucirumab with a range of methodologies.

The primary structure of ramucirumab was elucidated using techniques including amino acid analysis, N-terminal and C-terminal sequencing and LC-MS/MS peptide mapping.  Amino acid analysis yielded an amino acid composition that was consistent with the theoretical composition.  The N-terminal and C-terminal sequencing results were consistent with expected data. Data obtained by LC-MS/MS peptide mapping accounted for 100% of the expected amino acid sequence for both the heavy chain and the light chain. Furthermore sulfhydryl groups, disulphide bridges and free thiols have been determined.

The higher order structure and conformational stability of ramucirumab was determined by using a variety of biophysical methods.  Ramucirumab has a predominantly β-sheet structure, which is consistent with the typical folded IgG structure, and has a higher order tertiary structure which is also consistent with mAbs.  The disulphide bond structure in ramucirumab was confirmed. The studies demonstrated expected results for a monoclonal antibody.  Data have been provided to show that ramucirumab is predominantly monomeric under the formulation conditions and thermal stability investigations also indicated the presence of a folded structure.

The carbohydrate composition and charge heterogeneity of ramucirumab drug substance has been thoroughly examined and there is no O-linked glycosylation present in ramucirumab as expected for IgG.

The biological activity of ramucirumab i.e. binding to the Kinetic Domain Region (KDR) has been demonstrated. The mechanism of action for ramucirumab does not involve effector functions.

The active substance specification includes methods to evaluate Purity, Identity, Protein Concentration and Potency.

The specifications follow the present guidelines and Ph. Eur monoclonal antibodies for human use (01/2012:2031). The proposed acceptance criteria have been established on the basis of batches manufactured throughout development, used in clinical and non-clinical studies, manufacturing experience, analytical variability, the stability of the DS at the recommended storage condition, and regulatory guidance.

Impurities

Potential product-related impurities may arise from the degradation of the molecule that may occur during routine manufacturing, processing, and storage. Two orthogonal methods are used to detect and quantify changes in the purity of ramucirumab drug substance. Process-related impurities have been identified and justified in the dossier, including DNA, HCP and other impurities.

The validation studies of analytical tests used for specifications were performed according to ICH Q2.

Potency assays

Two potency assays have been described. Appropriate system suitability criteria are defined and the method has been extensively validated.

<u>Batch analysis and justification of specification</u>

The batch analytical data for all manufactured batches have been provided. The provided results indicate that the manufacturing process is under control. Overall batch analysis results for the commercial scale Process C1 and C0 batches appear consistent and are highly similar. The Applicant has supported the proposed quantitative specification limits with batch analysis data and a statistical reasoning. The specifications are deemed acceptable.

<u>Container closure system</u>

Extensive information is provided regarding the bags and the closure system. This includes technical drawings and information on extractables, leachables, sterilisation by gamma-irradiation and stability.


*Stability*

The analytical methods used for assessing stability are a subset of DS batch release test methods and can be considered stability indicating and acceptable. The methods are able to detect changes of the DS colour, clarity, pH, osmolality, quantity, potency, purity, charge heterogeneity, endotoxins and bioburden. The applied acceptance limits were based on specifications at the time of testing. The studies follow the guidelines ICH Q5C, Q1A, Q1B and Q1E.

A storage period of 24 months at 2 – 8 ˚C is proposed. The Applicant has conducted real-time, real-condition stability studies (2-8°C), as well as studies under accelerated (23 - 27°C) and stressed conditions (38 - 42°C).

The claimed storage period of 24 months is mainly supported by the extensive primary stability studies and supporting studies from commercial scale clinical lots.

The stability results indicate that the drug substance manufactured by the proposed supplier(s) is sufficiently stable in the proposed container. In conclusion, the claim for a storage period of 24 months is acceptable.


*Comparability exercise for Active Substance*

Ramucirumab DS has been manufactured using four processes (Process A, B, C0 and C1). The manufacturing process has been scaled up during development to the commercial scale process (Process C0/C1). Process A DS was used for Phase 1 trials, Process B and Process C0 materials were utilized in Phase 2 studies and early Phase 3 studies. Process C0 material was used in the pivotal Phase 3 clinical studies.  All changes during development have been adequately described and mainly relate to more optimal process control and improvement of viral clearance.

A comprehensive comparability exercise was performed to justify the introduced changes into the manufacturing process during development. Assessment of the comparability between DS produced by the four processes is based on characterization data, batch release data and additional biochemical characterization. A comparability exercise was performed for Process A and Process B, Process B and Process C0 and finally Process C0 and Process C1 to demonstrate active substance of comparable quality. Additional characterization performed for Process A, B and C0 drug substance demonstrated that the DS has remained highly similar throughout the process changes.


## 2.2.3.  Finished Medicinal Product

Description and composition of the Drug Product

Ramucirumab, Concentrate Solution for Infusion, 10 mg/mL, is a sterile, single-use solution, The ramucirumab drug product is formulated in an aqueous buffered solution at pH 6.0, containing 10 mM

histidine buffer, 75 mM sodium chloride, 133 mM glycine (all isotonicity agents), and 0.01% w/v polysorbate 80 (as a stabiliser). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. No novel excipients are used and the excipients are not of human or animal origin.

Ramucirumab drug product is supplied in two presentations, 100 mg/10 mL and 500 mg/50 mL, in 14 mL or 50 mL vials respectively, to be stored at 2-8 °C. The vials are stoppered with rubber stoppers sealed with aluminium seals with a plastic flip-off cap. The drug product is diluted with 0.9% sodium chloride injection (normal saline) in an infusion bag prior to administration by intravenous infusion.


### *Pharmaceutical Development*

The DP manufacturing process is a dilution of drug substance with a formulation buffer identical to the drug substance formulation. There is no overage for Ramucirumab drug product. The development of the DP manufacturing process consists of changes in manufacturing site, filling technology, container closure system and scale. This is sufficiently described.

The development of the process parameter control strategy is described. Process parameter ranges are justified mainly based on historical data (including process data from manufacturing of clinical batches and platform knowledge). For specific parameters, additional commercial scale development studies have been completed in order to verify the control strategy.

An additional vial presentation was introduced and both the 10 mL and 50 mL presentations were filled into new primary packaging components. The primary packaging component changes comprise a change from moulded to tubing Type 1 glass vials, and the introduction of a new stopper of similar composition to the existing stopper. Studies were conducted to justify the changes.

Validation of the manufacturing processes was successfully completed. Comparability has been demonstrated.

Container closure integrity studies have been conducted and the effects of mechanical (shear) stress on ramucirumab have been evaluated. A toxicology assessment of potential leachables was also performed. The results demonstrate that ramucirumab DP is stable in the proposed container- closure system.


### *Adventitious agents*

Bovine serum albumin is the only raw material of animal origin that is used in the cell culture medium of the ramucirumab manufacturing process. The country of origin of BSA is New Zealand which is free from TSE therefore the risk of TSE contamination from the raw materials is considered negligible.

MCB and WCB have been adequately characterised for the presence of endogenous and adventitious agents (microbial and viral contaminants). Retrovirus particles (A- and C-type) have been identified, as expected for the NS0 cell line. Cells at the limit of in vitro cell age have been characterised for the presence of adventitious agents. Viral clearance steps of the manufacturing process have been demonstrated to be able to remove possible viral contaminants.

Viral Clearance Studies

Viral clearance challenge studies were performed for the different orthogonal viral reduction unit operations using various model viruses. The choice of steps and viruses to be validated for their virus removal capacity is deemed acceptable. Appropriate scaled-down models were developed and worst-case parameters were identified. An assessment of the virus risk potential using the viral clearance data for the commercial purification process has been submitted. The data from the viral clearance studies to support marketing authorization are robust. These cover an adequate range of properties, including size, genome content, as well as resistance to low pH inactivation treatment. The results from the viral clearance studies and calculated viral risk safety margin for ramucirumab commercial process as well as

the historical ramucirumab processes, demonstrate that there is an appropriate viral clearance control strategy for ramucirumab bulk drug substance. The data support that the process is sufficiently validated for its ability to remove/inactivate viruses.

### Manufacture of the product

Ramucirumab DP is manufactured as a sterile, non-pyrogenic solution at a concentration of 10 mg/mL and aseptically filled into vials. The DP manufacturing process consists of dilution of the bulk drug substance in histidine buffer containing sodium chloride, glycine, and polysorbate 80. The DP solution is sterile filtered and aseptically filled into depyrogenated Type I tubing glass vials (500 mg/50 mL or 100 mg/10 mL), stoppered with sterile stoppers and crimp sealed. No reprocessing is performed. Operating ranges for process parameters and acceptance criteria for controls have been provided. The process validation (PV) studies were executed at the proposed commercial manufacturing sites, according to the commercial scale and processes described. Overall the process validation has been appropriately described.

The overall approach of the PV activities encompassed three stages: (1) Process Design (2) Process Qualification, and (3) Continuous Process Verification, using a science and risk based approach and covered validation of the manufacturing process including the sterilisation process.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this product.

### Product specification

The finished product release specifications include appropriate tests for this kind of product and includes tests for Purity, Identity, Potency and Protein Concentration.

No new impurities have been identified for the drug product. Additional tests for Polysorbate 80, Sterility, Particulate Matter, Container Closure Integrity and Volume in Container have been included in the DP specifications.

Batch Analyses

Batch analytical data have been provided for DP lots manufactured from Process C1 DS, Process C0, Process B and Process A. Ramucirumab DP batches (Process A, B and C0) manufactured for use in clinical studies have been submitted. The C1 batches were used in consistency, stability and comparability studies. The analytical batch release results across the DP batches of Process C1, C0, B and A as well as DP versus DS are within the specification limits, consistent and highly similar. Comparability of Process C1 material filled at commercial manufacturing sites has been demonstrated. Batch analysis results have confirmed the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Reference standards

In house reference standards are used in analytical quality assays. DS batches manufactured by Processes A, C0 and C1 were used as reference standards throughout the development of ramucirumab. The same reference standards are used for DS and DP, this is considered justified. The formulation of the standards reflects the formulation changes in the processes The one-tiered system will be replaced with a two-tiered RS system that is stored frozen as Primary and Secondary RS (-80°C to -70°C). The secondary frozen RS batch will be the 'working RS' used for routine release, stability and characterization testing of ramucirumab. This is acceptable.

Container closure system

Ramucirumab drug product is packaged in a Type I tubing glass vial with a rubber stopper and an aluminium seal with a plastic flip-top. The drug product presentations are referred to as 500mg/50mL and 100mg/10mL.

*Stability of the product*

Primary stability studies are ongoing for full scale DP lots manufactured at the two proposed commercial DP manufacturing sites (both using Process C1 DS). Primary stability data of 21 months for most of the DP lots are available at the recommended (2-8°C) storage conditions (18 months for the remaining two lots). Twelve month data for these lots are also available under accelerated (23-27°C) conditions and six month data under stressed (38-42°C) storage conditions. The primary stability lots will continue to be evaluated at the recommended storage condition (2-8°C) up to 36 months according to the stability protocol.

In addition, supportive stability data have been provided and this includes five lots of drug product manufactured using Process C0 drug substance, for which data have been provided through 36 months. These Process C0 lots were within the proposed acceptance criteria for 36 months. At the recommended storage at 2-8°C there is no obvious trend for any parameter purity tests. Data from storage under accelerated (23-27°C) storage conditions and from a freeze thaw study and photostability data have also been presented. The secondary packaging provides adequate protection for ramucirumab DP against light. Freeze thaw study data show that temperature cycling does not adversely affect drug product stability.

Analytical methods used for stability studies are the same as those used for release testing of the drug product. In addition IEF testing has been continued for stability testing. At the recommended storage at 2-8°C there is no obvious trend for any parameter including SE-HPLC and SDS-PAGE. A shelf life of 36 months at 2-8°C is acceptable.

For administration, ramucirumab DP is diluted into 0.9% sodium chloride injection and administered via peripheral IV infusion. The stability of prepared ramucirumab dosing solutions was evaluated using commonly available infusion containers and infusion sets. In addition, a microbiological challenge study was performed to evaluate microbial growth promoting activity of ramucirumab dosing solution stored at 20–25°C.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Drug substance

Description of manufacturing process and process controls

The procedure for classification of critical quality attributes (CQAs) and critical process parameters (CPPs) are acceptable and questions on impurity removal, especially process related impurities, were addressed during assessment. Established CQAs are similar to those for other monoclonal antibodies.

The manufacturing process, its description, and the associated control strategy are deemed acceptable, after the Applicant provided clarification and made several (mostly minor) amendments, particularly regarding the robustness of impurity removal.

Batch analysis and justification of specification

The Applicant amended its original approach upon request and submitted a completely new justification of specification. This resulted in the introduction of separate release and shelf life limits for several

quantitative parameters and amendments to the limits themselves. Finally, the Applicant committed to introduce a more quantitative purity method post-approval. This will improve the current control strategy, which is itself satisfactory for the purposes of approval. All specifications are now properly justified.

Drug product

Reference standards

The Applicant sufficiently addressed the issue of potency drift of the standards and justified that more robust strategies have been implemented with each successive manufacturing campaign. Since RS specifications/acceptance criteria are aligned with the current DS release criteria, a commitment was requested from the Applicant to update the specifications/acceptance criteria for the primary and working reference standards should the drug substance specifications be updated in the future.

Adventitious agents' safety evaluation

Upon final clarification, the data support that the materials (MCB, WCBs etc.) are tested and qualified, that the process is sufficiently validated for its ability to remove/inactivate viruses and that the viral safety of the product is assured.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. The CTD is of appropriate quality and provides a satisfactory description of the characterisation, manufacture and control of drug substance and drug product. Data has been presented to give reassurance on viral/TSE safety.

## 2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The Applicant will introduce a more quantitative purity method for the drug substance.

The Applicant will update the specifications/acceptance criteria for the primary and working reference standards should the drug substance specifications be updated in the future.

## 2.3. Non-clinical aspects

### 2.3.1. Introduction

The non-clinical studies were conducted in accordance with current international regulatory guidelines relevant to therapeutic development (ICH S6, ICH S9, ICH M3).

The pivotal toxicology studies were performed in compliance with the principles of Good Laboratory Practice (GLP). Toxicokinetic and immunogenicity analyses as well as immunophenotyping in the two pivotal *Cynomolgus* monkey toxicity studies were not formally GLP-compliant.

Scientific advice has not been sought for the non-clinical aspects of ramucirumab development.

### 2.3.2. Pharmacology

**Primary pharmacodynamic studies**

A series of *in vitro* and *in vivo* studies were carried out for the biochemical characterisation of ramucirumab. Since ramucirumab is not cross-reactive in mouse, its antitumour activity and antiangiogenic mechanism of action could not be studied in these species. A rat-anti mouse flk-1 monoclonal IgG1 antibody, DC101, was developed for use in *in vivo* studies.

The key biochemical and pharmacodynamic characteristics of ramucirumab are summarised in Table 1.

**Table 1. Summary of key findings *in vitro* pharmacodynamics studies with ramucirumab**

| Type of study | assay | Test system | results | Report/reference |
|---|---|---|---|---|
| **Binding/ Blocking** | Binding to human VEGFR-2 | BIACore | $K_d = 5 \times 10^{-11}$ M | Lu et al. (2003); 1001-09 |
| | | ELISA | $EC_{50} = 0.16$ nM | 1001-09 |
| | Blocking VEGF binding to human VEGFR-2 | ELISA | $IC_{50} = 0.8$ nM | Lu et al. (2003); Zhu et al. (2003); |
| | | $^{125}$I-VEGF binding to VEGFR-2$^+$cells (HUVEC) | Inhibition seen at ≥ ~ 0.5 nM | Zhu et al. (2003); |
| **VEGFR-2 Specificity** | Pan-Target Assay | ELISA | Binding to VEGFR2 and not to the other growth factor RTKs tested[a] | PT-1202 |
| | Binding to VEGFR | ELISA | No Binding to VEGFR-1, VEGFR-3 | PT-1202 IMC01 |

| **Functional Assays:** Inhibition of VEGF-induced/ stimulated | VEGFR2-phosporylation | HUVEC and PAE-KDR cells | $IC_{50}$: ~10-50nM | Lu et al. (2003) Miao et al. (2006) [b] |
|---|---|---|---|---|
| | phosphorylation of PLCγ, MAPK[c] | PAE-KDR cells | Complete inhibition at 30 nM by 1121 Fab | Miao et al. (2006) [b] |
| | calcium mobilization | PAE-KDR cells | Complete inhibition at 3 nM by 1121B Fab | Miao et al. (2006) [b] |
| | migration of VEGFR$^+$ cells | HL60 and HEL cells | IC: 2.5-40 nM | Zhu et al. (2003) |
| | | PAE-KDR cells | $IC_{50}$ ~0.2 for Fab fragment | Miao et al. (2006) [b] |
| | cell proliferation | HUVEC and PAE-KDR cells | $IC_{50}$ ~20 nM for Fab fragment | Miao et al. (2006) [b] |
| | VEGFR-2 expression | PAE-KDR cells, AEC, hDMEC | Max down modulation of surface VEGFR2 at ~25 nM | IMC02 |
| VEGFR-2/ VEGF-ligand interactions | Inhibition of VEGF-A, -C and -D binding to VEGFR-2 | ELISA | VEFG-A $IC_{50}$: 2.3 nM VEGF-C: $IC_{50}$: 0.7 nM VEGF-D: $IC_{50}$: 0.3 nM | IMC04 |
| | Inhibition of VEGF-C binding and/or VEGF-C activation of VEGFR-2 | Receptor phosphorylation, cell proliferation and migration (LEC or hDMEC) | $IC_{50}$ ~0.8 nM | Jimenez et al. (2005); Goldman et al.(2007); Tvorgov et al. (2010) |
| | VEGF-C-induced endothelial cell sprouting | hDMEC | > 90 % inhibition | Tvorgov et al. (2010) |

a: Test panel of RTK consisted of: VEGFR1, VEGFR2, VEGFR3, EGFR, IGF1R, PDGFα, Flt3R, PDGFβ, RON, CSF-1R, TGFβRIII, FGFR3b, c-kit, TrkA, VEGF165, GP75.
b: the 1121B Fab fragment was used in these studies
c: PLCγ and MAPK are VEGFR2 downstream signalling molecules.

The in vitro binding assays showed that ramucirumab binds with high affinity to human VEGFR-2 (Kd ~ 5 × 10-11M and EC50=0.16 nM obtained from an ELISA assay) and it inhibits VEGFR-2 binding to its ligand VEGF-A with an IC50 of ~0.8 nM. Competitive blocking assays showed that anti-VEGFR-2 antibodies effectively inhibited 125I-VEGF binding to HUVEC-expressed VEGFR-2. Furthermore, it was shown that ramucirumab is highly specific for human VEGFR-2 and does not cross-react with the related receptors VEGFR-1 and VEGFR-3, or other growth factor receptor tyrosine kinases.

The results of competitive blocking by three different anti-VEGFR-2 antibodies of radiolabeled VEGF binding to VEGFR-2 expressed in HUVECs (Zhu et al. 2003) showed that ramucirumab inhibited VEGF-induced mitogenesis with an ED50 ≈ 0.7 nM, in comparison to that of 1.5 nM for the other two antibodies (IMC-1C11 and IMC-2C6) tested. In addition, ramucirumab and other anti-VEGFR-2 antibodies (IMC-1C11, IMC-2C6) inhibited VEGF-induced migration of HL60 and HEL cells expressing VEGFR-2 in a dose-dependent manner, but it did not inhibit migration of U937 cells that do not express VEGFR-2.

VEGF stimulation resulted in significant VEGFR-2 phosphorylation in both HUVEC and PAE-KDR cells. However, in the presence of VEGF, ramucirumab antagonized the VEGFR-2 phosphorylation in a dose-dependent manner. Ramucirumab was a more potent inhibitor of VEGFR-2 phosphorylation than the parent antibody IMC-2C6 (>5- to 25-fold) in both cell-based assays.

The binding inhibition of VEGF-A, VEGF-C and VEGF-D to human VEGFR-2 by ramucirumab was assessed in an in vitro (cell-free) model (Report IMC04). Ramucirumab inhibited the binding of VEGF-A (IC50 = 2.3 nM), VEGF-C (IC50 = 0.7 nM), and VEGF-D (IC50 = 0.3 nM) to soluble extracellular domain of human VEGFR-2 in a dose-depended manner.

Functionally, ramucirumab blocks VEGF-A-stimulated activation of VEGFR-2, and inhibits VEGF-A-induced migration of endothelial cells and human leukemia cells. Additional evidence in the literature has shown that it also blocks the interaction of other VEGFR-2 ligands VEGF-C and VEGF-D with VEGFR-2 receptor (Lu et al, 2003; Jimenez et al. 2005; Goldman et al. 2007; Tvorogov et al. 2010). Ramucirumab is also capable of inhibiting VEGF-C-induced activation of VEGFR-2, and blocking VEGF-C-induced hetero-dimerization of VEGFR-2 and VEGFR-3 (Nillson et al. 2010). Ramucirumab also inhibits sprouting and proliferation of endothelial cells following stimulation with VEGF-C (Miao et al. 2006; Tvorogov et al. 2010; Goldman et al. 2007).

Experiments with primary human aortic endothelial cells and dermal microvascular endothelial cells showed that ramucirumab can induce downregulation of surface VEGFR-2. The effect is concentration-dependent with optimum endocytosis occurring at 25 nM (Report IMC02). Ramucirumab recognises human VEGFR-2, but does not recognise mouse VEGFR-2 (Flk1). Therefore, a rat surrogate antibody DC101 was used in proof-of-concept studies in human cancer xenograft models in mice. The characterisation data of DC101 surrogate antibody showed that DC101 is specific for murine VEGFR-2 and did not bind to human VEGFR-2 or mouse VEGFR-1. DC101 binds to murine VEGFR-2 with a 10-fold lower binding affinity than ramucirumab to the human receptor. Similarly to humans it blocks VEGFR-2 signalling in vitro. Functionally, DC101 inhibited VEGF-stimulated phosphorylation of mouse VEGFR-2.

In vitro experiments were conducted using both direct binding ELISA and BIACore analyses to assess the binding of DC101 and ramucirumab to mouse and human VEGFR2 (Report 1001-09). Ramucirumab, but not DC101, bound to immobilized human VEGFR-2 (KDR) with an EC50 of 0.16nM. Conversely, only DC101, but not ramucirumab, bound to mouse VEGFR-2 (Flk-1) with EC50 = 0.28 nM. Endothelial cell apoptosis is induced in mouse metastatic tumour xenograft models upon treatment with DC101 and precedes initiation of tumour cell apoptosis by about 1 week (Sweeney et al. 2002; Bruns et al. 2000). Several studies using different imaging modalities such as Doppler ultrasound (Franco et al. 2006; Krix et al. 2003; Jugold et al. 2008; Cheung et al. 2007), dynamic contrast-enhanced CT (DCE-CT) (Stantz et al. 2011; Cheung et al. 2007), and dynamic contrast-enhanced magnetic resonance (DCE-MRI) (Kiessling et al. 2004) showed that reduction in tumour microvascular density and subsequent tumour growth

inhibition upon treatment with DC101 correlate with functional reduction in blood flow in living, tumour bearing mice.

Non-invasive measurements of tumour oxygenation in tumours grown in transparent skin-fold chambers showed induction of hypoxia and tumour vessel regression upon administration of DC101 (Hansen-Algenstaedt et al. 2001). Induction of tumour hypoxia has also been shown in several tumour models by the uptake of Hypoxyprobe (pimonidazole) which homes to hypoxic tissues in living animals and is subsequently detected immunohistochemically (Paez-Ribes et al. 2009; Franco et al. 2006).

Characterization of the mechanism of the anti-angiogenic effects of ramucirumab in rodent was shown in one study (Report IMC03). Purified human endothelial progenitor cells (EPC) and ADSC (adipose derived stem cells) were mixed with matrigel and implanted under the skin of mice. The EPC and ADSC form branching endothelial cords within the matrigel matrix. The endothelial cords appear to form a functional capillary network that anastomoses with the dermal vasculature of the mouse, as evidenced by perfusion of the matrigel plug with erythrocytes. The formation of the human capillary network within the plugs was inhibited in mice when ramucirumab was administered at 10 mg/kg every 3 days for the duration of the experiment.

Proof of concept was shown in a human gastric cancer xenograft model in mice where DC101 exhibited a significant tumour growth inhibitory effect as measured by >50 % inhibition of tumour growth (Report 2212-03).

DC101 efficacy was tested in several other human cancer (hepatic, colorectal, breast, non-small cell and leakemia) xenograft models in mice. Based on the results, in most of these studies, DC101 as monotherapy and in combination with approved chemotherapies inhibited tumour growth.

### Secondary pharmacodynamic studies

No secondary pharmacodynamic studies of ramucirumab have been conducted (see discussion on non-clinical aspects). However several cell-based assays have been conducted by the applicant in order to determine if ramucirumab is capable of triggering complement-dependent cytotoxicity (CDC) activity and to evaluate the potential of ramucirumab to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) activity.  Neither CDC nor ADCC functions were observed with ramucirumab in these assays (data not shown).

### Safety pharmacology programme

No dedicated safety pharmacology studies have been performed with ramucirumab but safety pharmacology parameters were assessed as part of the GLP-compliant 5-and 39-week toxicology studies in *Cynomolgus* monkeys.

In these studies, no treatment-related effects were evident upon physical examination, or on assessments of blood pressure, ECG, and rectal body temperature. No specific examination or data collection was performed on the respiratory or central nervous system, but no effects were noted on these systems post-dosing during physical examinations.

### Pharmacodynamic drug interactions

No studies were submitted (see discussion on non-clinical aspects).

## 2.3.1. Pharmacokinetics

The pharmacokinetics and toxicokinetics of ramucirumab were characterised in 2 repeat-dose toxicology studies after a single dose and multiple doses in monkeys, after a single dose in a monkey wound-healing study and in a single dose comparability study in monkeys. A pharmacokinetic study of the rodent anti-VEGFR-2 surrogate for ramucirumab antibody, DC101, was conducted in mice to estimate plasma concentrations associated with the regimen planned to be used in mouse efficacy studies of DC101.

**Table 2 Pharmacokinetic Study Overview**

| Study Type and Duration | Species | Test Article (Mfg Process) | Route of Administration | Doses (mg/kg) | Report Number |
|---|---|---|---|---|---|
| Single-Dose Pharmacokinetics | Nude mouse | DC101 | IP | 40 | 2034-03 |
| Single-Dose Pharmacokinetics Comparability | Cynomolgus monkey | Ramucirumab (Process B and C) | IV infusion | 12 | BDZ00030 |
| Single-Dose Pharmacokinetics (Wound-Healing) | Cynomolgus monkey | Ramucirumab (Process C) | IV infusion | 5, 15, 50 | 20018776 |
| Toxicokinetics (5 weeks – weekly dosing[a]) | Cynomolgus monkey | Ramucirumab (Process A) | IV bolus | 4, 12, 40 | SNBL 023.04-SSR04014[b] |
| Toxicokinetics (39 weeks – weekly dosing) | Cynomolgus monkey | Ramucirumab (Process A) | IV infusion | 5, 16, 50 | 1163-110 |

a Dosing on Days 1, 15, 22, 29
b The bioanalytical, pharmacokinetic and immunogenicity data and analyses are submitted as a standalone report SSR04014. This report will be referenced as Report SNBL023.04-SSR04014.

PK/TK evaluations of ramucirumab were conducted as part of the 5-week (4-dose) (Report SNBL 023.04-SSR04014) and 39-week (Report 1163-110) intravenous repeat dose toxicity studies in *Cynomolgus* monkeys. Ramucirumab was administered intravenously (i.v.) as either a slow bolus in the 5-week study, or an approximate 10 minute i.v. infusion in the 39-week study. Doses were administered once weekly, except in the 5-week study in which a 2-week interval was allotted between Days 1 and 15 to enable capture of the terminal elimination phase following the first ramucirumab treatment. Non-compartmental analysis of the concentration versus time data in the repeat-dose toxicity studies indicated that the PK behaviour of ramucirumab was non-linear over the 4 to 50 mg/kg test dose range. The mean $AUC_{0-\infty}$ increased in a greater than dose-proportional manner. The mean serum elimination half-life (t1/2) for ramucirumab increased, and clearance (CL) decreased with increasing dose on Study Day 1. Samples were also analysed for anti-drug antibodies (ADA) to assess their impact on serum concentrations of ramucirumab. In the 5-week study, ADA were detected in mainly the low and mid-dose groups. ADA were detected in only 1/6 evaluable animals in the high-dose group. In the 39-weeks study, the highest incidence of ADA was found in the lowest dose group; ADA were not detected in any animals of the 50-mg/kg dose group.

A PK study was conducted in Cynomolgus monkeys to assess the comparability of materials manufactured by two different processes (Report BDZ00030). Drug product from these two processes was formulated in the same histidine-based formulation buffer system, but at different antibody concentrations. Process B material was formulated at a concentration of 5.3 mg/mL, and was used in early clinical development. Process C material (also referred to as Process C0) was formulated at a concentration of 10 mg/mL, and was used in Phase 3 clinical trials. A total of 40 experimentally-naïve Cynomolgus monkeys (20 males, 20 females) were assigned to the dose groups. No significant differences were evident in the PK of

ramucirumab manufactured by either Process B or C0. To confirm the PK comparability between the Process B and Process C materials, a comparative analysis using average bioequivalence criteria was conducted using all 20 animals in each group. Process B and Process C were considered comparable if for both Cmax and AUC0-∞ the 90% confidence interval of the geometric mean ratio of each process was within the bounds (80%, 125%). For Cmax, the geometric mean ratio was 103.2 and the 90% confidence interval was (91.4, 116.5). Similarly, for AUC0-∞, the geometric mean ratio was 101.8 and the 90% confidence interval was (92.0, 112.7). Based on these results and according to the criteria applied, there were no differences in the PK of ramucirumab manufactured by Process B and C. All animals were evaluated for the presence of ADAs against ramucirumab. The majority of the animals were negative for ADA at the Day 1 pre-dose time point. By Day 14, the majority of animals were positive for ADA, irrespective of whether Process B or C0 was given. An assessment of the impact of ADA on circulating ramucirumab concentrations is limited by the high incidence of ADA in each treatment group, but no clear indication that ADA decreased circulating ramucirumab concentrations was inferred from the data.

The PK of ramucirumab was determined after a single 10 minute i.v. infusion of ramucirumab dose of 5, 15, or 50 mg/kg in a wound-healing study in male *Cynomolgus* monkeys (n = 4) to enable correlation of serum ramucirumab exposures with any adverse impact of ramucirumab on wound-healing (Report 20018776). Serum concentrations were determined over the entire study observation period up to 3 weeks (504 hours) post-dosing. Systemic exposure to ramucirumab increased with increasing dose levels. The serum elimination half-life (t1/2) ranged from 41.4 to 94.0 hours in the 5- and 15-mg/kg groups and from 131 to 176 in the 50-mg/kg group. The apparent volume of distribution (Vd) range was in the range of plasma volume for monkeys.

The PK of DC101 was characterised in naïve non-tumour bearing female nude mice treated by i.p. injection with an approximate dose of 40 mg/kg of DC101 (Report 2034-03). At baseline or 0.5, 1, 2, 4, 8, 24, 48, and 72 hours following DC101 treatment, plasma was collected from three mice per group for DC101 concentration analysis by ELISA. After about the third treatment the mice will be in steady state and the AUC during the first 48 hours after a dose will be about 1.5 times higher in steady state than after the first treatment. The estimated terminal elimination half-life (t1/2) for DC101 according to this model was 29 hours.

## 2.3.2. Toxicology

### *Single dose toxicity*
No single-dose toxicity studies were submitted (see discussion on non-clinical aspects).

### *Repeat dose toxicity*

Repeat-dose toxicity studies applying i.v. dosing of ramucirumab for 5 and 39 weeks were conducted in *Cynomolgus* monkeys. Results of repeat-dose toxicity studies are summarised in Table 3.

**Table 3 Overview of repeated dose toxicity studies with ramucirumab**

| Study ID | Species/Sex/ Number/Group | Dose/Route | Duration | NOEL/ NOAEL (mg/kg) | Major findings |
|---|---|---|---|---|---|
| SNBL-023 -04 GLP | *Cynomolgous* monkeys/3f,6m /dose* | 0, 4, 12, 40 mg/kg IV on days 1, 15, 22, 29 | 5 wks + 6 wks recovery (3m/dose) | < 4 mg/kg | **≥4:** focal muscle fiber degeneration and mononuclear cell infiltration in skeletal muscle (f/m), decreased width of the knee joints growth plates (left and/or right) (m), ↓ weight thyroid (m), ↓ weight ovaries (f) |
| 1163-110 GLP | *Cynomolgous* monkeys, 3m,6f/dose | 0, 5, 16, 50 mg/kg IV weekly | 12 wks (3f/dose) and 39 wks 3f,3m/dos e | < 5 mg/kg | **12 weeks (f):** <br>**≥5:** ↑ trachea inflam. <br>↑ infiltration lymphoid cells in mandibular salivary gland <br>**≥16:** ↑ severity liver inflam., ↑ severity kidney inflam., <br>**39 weeks (f/m):** <br>**≥5:** ↓ weight uterus (f), ↑ WBC, ↑ mononuclear cell infiltration in heart (f/m), aggregates and inflam. urinary bladder, thickening and osteochondro-pathy of the epiphyseal growth plate in femurs <br>**≥16 :** glomerulonephritis kidney, ↑ mineralization ovaries (f), involution thymus (m) <br>**=50:** swollen scrotum and lower extremities (1m), enlarged genital organs (2m), pale kidneys (1m), red skin of thoracic limbs (bil.) (1m) <br>↑ adrenal and kidney weight (f), ↓ weight ovaries (f), ↓ RBC and HBG (1m), ↑ monocytes (f), ↑ protein level (1m, 3f), inflam. colon (m), inflam. MLN (m), inflam. skin, mild inflam. stomach (m), thrombosis mandibular lymph node (f) |

**\*** control group 4f, 2m

### Genotoxicity

No studies were submitted (see discussion on non-clinical aspects).

### Carcinogenicity

No studies were submitted (see discussion on non-clinical aspects).

### Reproductive and developmental toxicity

No studies were submitted (see discussion on non-clinical aspects).

### Toxicokinetic data

See pharmacokinetics.

*Local Tolerance*

No dedicated local tolerance studies have been conducted. However local tolerance was investigated in the two pivotal repeat-dose toxicity evaluations in *Cynomolgus* monkeys by clinical observations, and as part of the histopathological evaluations (Report SNBL-023-04, Report 1163-110). Inflammatory reactions were observed at the majority of injection sites consisting of mononuclear cells or mononuclear and polymorphonuclear cells in perivascular areas in both control and treated groups in the 5-weeks repeat dose toxicity study.

*Other toxicity studies*

The anticipated mechanism-based impairment of wound-healing by ramucirumab was assessed in an incisional model of wound healing after administration of a single i.v. dose at 5, 15, or 50 mg/kg in *Cynomolgus* monkeys (Report 20018776). Serum concentrations of ramucirumab were determined to characterise the exposure to response relationship for wound-healing impairment. Samples of full-thickness punch biopsies of the skin and subcutaneous tissue were collected on Days 4, 8, 15, and 22 for histopathology. By Day 8, most incisions were closed at the surface and all incisions remained closed at Day 15 and Day 22.

To characterise the tissue binding profile of ramucirumab and to confirm the relevance of the animal model (based on target distribution) used for the ramucirumab safety assessment, a comprehensive tissue cross-reactivity study was conducted in cryosections of normal human and *Cynomolgus* monkey tissues (Report IM1025). Tissue samples from human and *Cynomolgus* monkeys were stained with ramucirumab at 2 protein concentrations (5 µg/mL and 0.5 µg/mL). Tissue cross-reactivity was observed in vascular endothelium in both human and *Cynomolgus* monkey tissues, consistently with the distribution of the molecular target of ramucirumab, VEGFR-2. Cytoplasmic (and possibly membrane-associated) reactivity was also detected in the retina of the eye of both species. The test article stained several cell types of the monocyte-macrophage lineage in the lung (human only), liver (human and monkey), lymph node (human only), and spleen (monkey only). Granular cytoplasmic staining was seen in the connective tissues of the central and peripheral nervous system, including the meninges of the brain and spinal cord (both species), and the perineurium (both species). Labeling occurred also in the interstitial stroma of the lung (human only). The test article stained of several epithelial cell types, including alveolar epithelium in the lung (both species), epithelium of remnants of Rathke's pouch in the pituitary (human only), glandular epithelium of the salivary gland (both species), and choroid plexus epithelium of the brain (monkey only).

### 2.3.3. Ecotoxicity/environmental risk assessment

No ERA was submitted (see discussion on non-clinical aspects).

### 2.3.4. Discussion on non-clinical aspects

Non-clinical pharmacodynamic data adequately showed that ramucirumab binds specifically and with high affinity to human VEGFR-2 thereby inhibiting VEGFR-2 pathway, and provided a proof-of-concept in human cancer xenograft models in mice to support treatment of gastric cancer patients.

Vascular Endothelial Growth Factor (VEGF) Receptor 2 is the key mediator of VEGF induced angiogenesis. Ramucirumab is a human receptor-targeted antibody that specifically binds VEGF Receptor 2 and blocks binding of VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand stimulated activation of VEGF Receptor 2 and its downstream signalling components, including p44/p42 mitogen-activated protein kinases, neutralizing ligand-induced proliferation and migration of human endothelial cells (see SmPC, section 5.1).

Ramucirumab has the potential to bind to C1q. However, apparently this potential to bind to C1q does not translate into a potential to induce CDC. While no formal secondary pharmacodynamic studies have been conducted, the results of the ADCC assays were provided. Both the ADCC receptor gene assay and the classical cytotoxicity assay using ramucirumab and PBMC indicated that ramucirumab did not induce an ADCC response. As an explanation for this lack of ADCC, even though ramucirumab can bind to CD16, was suggested to lie in other factors such as receptor density and availability, and interfering receptors on the target cells. This raised the question whether the appropriate target cells were used in these assays. To accurately determine the ability of the antibody to induce ADCC, these target cells should display a similar receptor density/availability as the target cells in vivo. In the ADCC assays, two different target cell populations were used, VEGFR2 transfected porcine cells and the HCC-827 cell line. No information on the VEGFR2 density/availability on these target cells was provided. However, in general target gene expression is usually rather high in transfected cells. Furthermore, it is not very likely that both cell lines would exhibit high levels of interfering receptors prohibiting ADCC. Overall, ramucirumab was negative in two different ADCC assays *in vitro*, using two different target cell lines and it is considered unlikely that ramucirumab will display ADCC activity *in vivo*

The *Cynomolgus* monkey can be considered an appropriate nonclinical species for ramucirumab toxicity testing given the comparable binding affinity of ramucirumab to its receptor in humans and *Cynomolgus* monkeys, and the fact that pharmacological effects have been seen in this test species.

A target-mediated saturation of a clearance pathway for ramucirumab in *Cynomolgus* monkeys was observed. In addition, no differences in kinetics were observed between the different ramucirumab production processes. The data obtained after repeated dosing was very limited, but the available data indicated that similar $C_{max}$ and AUC values were reached after Dose 1 compared to Dose 39. Regarding the possible correlation between the presence of ADAs in the *Cynomolgus* monkey serum samples and the lower serum concentrations of ramucirumab, it is possible that the development of ADAs has decreased the exposure of animals to ramucirumab. However, since the pharmacology related effects were observed and due to a slower clearance of ramucirumab in the high-dose group animals it can be concluded that the monkeys were sufficiently exposed to ramucirumab, and that the toxicity data are considered reliable. The apparent volume of distribution (Vd) range was in the range of plasma volume for monkeys, indicating that ramucirumab did not substantially distribute beyond the vasculature. In general, the kinetics of ramucirumab in toxicological test species matches that of human kinetics (non-linear, distribution limited to vascular space, relative long half-life time) and are what it is expected from an antibody. Exposures in animals were similar or exceeded those in humans.

Hypertension, an established clinical adverse drug reaction of therapies targeting inhibitors of the VEGF/VEGF Receptor 2 pathway, was not observed in monkey repeat-dose toxicity studies of ramucirumab based on limited assessment of blood pressure in these toxicology studies. However hypertension was observed in the clinical studies. Based on published information and pharmacology reviews of approved inhibitors of the VEGF/VEGF Receptor 2 pathway, nonclinical animal species are poor predictors of anti-VEGF receptor-induced hypertension in the clinic. Other factors that may be contributing to poor predictability of nonclinical studies with ramucirumab and with other inhibitors of the VEGF/VEGF Receptor 2 pathway included techniques used in assessing blood pressure, frequency and duration in which blood pressure is measured (single time point versus continuous direct intravascular measurement of blood pressure), small number of animals used in toxicology studies compared to large clinical trial patient population and health status of the animals (healthy animals used in toxicology studies).

No safety pharmacology studies have been conducted. However safety pharmacology parameters were assessed as part of the GLP-compliant in the 5- week and 39-weeks toxicology studies in *Cynomolgus* monkey and no treatment-related effects were observed.

No single-dose toxicity studies were conducted since no signs of acute toxicity were observed after administration of the highest single ramucirumab test dose of 50 mg/kg in the 39-week and wound healing studies.

The target organs identified in repeated dose *Cynomolgus* monkey toxicity studies were kidney (glomerulonephritis), bone (thickening and abnormal endochondral ossification of the epiphyseal growth plate) and female reproductive organs (decreased weight of ovaries and uterus) (see SmPC, section 5.3). Glomerulonephritis was seen in animals after treatment with a dose of $\geq$ 4 mg/kg. Severity increased in a dose related manner. In principle kidney effects may be related to the pharmacodynamics action of ramucirumab (i.e. interfering with VEGF/VEGFR2 signaling). However the formation of immune complexes resulting from ADA formation is also a possible explanation. In some clinical trials, proteinuria has been reported. A clear effect of ramucirumab treatment of *Cynomolgus* monkeys was the thickening and osteochondropathy of the epiphyseal growth plates in both femurs. This effect was already observed in the lowest dose treatment group in both the 5 and the 39 weeks study. These bone growth plate related effects appear to be class related and might be clinically relevant for children, but probably not for adult patient population.

A minimal grade of inflammation and/or mononuclear cell infiltration was seen in several organs (see SmPC, section 5.3). It is not clear whether this specific inflammation is clinically relevant since in the clinical trials no clear signs of inflammation have been observed.

Genotoxicity, carcinogenicity, developmental or reproductive toxicology studies were not conducted with ramucirumab in line with available guidance [ICH S9 (EMEA/CHMP/ICH/646107/2008)] as ramucirumab is indicated for the treatment of patients with advanced gastric cancer. However the applicant will perform analysis of incidence of secondary malignancies observed in clinical trials (see Risk Management Plan).

No reproductive toxicity studies with ramucirumab were conducted; however, animal models link angiogenesis, VEGF and VEGFR-2 to critical aspects of female reproduction, embryo-foetal development, and postnatal development. Literature data indicated potential risks to fertility, pregnancy and development if VEGF signaling is inhibited leading to anti-angiogenic effects. Based on ramucirumab's mechanism of action, it is likely that in animals, ramucirumab will inhibit angiogenesis and result in adverse effects on fertility (ovulation), placental development, developing foetuses and postnatal development (see SmPC, section 5.3). Reproductive and developmental toxicity has been categorized as a potential risk (see Risk Management Plan).

Cyramza should only be used if the potential benefit to the mother justifies the potential risk during pregnancy. If the patient becomes pregnant while being treated with ramucirumab, she should be informed of the potential risk to the maintenance of pregnancy and the risk to the foetus. Cyramza is not recommended during pregnancy and in women of childbearing potential not using contraception (see SmPC, section 4.6).

Women of childbearing potential should be advised to avoid becoming pregnant while on Cyramza and should be informed of the potential hazard to the pregnancy and foetus. Women of child bearing potential should use effective contraception during and up to 3 months after the last dose of ramucirumab treatment. It is unknown whether ramucirumab is excreted in human milk. Excretion in milk and oral absorption is expected to be low. As a risk to newborns/infants cannot be excluded, breast-feeding should be discontinued during treatment with Cyramza and for at least 3 months after the last dose (see SmPC, section 4.6).

The animal data did not indicate non-tolerable adverse reactions at the injection sites.

A single dose of ramucirumab did not impair wound healing in monkeys using a full-thickness incisional model (see SmPC, section 5.3).

Tissue cross-reactivity was observed in vascular endothelium in both human and *Cynomolgus* monkey tissues, consistently with the distribution of the molecular target of ramucirumab, VEGFR-2. Cytoplasmic (and possibly membrane-associated) reactivity was also detected in the retina of the eye of both species. An unexpected binding of ramucirumab to certain tissues with partially different pattern in human and *Cynomolgus* monkeys was observed. However, toxicities related to those tissues were not observed in repeat dose toxicity studies, and those could be regarded as insignificant.

Antibodies, as other peptides and proteins, are exempted from environmental risk assessment (ERA) based on the EMA 2006 Guideline on Environmental Risk Assessment (EMEA/CHMP/SWP/4447/00).

### 2.3.5. Conclusion on the non-clinical aspects

In general, the non-clinical data submitted were of good quality and meet the requirements to support this application. The relevant information has been included in the SPC (sections 4.6, 5.1 and 5.3).

## 2.4. Clinical aspects

### 2.4.1. Introduction

**GCP**

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

*GCP inspection*

A GCP inspection was carried out of the conduct of the clinical study I4T-IE-JVBD. The inspection had a positive outcome and the inspectors concluded that the study report can be used for evaluation and assessment of the application.

• Tabular overview of clinical studies

| Study no | Type of study | Tumour type | Endpoint | Dosing | No. of patients |
|---|---|---|---|---|---|
| I4T-IE-JVBD | phIII | Gastric cancer 2nd line | OS | R8mg/kg q 2w I.V. | 351 |
| I4T-IE-JVBE | phIII | Gastric cancer 2nd line | OS | R 8 mg/kg I.V. on Days 1 and 15, + 80mg/m$^2$ paclitaxel on Days 1, 8, and 15 of a 28-day cycle. | 665 |
| **Single agent studies – supportive** | | | | | |
| I4T-IE-JVBM | phI | Adv cancer | Safety | R2 – 16mg/kg weekly 4/2 | 37 |
| I4T-IE-JVBN | phI | Adv cancer | Safety | R6 – 10 q 2w and 15 – 20mg/kg q3w | 25 |
| I4T-IE-JVBI | phI | Adv cancer | Safety | R6 – 8 q 2w and 10mg/kg q 3w | 15 |
| I4T-IE-JVBK | phII | Adv cancer | QT | R10mg/kg q 3w | 66 |
| I4T-IE-JVBP | phII | RCC 2nd line | ORR | R8mg/kg q 2w | 39 |
| I4T-IE-JVBQ | phII | HCC 1st line | PFS | R8mg/kg q 2w | 42 |
| I4T-IE-JVBR | phII | Ovarian cancer | PFS 6m | R8mg/kg q 2w | 60 |
| **Combination studies – supportive:** | | | | | |
| Study no | Type of study | Tumour type | Endpoint | Dosing | No. of patients |
| I4T-IE-JVBx | phIb | Breast cancer | Safety | R10mg/kg q 3w + Docetaxel 75mg/m$^2$ | 7 |
| I4T-IE-JVBW | phIb | Gastric cancer 2nd line | Safety | R8mg/kg q 2w + Taxol D1, 8 and 15 | 6 |
| I4T-IE-JVBY | phIb | Colorectal cancer 2nd line | Safety | R8mg/kg q 2w + Folfiri | 6 |
| I4T-IE-JVCA | Phi-DDI | Adv cancer | Part A:DDI Part B:PK | Part A: Paclitaxel 80m/m$^2$ D1 (C1) R8mg/kg D1,15 + Paclitaxel 80m/m$^2$ D1,8,15 (C2) Part B: R8mg/kg D1 (C1) R8mg/kg D1,15 (C2) OR R8mg/kg D1,15 + Paclitaxel 80m/m$^2$ D1,8,15 (C2) | 40 |
| I4T-IE-JVCC | Phi-DDI | Adv cancer | DDI | C1:Docetaxel 75mg/m$^2$ q 3W C2, C3 and beyond: R10mg/kg + | 22 |

| Study no | Type of study | Tumour type | Endpoint | Dosing | No. of patients |
|---|---|---|---|---|---|
| | | | | Docetaxel 75mg/m$^2$ 3w | |
| I4T-IE-JVBS | phII | Prostate cancer 2nd line | PFS | R6mg/kg D1, 8 and 15 + Mitox q 3w | 132 |
| I4T-IE-JVBO | phII | Melanoma 1st line | PFS | R10mg/kg q 3w + DTIC q 3w | 102 |
| I4T-IE-JVBJ | phII | NSCLC 1st line | PFS 6m | R10mg/kg q 3w + Taxol/Carbopl q 3w | 40 |
| I4T-IE-JVBH | phII | Colorectal cancer 1st line | PFS | R8mg/kg q 2w + mFolfox6 q 2w | 48 |

## 2.4.2. Pharmacokinetics

The pharmacokinetics of ramucirumab were evaluated in 8 studies (JVBW, JVBX, JVBY, JVBJ, JVCA [DDI study], JVCC [DDI study], JVBD [REGARD], and JVBE [RAINBOW]), a population pharmacokinetic analysis, an exposure-response analysis based on RAINBOW study and updated immunogenicity data with 6 additional studies. The population pharmacokinetic analysis (PopPK) dataset consisted of 497 patients with 2782 observations. Ramucirumab was administered as an i.v. infusion over approximately 60 minutes, at either 8 mg/kg every two weeks on a 14 day (JVBD, JVBY), 28 day (JVBW, JVCA, JVBE) cycle or 10 mg/kg every three weeks on a 21 day (JVBJ, JVBX, JVCC) cycle.

### *Absorption*

Cyramza is administered as an intravenous infusion. There have been no studies performed with other routes of administration Following the dose regimen of 8 mg/kg every 2 weeks, the geometric means of ramucirumab Cmin were 49.5 µg/ml (range of 6.3-228 µg/ml) and 74.4 µg/ml (range of 13.8-234 µg/ml) prior to administration of the fourth and seventh dose, respectively of ramucirumab given as a single agent, in serum from patients with advanced gastric cancer (see SmPC, section 5.2).

### *Distribution*

Based on population pharmacokinetic approach (PopPK), the mean volume of distribution at steady state for ramucirumab was 5.5L (see SmPC, section 5.2).

### *Elimination*

Based on PopPK, the mean clearance of ramucirumab was 0.014L/hour and the mean half-life was 15 days (see SmPC, section 5.2).

### Dose proportionality and time dependencies

**Table 4 Summary of Non Compartmental Pharmacokinetic Parameters for ramucirumab following weekly multiple IV infusions in Cycle 1, Week 4 (The 5th dose for 2, 4, 6 mg/kg; the 4th dose for 6, 8, 10, 13, 16 mg/kg).**

| | Geometric Mean (CV%)[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2 mg/kg (N=3) | 4 mg/kg[b] (N=4) | 6 mg/kg[c] (N=4) | 8 mg/kg[d] (N=3) | 10 mg/kg[e] (N=7) | 13 mg/kg (N=5) | 16 mg/kg[f] (N=4) |
| $C_{max}$ (µg/mL) | 75.3 (33) | 142 (49) | 273.208,543.019[g] 287.678,350.755[h] | 557 (21) | 608 (17) | 859 (27) | 934 (63) |
| $t_{max}$ (h)[i] | 1.80 (1.37-3.00) | 3.04 (1.68-5.00) | 1.50,3.28[g] 7.00,96.37[h] | 2.22 (2.08-3.00) | 2.05 (1.07-8.98) | 2.00 (1.00-2.25) | 2.01 (1.73-3.03) |
| $C_{min}$ (µg/mL) | 17.9 (35) | 34.4 (87) | 59.031,76.537[g] 73.582,188.093[h] | 174 (8) | 197 (29) | 289 (26) | 246 (60) |
| $C_{av,ss}$ (µg/mL) | 36.8 (26) | 63.9 (46) | 142.848,171.237[g] 242.683[h] | 268 (7) | 372 (19) | 457 (24) | 425 (51) |
| $AUC_{0-\tau,ss}$ (µg·h/mL) | 6190 (26) | 10700 (46) | 24000,28800[g]40800[h] | 44900 (7) | 62500 (19) | 76800 (24) | 71400 (51) |
| $t_{1/2}$ (h) | 78.3 | NC | NC | NC | 184 | NC | 252,291 |
| $CL_{ss}$ (mL/h/kg) | 0.323 (26) | 0.372 (46) | 0.209,0.250[g] 0.147[h] | 0.178 (7) | 0.160 (19) | 0.169 (24) | 0.224 (51) |
| $V_z$ (mL/kg) | 45.8 | NC | NC | NC | 40.8 | NC | 73.7,166 |
| $V_{ss}$ (mL/kg) | NC | NC | NC | NC | 36.6 | NC | 63.3 |
| PTF (%) | 156 (7) | 162 (33) | 138,283[g] 41[h] | 143 (27) | 107 (16) | 125 (16) | 162 (35) |
| LI | 1.46 (27) | 1.27 (36) | NC | NC | NC | NC | NC |
| $R_A$, $C_{max}$ | 1.70 (33) | 1.78 (41) | 1.27,2.90[g] 1.63[h] | 1.84 (26) | 1.60 (45) | 2.09 (38) | 1.57 (35) |
| $R_A$, AUC | 1.78 (29) | 1.79 (35) | 1.86[g] 2.94[h] | 1.88 (19) | 2.62 (30)[j] | 3.07 (49)[k] | 1.66 (35) |

Dosing interval tau (τ) is 168 hour; PTF: Percent peak-trough-fluctuation; LI: linearity index; $R_A$: accumulation ratio. $R_A$ Cmax: accumulation ratio based on Cmax, $Cmax_{multiple\ dose}/Cmax_{single\ dose}$. $R_A$ AUC: accumulation ratio based on AUC, $AUC_{(0-\tau,ss),multiple\ dose}/AUC_{(0-169),single\ dose}$.
[a] The value(s) are given when N=1 or 2.
[b] One patient had delayed infusion for 3 days.
[c] PK parameters were calculated for the 4th dose in two patients and for the 5th dose in two patients at 6 mg/kg.
[d] One patient had delayed infusion for 7 days and was excluded from mean summary.
[e] One patient had infusion ahead of schedule for 2 days.
[f] One patient had reduced dose from 16mg/kg to 13mg/kg and the infusion was delayed for 1 week. This patient was excluded from mean summary.
[g] PK parameters for the 4th dose
[h] PK parameters for the 5th dose
[i] Median (range:minimum-maximum)
[j] N=5
[k] N=4

There was no clear deviation from dose proportionality in pharmacokinetics of ramucirumab from 6 mg/kg to 20 mg/kg. An accumulation ratio of 1.5 was observed for ramucirumab when dosed every 2 weeks. Based on simulations using the PopPK model, steady state would be attained by the sixth dose (see SmPC, section 5.2).

### Special populations

In the pivotal studies there has been no indication that patients 65 years of age or older are at increased risk of adverse events compared to patients younger than 65 years old. No dose reductions are recommended (see SmPC, section 4.2). Based on PopPK, there was no difference in ramucirumab exposure in patients $\geq$ 65 years of age compared to patients < 65 years old (see SmPC, section 5.2).

No formal studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of ramucirumab. Based on PopPK, ramucirumab exposure was similar in patients with mild renal impairment (calculated creatinine clearance [CrCl] $\geq$ 60 to < 90 ml/min) and moderate renal impairment (CrCl $\geq$ 30 to <60 ml/min) as to patients with normal renal function (CrCl $\geq$ 90 ml/min). No data are available from patients with severe renal impairment (CrCl < 30 ml/min) (see SmPC, section 5.2). Clinical data suggest that no dose adjustments are required in patients with mild or moderate renal impairment (see SmPC, section 4.2).

No formal studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of ramucirumab. Based on PopPK, ramucirumab exposure in patients with mild hepatic impairment (total bilirubin 1.0-1.5 upper limit of normal (ULN) or AST > ULN as defined using NCI criteria) were similar to those in patients with normal hepatic function (total bilirubin and AST $\leq$ ULN). Ramucirumab has not been studied in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 to $\leq$ 3.0 ULN and any AST; and total bilirubin > 3.0 ULN and any AST, respectively) (see SmPC section 5.2). No dose reductions are recommended (see SmPC, section 4.2). Prior to each paclitaxel infusion, patients should have a complete blood count and blood chemistry performed to evaluate hepatic function (see SmPC, section 4.2).

Based on PopPK, the following covariates were found to have no impact on ramucirumab disposition: age (range, 19 to 86 years), sex (316 males, 181 females), race (337 White and 139 Asians), body weight (range, 31.9 to 133.0 kg), albumin levels (range, 15.5 to 64.8 g/L) (see SmPC, section 5.2).

### Pharmacokinetic interaction studies

Two studies were conducted to assess the effect of concomitant ramucirumab on the PK of paclitaxel (JVCA) and docetaxel (JVCC), respectively.

In Study JVCA, concomitant administration of ramucirumab had no effect on paclitaxel exposure with ratios of geometric least squares (LS) means at 1.09 (90% confidence interval [CI]: 0.93, 1.29) for $AUC_{(0-\infty)}$ and 0.97 (90% CI: 0.83, 1.13) for $C_{max}$. In addition, similar ramucirumab PK parameters were observed with or without paclitaxel administration (ratio with paclitaxel vs. alone were 1.00 (90% CI: 0.84, 1.19) for $AUC_{(0-\infty)}$ and 1.07 (90% CI: 0.93, 1.24) for $C_{max}$, respectively.

In Study JVCC, dose-normalized $AUC_{(0-\infty)}$ and $C_{max}$ of docetaxel were similar whether docetaxel was administered with or without ramucirumab. The reported ratios of geometric LS means and 90% CI were 0.97 (90% CI: 0.84, 1.10) for $AUC_{(0-\infty)}$ and 1.14 (90% CI: 0.84, 1.55) for $C_{max}$.

### Pharmacokinetics using human biomaterials

## 2.4.3. Pharmacodynamics

### Mechanism of action

No clinical studies addressing the mechanism of action were submitted (see discussion on clinical pharamacology).

### Primary and Secondary pharmacology

Biomarkers were not systematically investigated in the phase 1 and phase 2 studies. VEGF overexpression has been correlated with poor prognosis of gastric adenocarcinoma, and VEGFR-2 inhibition by ramucirumab is part of the rationale to investigate ramucirumab in advanced gastric cancer. However, patients were not stratified for VEGF or VEGFR-2 baseline expression in the REGARD or RAINBOW studies.

In REGARD, biomarkers were evaluated in part of the study population. VEGF-A was not determined. Immunohistochemical assay for VEGFR2 protein expression in tumour tissue showed very little VEGFR2 staining in the tumour nuclei 14/144 (9.7%), cytoplasm 33/148 (22.9%), or membrane 11/144 (7.6%). The number of positive samples is too small for correlative analyses. Further, expression of soluble VEGFR was not determined while ramucirumab is likely first to bind to soluble VEGFR-2. Positive VEGFR-2 staining of neoplastic vessels was observed in 86.7% of the patients. No correlation with PK of ramucirumab and VEGFR-2 staining in neoplastic vessels was observed. In contrast, patients with high VEGFR-2 staining compared to low VEGFR-2 staining seemed to have a better OS/PFS effect of ramucirumab compared to placebo although this seemed mainly due to shorter OS/PFS for the placebo arm in patients with high VEGFR-2 staining.

In the RAINBOW study, no tissue samples were collected, and therefore, the potential correlation between VEGFR-2 staining of the neoplastic vessels and clinical outcome as observed in REGARD could not be evaluated in RAINBOW. Plasma concentrations of VEGF-C, VEGF-D and sVEGFR-2 were analysed but VEGF-A could not be analysed reliably. Data from 56% of the ITT were available. Based on the available data, there were no significant interactions between clinical outcome (OS and PFS) and any of the baseline plasma biomarker measures: VEGF-C, VEGF-D, or sVEGFR-2. Additional results from developed assays are on-going and not yet available. Results of these exploratory assays are expected in late Q4 2014 or Q1 2015 and will be submitted by the applicant further to the CHMP's recommendation.

The potential for ramucirumab to prolong the corrected QT (QTc) interval was assessed in Study JVBK in patients with advanced cancer (of solid tumour origin). Sixty-eight patients were enrolled. Patients received ramucirumab 10 mg/kg, administered as an intravenous (IV) infusion over 60 minutes, once every 3 weeks for a minimum of 9 weeks. QTc values that corrected to heart rate effect were used as a dependent variable. The time-matched mean change from the baseline QTc interval was estimated at each ECG sampling time point for each patient. Sixty-five patients completed the study according protocol. Assay sensitivity was demonstrated by moxifloxacin 400 mg. For ramucirumab, the 90% two-sided (95% one-sided) upper confidence limit never exceeded 10 msec at any time following 10 mg/kg ramucirumab administration. An increase in QTcF of >30 msec and ≤ 60 msec was seen in 3 patients (5 time points) in Cycle 3 and an increase of >60 msec was observed in one patient but the QTcF value remained <450 msec. No correlation between ramucirumab concentration and QTc prolongation was observed.

Premedication with diphenhydramine was implemented in the REGARD study as result of the incidence of grade 3 and grade 4 IRRs in six patients and one patient, respectively, in studies JVBO and JVBQ.

Patients in REGARD and RAINBOW were tested at multiple time-points for anti-drug antibodies (ADAs). Samples were tested from 956 patients: 527 ramucirumab-treated patients and 429 control treated patients. Eleven (2.2%) of ramucirumab-treated patients and 2 (0.5%) of control-treated patients developed ADAs. None of the patients with ADAs experienced an IRR. In the REGARD and RAINBOW studies, no patients had neutralising antibodies to ramucirumab (see SmPC section 5.1).

In RAINBOW study, Exposure-response analyses indicated that efficacy and specific measures of safety of ramucirumab were correlated with ramucirumab exposure. Efficacy, as measured by improvements in OS and PFS, was associated with increasing ramucirumab exposure range produced by 8 mg/kg ramucirumab given on days 1 and 15 of a 28 day cycle (see SmPC section 5.2).

The incidences of Grade ≥ 3 hypertension, neutropenia, and leukopenia were also increased with higher ramucirumab exposure (see SmPC section 5.2).

Based on limited PK data, exposure-response analysis suggested in RECARG study, that efficacy of ramucirumab was correlated with ramucirumab exposure (see SmPC section 5.2).

## 2.4.4. Discussion on clinical pharmacology

Pharmacokinetic characteristics of ramucirumab were typical IgG antibody pharmacokinetics i.e. low distribution volume, slow clearance and long elimination half-life. No dose modifications are considered necessary for gender, age, race, weight, mild and moderate renal impairment.

Bodyweight was no covariate in the final popPK model and as such dosing based on bodyweight is disputable. There was a trend for concentrations to increase in the higher body weight patients using the current weight-based dosing regimen: the median-predicted ramucirumab exposure at steady state in the highest body weight quartile group was 41.6% greater than that of the lowest body weight quartile group. Post-hoc exposure covariate analysis showed a relation between clearance body weight and between volume of distribution and body weight, supporting a body-weight based dose regimen. As the correlation was less than proportional, which is common for antibodies this results in a somewhat lower exposure in patients with low bodyweight compared to patient with a high bodyweight. There was a considerable overlap in the distributions of the concentrations when comparing the different weight quartiles. Bodyweight was considered no covariate in the popPK model as inclusion of bodyweight did not reduce the inter-patient variability with >5% as was predefined in the protocol. Body weight had no effect on clinical outcomes but exposure was the primary factor predictive of clinical outcome (see discussion on dose-response study).

Data on renal function did not indicate significant differences in $C_{trough}$ in patients with normal renal function or mild to moderate renal impairment. There are no data in patients with severe renal impairment. The rather constant Vss observed represent rather homogenous study population and might wrongly represent overhydrated patients in a clinical setting. Simulation results indicated that over hydration with 25% to 50% Vss increase may reduce maximum concentration ($C_{max}$) by 10% to 20%, but is unlikely to impact area under the curve and minimum concentration ($C_{min}$). Therefore, the possibility of significant exposure reduction due to overhydration is low.

VEGF overexpression has been correlated with poor prognosis of gastric adenocarcinoma and a potential imbalance of the two arms for VEGF overexpression may affect the outcome of the pivotal REGARD study.

The non-clinical studies showed that binding of ramucirumab to VEGF Receptor 2 prevents interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits activation of VEGF Receptor 2 and its downstream intracellular signalling components, including p44/p42 mitogen-activated protein kinases, neutralizing ligand-induced proliferation and migration of human endothelial cells and leads to increased levels of ligands. The impact on VEGFR-2 signalling pathway seems relevant to primary pharmacology of ramucirumab.

In REGARD, positive VEGFR-2 staining of neoplastic vessels was observed in 86.7% of the patients. Patients with high VEGFR-2 staining compared to low VEGFR-2 staining seemed to have a better OS/PFS effect of ramucirumab compared to placebo although this seemed mainly due to shorter OS/PFS for the placebo arm in patients with high VEGFR-2 staining suggesting that VEGFR-2 could be a prognostic factor. Unfortunately no tumour tissue was collected in the RAINBOW study, thus the potential correlation between VEGFR-2 staining of the neoplastic vessels and clinical outcome as observed in REGARD could not be evaluated in RAINBOW. In RAINBOW, plasma concentrations of VEGF-C, VEGF-D and sVEGFR-2 but not VEGF-A were analysed in 56% of ITT. Based on the available data, there were no significant interactions between clinical outcome (OS and PFS) and any of the baseline plasma biomarker measures: VEGF-C, VEGF-D, or sVEGFR-2.

The number of HER-2 positive samples (12 out of 147) in REGARD was too low to conclude on a beneficial effect of ramucirumab in patients with HER2 positive tumours. The absence of tumour tissue in the RAINBOW study limits the potential identification of specific biomarkers involved in efficacy of

ramucirumab.Immunogenicity of ramucirumab was rather low. It was not certain that the screening and confirmation assay will detect all ADAs as during the development of the assay no attention has been paid to the potential presence of NGNA and α-Gal in the reagents. In particular the α-Gal site in ramucirumab may be of concern as specific IgE to galactose-α-1,3-galactose (α-gal) was shown to be linked with hypersensitivity reactions to cetuximab (Chung et al. 2008, Jacquenet et al 2009). The applicant discussed that mAbs that are only glycosylated in their Fc domains such as ramucirumab and produced in rodent cell lines do not bind α-Gal–specific IgE antibodies (Lammerts van Beuren et al. 2011 and Qian et al. 2007). This is considered reasonable. Further, presence of IgE anti-α-Gal antibodies was evaluated by a separate assay. There was a lack of any relationship between the presence of IgE anti-α-Gal antibodies and IRRs in sera from patients in REGARD and RAINBOW. The overall rate of IRRs, acute allergic or anaphylactic reactions was low in REGARD and RAINBOW.

Ramucirumab exposure in patients with mild hepatic impairment (total bilirubin 1.0-1.5 upper limit of normal (ULN)) or AST >ULN as defined using NCI criteria) were similar to those in patients with normal hepatic function (total bilirubin and AST < ULN). However, liver events were higher in phase II JVBQ study among hepatocellular carcinoma patients. This safety concern has been adequately addressed in section 4.4 of the SmPC. Patients with Child-Pugh Class A and Class B have been enrolled in the on-going Phase 3 study of RAM treatment in patients with hepatocellular carcinoma (JVBF). The CHMP recommended the MAH to submit the results upon completion of the study.

Ramucirumab has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 to ≤ 3.0 ULN and any AST; and total bilirubin >3.0 ULN and any AST, respectively). This has been addressed in the SmPC.

The risks for pharmacokinetic interaction of ramucirumab as a monoclonal antibody are considered low. Interaction studies of ramucirumab with paclitaxel and docetaxel indicated that ramucirumab does not affect the pharmacokinetics of paclitaxel or docetaxel and vice versa.

In RAINBOW study, exposure-response analyses indicated that efficacy and specific measures of safety of ramucirumab were correlated with ramucirumab exposure. Efficacy, as measured by improvements in OS and PFS, was associated with increasing ramucirumab exposure range produced by 8 mg/kg ramucirumab given on days 1 and 15 of a 28 day cycle. The incidences of Grade ≥ 3 hypertension, neutropenia, and leukopenia were also increased with higher ramucirumab exposure) (see SmPC section 5.2).

Based on limited PK data in REGARD study, exposure-response analysis suggested that efficacy of ramucirumab was correlated with ramucirumab exposure (see SmPC section 5.2).

## 2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of ramucirumab has been investigated sufficiently.

## 2.5. Clinical efficacy

## 2.5.1. Dose response study

A target concentration of 18 µg/mL was aimed for in gastric cancer patients based on tumour growth inhibition of human xenografts in nude mice by rat anti-VEGFR-2 antibody DC-101.

Weekly doses of ramucirumab ranging from 2 to 16 mg/kg were evaluated in Phase 1 Study JVBM. A maximum tolerated dose for weekly dosing was identified as 13 mg/kg (2 dose-limiting toxicities were

observed in patients receiving the 16-mg/kg weekly dose, Grade 3 deep vein thrombosis and Grade 3 hypertension).

Preliminary efficacy was observed across a range of doses, including the 2-mg/kg dose. Pharmacokinetic results from Study JVBM suggested that ramucirumab exhibited nonlinear PK characteristics. Apparent nonlinear PK profiles were observed between 2 and 8 mg/kg; PK profiles appeared to be linear at doses of 8 mg/kg and above, suggesting saturation of the target-mediated (VEGF Receptor 2) clearance pathway. Every-2-week (6 to 10 mg/kg) and every-3-week (15 to 20 mg/kg) dose regimens were evaluated in an additional dose-ranging study (Study JVBN). No MTD was identified for every-2-week or every-3-week dosing; all dose regimens were well tolerated.

Two dose regimens, 8 mg/kg every 2 weeks and 10 mg/kg every 3 weeks, were selected for subsequent Phase 2 and Phase 3 studies. These doses and schedules were selected because they were associated with PK profiles suggesting target receptor saturation; Ctrough concentrations were higher than 18 µg/mL a concentration shown to be efficacious in mice, and activity was observed at and below these doses and with these schedules in Phase 1 studies.

Exposure-response (E-R) analyses were performed to characterize the relationship between ramucirumab exposure and selected measures of efficacy and safety in REGARD and RAINBOW. Two of the E-R analyses pertained to efficacy endpoints: overall survival (OS) and progression-free survival (PFS). In REGARD study, clear separations between the OS curves were observed among the 2 exposure groups, suggesting that higher exposure is associated with longer survival (median OS 11.0 vs. 5.8 months). The Kaplan–Meier plots of PFS curves showed comparable relationship for PFS and ramucirumab exposure (data not shown). In RAINBOW study, ramucirumab exposure was divided in quartiles. Separations between the OS curves were observed among 4 exposure groups, indicating that the higher the exposure within the exposure range of 8 mg/kg, the longer is the associated survival.

The E-R analysis for safety evaluated the most frequent severe (that is, Grade $\geq$ 3) treatment-emergent adverse events (TEAEs) occurring in at least 10% of patients and at higher incidence in the ramucirumab plus paclitaxel arm were neutropenia, leukopenia, and hypertension. In RAINBOW, the incidences of Grade $\geq$ 3 hypertension, neutropenia, and leukopenia were also increased with higher ramucirumab exposure. For both arms, patients with a previous history of hypertension had an increased incidence of Grade $\geq$ 3 hypertension, older patients had increased incidence of Grade $\geq$ 3 neutropenia, and Asian patients had increased incidence of both Grade $\geq$ 3 neutropenia and Grade $\geq$ 3 leukopenia.

## Main studies

### Study I4T-IE-JVBD (REGARD)

#### *Methods*

Study REGARD (I4T-IE-JVBD) was a pivotal, global, multicentre, randomized, double-blind phase 3 study comparing the safety and efficacy of single-agent ramucirumab plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on first-line platinum- or fluoropyrimidine-containing combination therapy.

#### *Study participants*

The REGARD study population included patients with histologically or cytologically confirmed metastatic or locally recurrent, unresectable gastric or gastro-esophageal junction (GEJ) adenocarcinoma not amenable to curative resection. Patients were required to have experienced disease progression during or within 4 months after the last dose of first-line therapy for metastatic disease, or during or within 6 months after the last dose of adjuvant therapy. Acceptable first-line regimens for this study were combination chemotherapy regimens that included platinum and/or fluoropyrimidine components. All patients had received prior anticancer therapy, 81% of which received at least a combination of platinum

and fluoropyrimidine as first line treatment. Other inclusion criteria included an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-1, adequate hepatic function (total bilirubin $\leq$ 1.5 mg/dL, AST and ALT $\leq$ 3.0 x the upper limit of normal (ULN), adequate renal function (creatinine $\leq$ 1.5 x the ULN or creatinine clearance (measured or calculated) $\geq$ 40 mL/minute), adequate coagulation function as defined by INR $\leq$ 1.5 and a PTT$\leq$ 5 above the ULN unless receiving anticoagulation therapy).

Patients were excluded if they had documented and/or symptomatic brain or leptomeningeal metastases, an on-going or active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, uncontrolled thrombotic or haemorrhagic disorder, uncontrolled or poorly-controlled hypertension despite standard medical management, or any other serious uncontrolled medical disorders in the opinion of the investigator, any Grade 3-4 gastrointestinal bleeding within 3 months prior to randomization, arterial thromboembolic events, serious or non-healing wound, ulcer, or bone fracture within 28 days prior to randomization, prior therapy with an agent that directly inhibits VEGF or VEGF receptor 2 activity (including bevacizumab), or any anti-angiogenic agent and current chronic antiplatelet therapy.

**Treatments**

Patients were randomized (2:1) to receive either ramucirumab (administered i.v.) every 2 weeks at a dose of 8 mg/kg) or placebo plus BSC. BSC could not include additional concurrent anticancer treatment (for example, chemotherapy, hormonal therapy, radiation therapy, biologic response modifiers, or other investigational agents). BSC could include antiemetic agents, opiate and non-opiate analgesic agents, appetite stimulants, and other supportive care agents.

Ramucirumab or placebo was administered every 2 weeks until disease progression, the development of unacceptable toxicity, noncompliance, or withdrawal of consent by the patient. Up to 2 reductions to the dose of ramucirumab (to 6 mg/kg and subsequently to 5 mg/kg) were permitted in case of non-life-threatening, reversible grade 3 or 4 AEs that improved to grade 0 or 1 or resolved to grade 0 within 1 cycle.

Patients underwent radiographic assessments of disease status approximately every 6 weeks following start of treatment.

**Objectives**

The primary objective of the study was to show superiority of ramucirumab plus BSC versus placebo plus BSC in terms of overall survival (OS). Secondary objectives included the evaluation of Progression Free Survival (PFS), including 12-week PFS rate, Objective Response Rate (ORR), Duration of Response (DoR), Quality of life (QoL), safety, pharmacodynamic profile of ramucirumab and immunogenicity of ramucirumab.

**Outcomes/endpoints**

The primary study endpoint was overall survival (OS), defined as the interval between date of randomization and the date of death from any cause. Patients who were alive at the time of data cut off or who were lost to follow-up had data censored at the time they were last known to be alive.

Secondary endpoints included Progression-Free Survival (PFS) (defined as the time from the date of randomization until the date of objectively determined PD or death due to any cause, whichever was first) -Objective response rate (ORR) (defined as the proportion of patients achieving a best overall response of partial (PR) or complete response (CR) and Quality of life as measured by European Organisation for

Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30), a self-administered, cancer-specific questionnaire with multidimensional scales, was completed at baseline (within 14 days prior to randomization) and prior to the infusion of Cycles 4, 7, and 10 (that is, after approximately 6, 12, and 18 weeks on study). QoL was not evaluated at the time of discontinuation.

## Sample size

The sample size of this study was estimated to be 348 patients with 268 events based on the following assumptions: overall one-sided type I error rate to be 0.025 (or two-sided at 0.05) and study power 80%; median OS of 5 months in the placebo + BSC control arm; an increase of at least 45% (2.25-month) improvement in median OS in the ramucirumab arm (i.e., 7.25 months, or HR = 0.69); randomization ratio 2:1 (ramucirumab: placebo); one interim futility analysis at 35% of total number of OS events; a 30-month accrual period and a drop-out rate of 10%.

## Randomisation

Patients were randomised to receive ramucirumab or placebo with a ratio of 2:1. Randomization was stratified by:

- Weight loss (≥ 10% over the prior 3 months vs. <10%)

- Geographic region (North America, Europe, Australia, and New Zealand vs. South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia vs. Asia)

- Location of the primary tumour (gastric [including tumours of the gastric cardia that extend into the GEJ] vs. GEJ [including tumours of the distal oesophagus that extend into the GEJ, and tumours involving the GEJ when precise identification of the organ of origin was not possible]).

## Blinding (masking)

This was a double-blinded study.

## Statistical methods

The primary population for the efficacy analysis was the ITT population which included all randomized patients. The Modified Intention-to-Treat (mITT) population was a subset of the ITT population including only randomized patients who received any dose of investigational product and was to be used for secondary analyses. The safety population included all patients who received any dose of an investigational product (ramucirumab or placebo). The Per-Protocol (PP) population consisted of the randomized and treated patients who did not have a major protocol violation. The PP population was to be used for supportive efficacy analyses.

The primary and secondary efficacy analyses were not adjusted for any covariates, except via stratification for the randomization factors.

An interim futility analysis was to be conducted when 35% of the expected number of OS events was observed.

*Results*

**Participant flow**
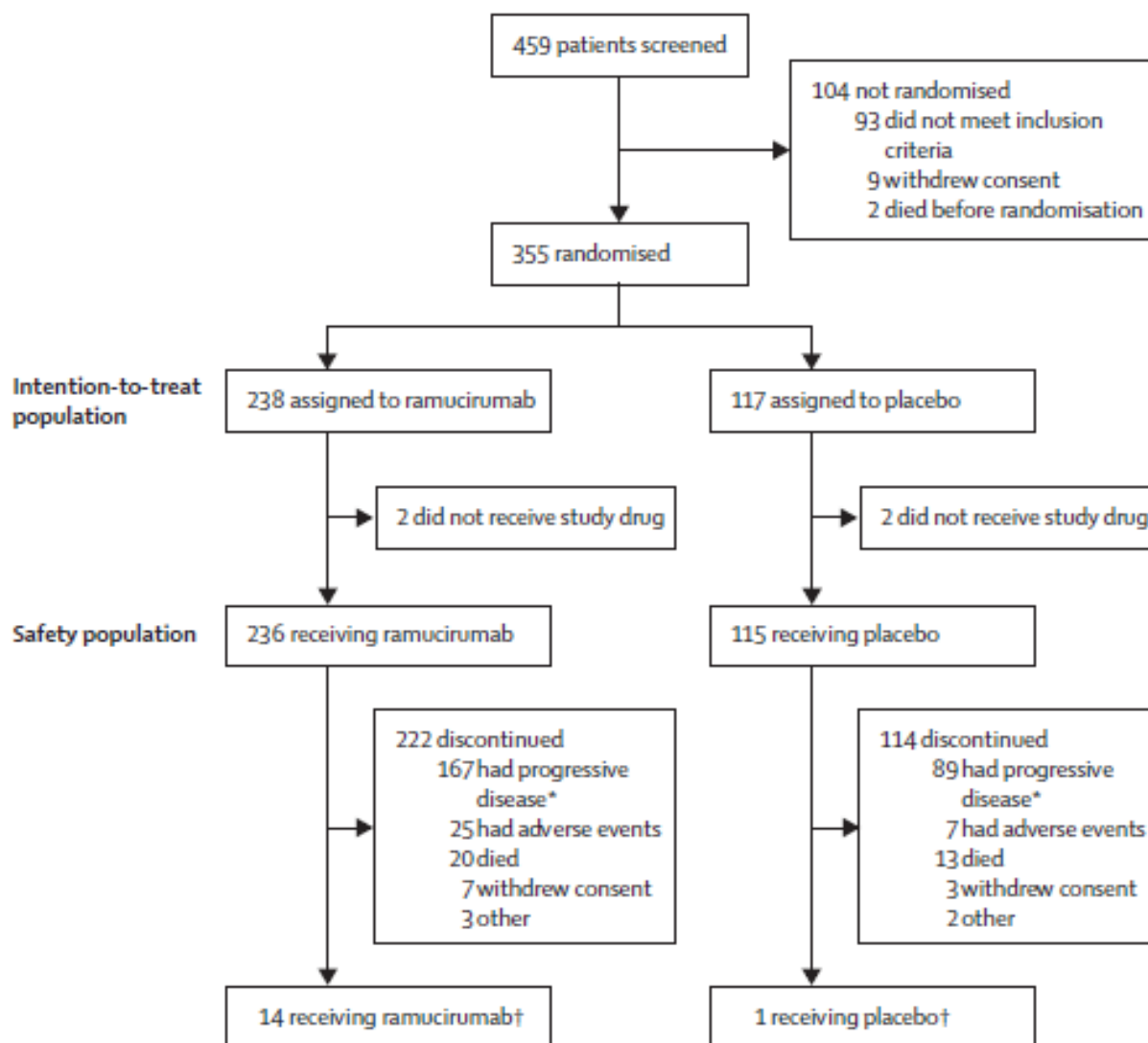


**Recruitment**

Patients were enrolled between 6 October 2009 and 26 January 2012. A total of 119 centres in 29 countries were involved.

**Conduct of the study**

The original protocol was issued on 05 March 2008. The protocol was amended 8 times. No patients were enrolled under protocol amendments 1 through 3 inclusive. The major changes for amendments 4-8 are described below:

Amendment 4 (dated 01 July 2009) essentially included bleeding (haemorrhagic) events to the list of possible adverse events of concern, and discussion of these events in the context of ramucirumab treatment was included. Guidelines regarding the grading and treatment of infusion-related reactions and hypertension were updated to be consistent with NCI-CTCAE Version 4.0. In addition, guidelines for the management of proteinuria were updated, allowing patients with proteinuria ≥2+ per dipstick or routine urinalysis to receive ramucirumab or placebo as scheduled prior to 24-hour urine collection.

Amendment 5 (dated 08 February 2010) essentially added new markers at baseline.

Amendment 6 (dated 20 April 2010) included only minor changes and clarifications.

Amendment 7 (dated 23 November 2010). The major changes were a decrease in planned sample size from 615 patients to 315 patients (at this date, only 36 patients had been randomized into the study) in order to modify the trial to an appropriate size and minimize the number of patients required and a reduction of follow-up time for OS from 1.5 to 1 year. Finally, gastrointestinal perforation was added, reflecting newly available analysis of safety information from Phase 2 studies.

Amendment 8 (dated 31 October 2011). The number of OS events required for the final analysis was increased by 12 events to correct a calculation in previous sample size estimation. This resulted in an increase of the planned sample size by 33 to 348 patients. Other substantive changes from Version 6.0 included survival follow-up following discontinuation of study therapy to every 2 months from every 3 months and a clear definition of the end of the trial, to allow for patients to receive study therapy in a defined extension phase occurring after the number of events required for final analysis of the primary end point was observed, and defined the assessments and procedures to be performed during this extension phase (prior to the end of trial).

**Baseline data**

Baseline demographic and disease characteristics are summarised in Tables 5, 6 and 7.

**Table 5 Patient Demographic Characteristics at Baseline (ITT Population) – REGARD Study**

| Variable | Ramucirumab N = 238 | Placebo N = 117 | Total N = 355 |
|---|---|---|---|
| **Sex  n (%)** | | | |
| Male | 169 (71.0) | 79 (67.5) | 248 (69.9) |
| Female | 69 (29.0) | 38 (32.5) | 107 (30.1) |
| **Age (years)** | | | |
| Median age | 60.0 | 60.0 | 60.0 |
| (range) | (30-86) | (24-87) | (24-87) |
| **Age group  n (%)** | | | |
| Age <65 years | 156 (65.5) | 71 (60.7) | 227 (63.9) |
| Age ≥65 years | 82 (34.5) | 46 (39.3) | 128 (36.1) |
| **Race  n (%)** | | | |
| White | 181 (76.1) | 91 (77.8) | 272 (76.6) |
| Asian | 39 (16.4) | 17 (14.5) | 56 (15.8) |
| Black | 4 (1.7) | 2 (1.7) | 6 (1.7) |
| Other | 14 (5.9) | 7 (6.0) | 21 (5.9) |
| **Ethnicity  n (%)** | | | |
| Hispanic or Latino | 41 (17.2) | 19 (16.2) | 60 (16.9) |
| Not Hispanic or Latino | 197 (82.8) | 98 (83.8) | 295 (83.1) |
| **ECOG PS  n (%)** | | | |
| 0 | 67 (28.2) | 31 (26.5) | 98 (27.6) |
| 1 | 171 (71.8) | 85 (72.6) | 256 (72.1) |
| 2 | 0 (0.0) | 1 (0.9)[a] | 1 (0.3)[a] |

**Table 6 Stratification Factors at Randomization**

| | Ramucirumab<br>N = 238<br>n (%) | Placebo<br>N = 117<br>n (%) | Total<br>N = 355<br>n (%) |
|---|---|---|---|
| **Weight Loss Over the Prior 3 Months** | | | |
| ≥10% | 41 (17.2) | 20 (17.1) | 61 (17.2) |
| <10% | 197 (82.8) | 97 (82.9) | 294 (82.8) |
| **Location of Primary Tumor** | | | |
| Gastric | 178 (74.8) | 87 (74.4) | 265 (74.6) |
| GEJ | 60 (25.2) | 30 (25.6) | 90 (25.4) |
| **Geographic Region** | | | |
| Region 1 (NA) - North America, Europe, Australia, New Zealand | 165 (69.3) | 80 (68.4) | 245 (69.0) |
| Region 2 (LA) - South and Central America, India, South Africa, Jordan, Egypt, Saudi Arabia, Lebanon | 55 (23.1) | 29 (24.8) | 84 (23.7) |
| Region 3 (AS) – Asia | 18 (7.6) | 8 (6.8) | 26 (7.3) |

**Table 7 Summary of Baseline Disease Characteristics – REGARD Study**

| | Variable | Ramucirumab<br>N = 238 | Placebo<br>N = 117 | Total<br>N = 355 |
|---|---|---|---|---|
| **Pre-Treatment Disease Characteristics** | | | | |
| Measurable disease n (%) | Yes | 218 (91.6) | 106 (90.6) | 324 (91.3) |
| | No | 20 (8.4) | 11 (9.4) | 31 (8.7) |
| Histology n (%) | Intestinal | 52 (21.8) | 35 (29.9) | 87 (24.5) |
| | Diffuse | 96 (40.3) | 44 (37.6) | 140 (39.4) |
| | Undetermined/Not available | 90 (37.8) | 38 (32.5) | 128 (36.1) |
| Primary tumor present n (%) | Yes | 174 (73.1) | 86 (73.5) | 260 (73.2) |
| | No | 64 (26.9) | 31 (26.5) | 95 (26.8) |
| Site of metastasis n (%) | Peritoneal | 64 (26.9) | 45 (38.5) | 109 (30.7) |
| | Liver | 104 (43.7) | 56 (47.9) | 160 (45.1) |
| Number of metastatic Sites | 0 | 4 (1.7) | 2 (1.7) | 6 (1.7) |
| | 1 | 72 (30.3) | 24 (20.5) | 96 (27.0) |
| | 2 | 87 (36.6) | 45 (38.5) | 132 (37.2) |
| | ≥ 3 | 75 ( 31.5) | 46 (39.3) | 121 (34.1) |
| Progression-free interval on prior therapy n (%) | < 6 months | 154 (64.7) | 83 (70.9) | 237 (66.8) |
| | ≥ 6 months | 81 (34.0) | 34 (29.1) | 115 (32.4) |
| | Missing | 3 (1.3) | 0 (0.0) | 3 (0.8) |
| **Previous Anticancer Treatment** | | | | |
| Prior chemotherapy n (%) | First-line therapy | 199 (83.6) | 103 (88.0) | 302 (85.1) |
| | Adjuvant therapy only (no first-line therapy) | 37 (15.5) | 14 (12.0) | 51 (14.4) |
| | Neoadjuvant therapy only[a] | 2 (0.8) | 0 (0.0) | 2 (0.6) |

**Numbers analysed**

All 355 randomised patients were included in the intent-to-treat (ITT) population, the primary efficacy population.

Of them, 339 patients were included in the PP population and 351 patients who received at least one dose of study drug were included in the safety population.

**Outcomes and estimation**

**Primary objective: Overall Survival (OS)**

The efficacy results in terms of the primary endpoint of Overall Survival (cut-off date 25 July 2012) are summarised in table 8 and figure 3.

**Table 8 Summary of overall survival (ITT population), REGARD study, cut-off 25 July 2012**

|  | Ramucirumab | Placebo |
|---|---|---|
| Patients randomised | 238 | 117 |
| Death | 179(75.2%) | 99 (84.6%) |
| Censored | 59 (24.8%) | 18 (15.4%) |
| Overall Survival (months) | | |
| Median (95% CI) | 5.2 (4.4, 5.7) | 3.8 (2.8, 4.7) |
| | | |
| Log-rank p-value (stratified) | 0.0473 | |
| Hazard ratio (95% CI) | 0.776 (0.603, 0.998) | |
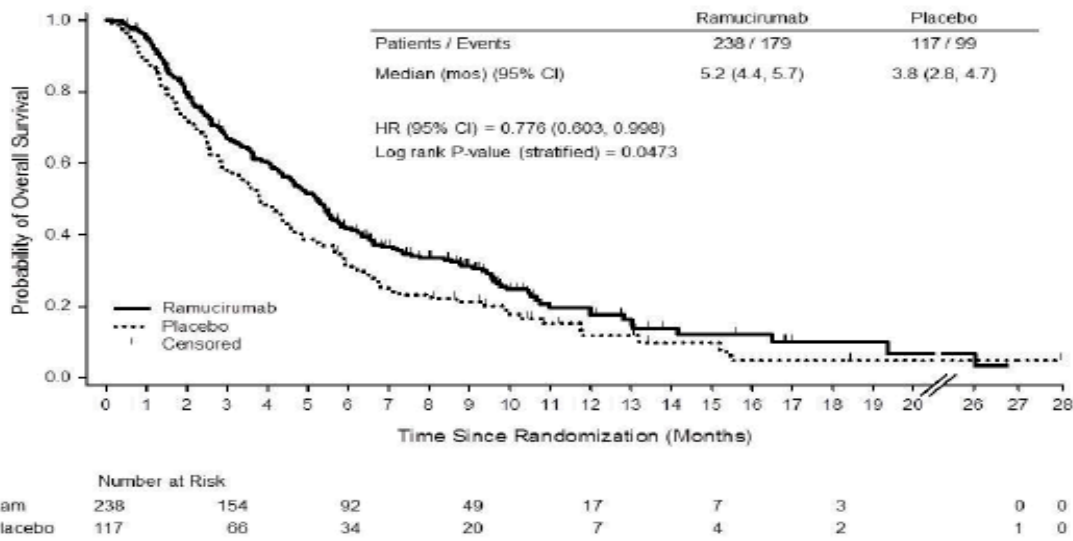
**Figure 1 Kaplan-Meier plot of overall survival (ITT population), REGARD study, cut-off 25 July 2012**

A summary of sensitivity analyses of OS is presented in table x.

**Table 9 Summary of sensitivity analyses-REGARD Study**

| Overall Survival | HR (95% CI) | p-Value |
|---|---|---|
| **Primary Analysis** | | |
| IVRS strata – 278 events | 0.776 (0.603, 0.998) | 0.0473 |
| **Pre-specified sensitivity analyses** | | |
| Unstratified analysis | 0.767 (0.600, 0.981) | 0.0347 |
| Using CRF Strata | 0.769 (0.597, 0.992) | 0.0419 |
| Adjust for prognostic factors using stepwise regression[a] | 0.774 (0.605, 0.991) | 0.0424 |
| Per-protocol analysis | | |
| Stratified | 0.755 (0.584, 0.977) | 0.0320 |
| Unstratified | 0.751 (0.584, 0.965) | 0.0252 |
| **Post-hoc sensitivity analyses** | | |
| Exactly 268 events | 0.771 (0.597, 0.996) | 0.0458 |
| Adjust for prognostic factors using stepwise regression (alternative model for selecting prognostic factors)[b] | 0.737 (0.573, 0.948) | 0.0175 |

[a] Stepwise Regression: treatment adjusted for the significant (p<0.05) prognostic covariates. Significant prognostic covariates selected from Cox regression model (without treatment group) fitted to all patients (n=355). Variables available for selection: weight loss (<10% vs. ≥10%), tumor location (GC vs. GEJ), geographic regions (Region 1 vs. Region 2 vs. Region 3) , age (<65, ≥65), gender, race (White, Asian, all others), ethnicity (Hispanic/Latino or not), ECOG PS (0 vs. ≥1), measurable vs. non-measurable disease, received prior therapy for metastatic disease (Yes vs. No), Histologic subtype (Diffuse vs. Intestinal vs. Undetermined/not available/missing), # metastatic sites (≤2 vs. ≥3), peritoneal metastasis, progression-free interval on prior therapy (<6 months vs. ≥6 months). Final model (N = 355): treatment adjusted for peritoneal metastasis, ECOG PS, and tumor location.

[b] Stepwise Regression (Alternative model). Same approach as in footnote a except that significant prognostic covariates selected from model fitted to placebo only patients (N = 117). Final model: treatment adjusted for ECOG PS, peritoneal metastasis, sex (M/F) and region.

## Key secondary endpoints

Results in terms of the key secondary endpoints of PFS and 12-weeks PFS rate (cut-off date 25 July 2012) are summarised in table 10 and figure 4.

**Table 10 Summary of PFS (ITT Population), REGARD study, cut-off 25 July**

| | Ramucirumab | Placebo |
|---|---|---|
| Patients randomised | 238 | 117 |
| Progressive disease or died | 199 (83.6%) | 108 (92.3%) |
| Censored | 39 (16.4%) | 9 (7.7%) |
| Progression free survival (months) | | |
| Median (95% CI) | 2.1 (1.5, 2.7) | 1.3(1.3, 1.4) |
| Log-rank p-value (stratified) | <0.0001 | |
| Hazard ratio (95% CI) | 0.483 (0.376, 0.610) | |
| PFS 12- week rate (%) | | |
| Median (95% CI) | 40.1 (33.6, 46.4) | 15.8 (9.7, 23.3) |
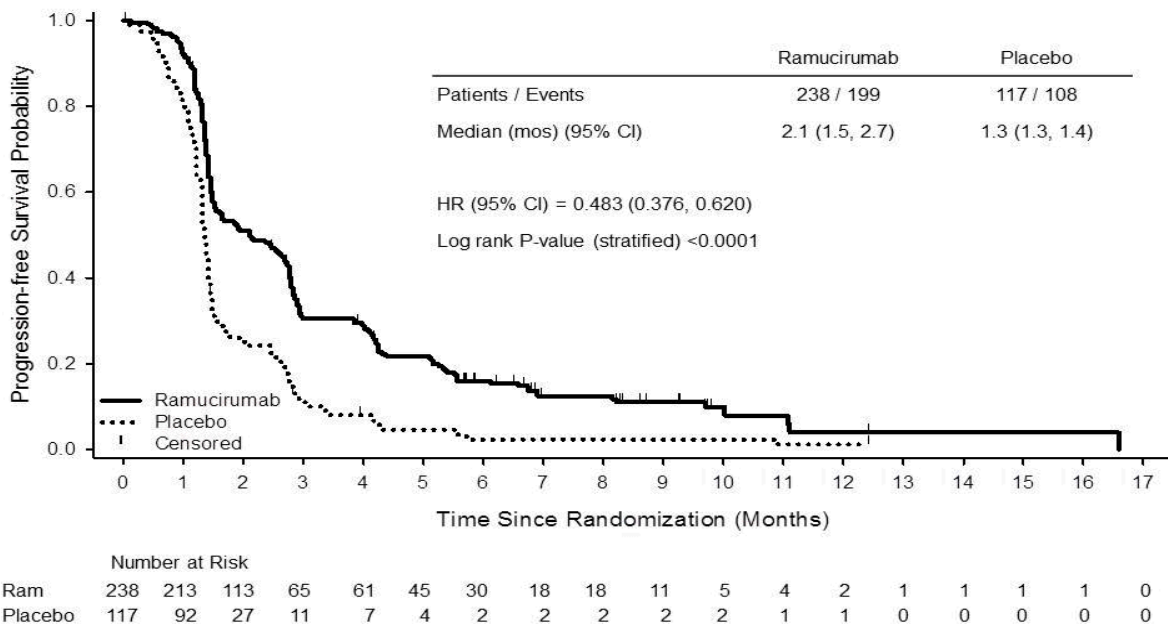


**Figure 2 Kaplan-Meier plot of PFS (ITT population), REGARD study, cut-off 25 July2012**

## Other secondary endpoints

Of the 238 patients assigned to ramucirumab, 1 patient experienced a complete response (CR), with 7 additional experiencing a PR. Of the 117 patients assigned to placebo, no patients experienced a CR and 3 experienced a PR. The ORR (CR + PR) for the ramucirumab arm was 3.4% compared with 2.6% in the placebo arm (p=0.7556).

A total of 234 (98.3%) patients in the ramucirumab arm and 113 (96.6%) patients in the placebo arm completed at least 1 QoL questionnaire. Compliance to complete a QoL questionnaire decreased sharply with each cycle of treatment, resulting in only 27.7% completing questionnaires at cycle 7 in the ramucirumab arm vs. 9.4% in the placebo arm. Across all QoL scales and items, mean change from baseline was similar between treatment arms. No significant difference regarding global health was observed between the two treatment arms in change from baseline at cycle 4 (p=0.4371) or cycle 7 (p=0.3744). Moreover, no significant difference was observed between the two arms in change from baseline for physical subscales: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite and diarrhoea.

ECOG PS was assessed at baseline, every 2 weeks during treatment, at the end of therapy and at the 30-day follow-up visit. Exploratory analyses of time to deterioration to ECOG PS ≥2 and time to deterioration in ECOG PS by ≥1 point and PS by ≥2 point indicated a delayed time to deterioration in performance status with ramucirumab (data not shown).

**Ancillary analyses**

Subgroup analyses for OS are shown in figure 5.
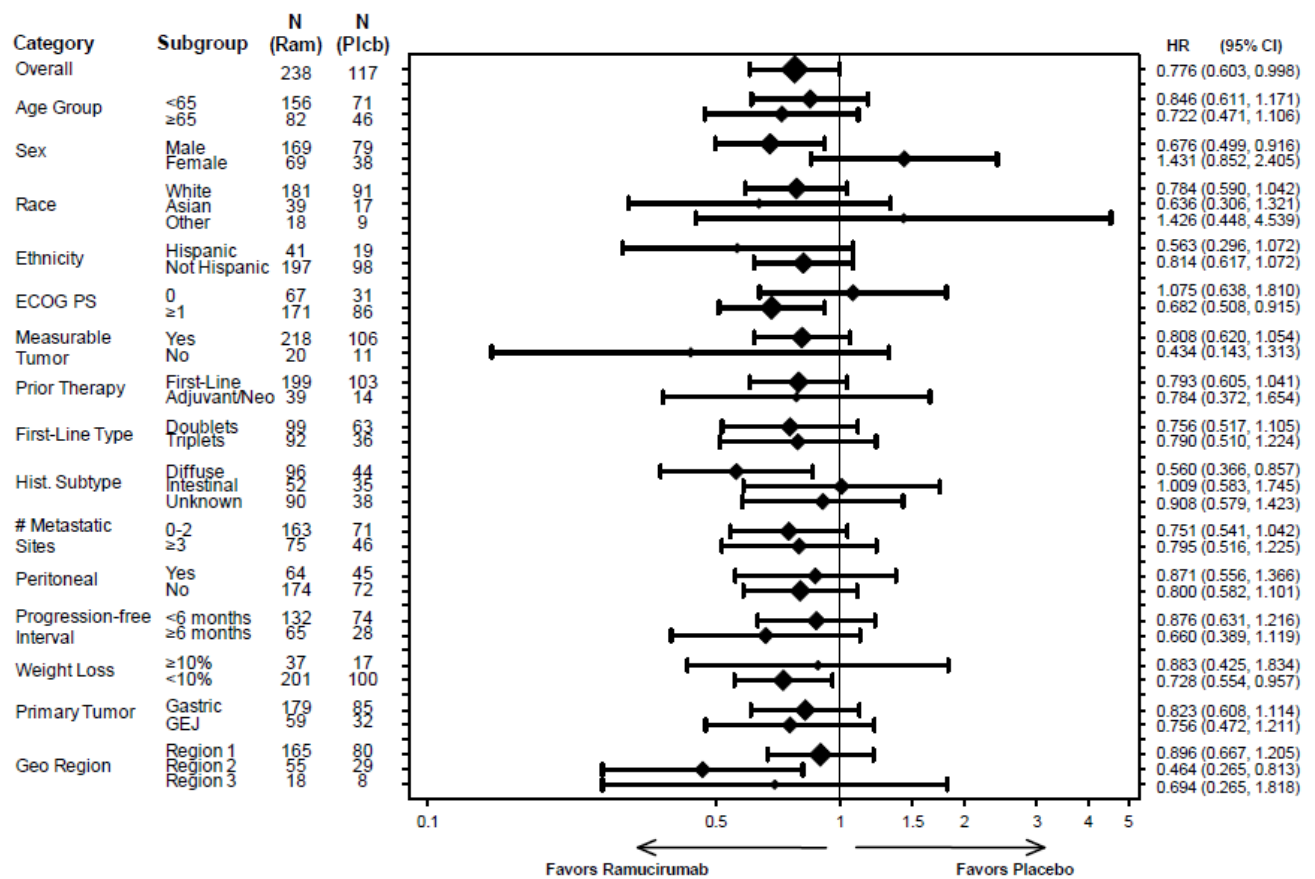


**Figure 3 Forrest plot for subgroup analysis of OS (stratified analysis-ITT population) REGARD study**

Part of the patients, received systemic anticancer treatment (mostly irinotecan or taxanes) after study treatment was discontinued (PDT). The systemic post discontinuation therapy by region and further subgroup analyses of OS by region are presented in tables 11, 12 and 13.

**Table 11 Systemic Post discontinuation Therapy by Region with Chemo Split by Taxane, Irinotecan and Other- REGARD Study**

| Type of Treatment | All Regions | | Region 1 | | Region 2 | | Region 3 | |
|---|---|---|---|---|---|---|---|---|
| | RAM N = 238 n (%) | Placebo N = 117 n (%) | RAM N = 165 n (%) | Placebo N = 80 n (%) | RAM N = 55 n (%) | Placebo N = 29 n (%) | RAM N = 18 n (%) | Placebo N = 8 n (%) |
| Any Systemic PDT | 72 (30.3) | 44 (37.6) | 53 (32.1) | 36 (45.0) | 14 (25.5) | 5 (17.2) | 5 (27.8) | 3 (37.5) |
| CHEMOTHERAPY | 69 (29.0) | 44 (37.6) | 50 (30.3) | 36 (45.0) | 14 (25.5) | 5 (17.2) | 5 (27.8) | 3 (37.5) |
| Irinotecan and/or Taxanes | 52 (21.8) | 35 (29.9) | 39 (23.6) | 29 (36.3) | 9 (16.4) | 3 (10.3) | 4 (22.2) | 3 (37.5) |
| Irinotecan | 36 (15.1) | 26 (22.2) | 28 (17.0) | 21 (26.3) | 5 (9.1) | 2 (6.9) | 3 (16.7) | 3 (37.5) |
| Taxanes | 23 (9.7) | 18 (15.4) | 15 (9.1) | 14 (17.5) | 5 (9.1) | 1 (3.4) | 3 (16.7) | 3 (37.5) |

Abbreviations: N = number of randomized patients; n = number of patients in category; PDT = postdiscontinuation therapy; RAM = ramucirumab.
Region 1 = North America, Europe, Australia, New Zealand; Region 2 = South and Central America, India, South Africa, Jordan, Egypt, Saudi Arabia, Lebanon; Region 3 = Asia.

**Table 12 Subgroup Analyses of OS by Region According to Whether Patients who Received Irinotecan or a Taxane as PDT are Censored or Not- REGARD Study**

| | Overall Survival | | | |
|---|---|---|---|---|
| | Median survival – months | | Not censoring patients who receive irinotecan or a taxane as PDT | Censoring patients at the time they started either irinotecan or a taxane as PDT |
| | Ramucirumab N = 238 | Placebo N = 117 | Hazard Ratio (95% CI) * | Hazard Ratio (95% CI) * |
| Overall | 5.2 | 3.8 | 0.776 (0.603, 0.998) | 0.666 (0.496, 0.894) |
| Region 1 | 5.2 | 4.5 | 0.896 (0.67, 1.21) | 0.758 (0.531, 1.082) |
| Region 2 | 5.1 | 2.6 | 0.464 (0.27, 0.81) | 0.441 (0.245, 0.794) |
| Region 3 | 6.5 | 4.8 | 0.694 (0.27, 1.82) | 0.788 (0.229, 2.713) |
| Interaction p-value | | | 0.0343 | 0.2910 |

Abbreviations: CI=confidence interval; N = number of randomized patients; PDT = postdiscontinuation therapy.
* Stratified by all 3 randomization factors for the overall analysis, and by the other 2 randomization factors for each of the 3 within-region analyses.
Region 1 = North America, Europe, Australia, New Zealand; Region 2 = South and Central America, India, South Africa, Jordan, Egypt, Saudi Arabia, Lebanon; Region 3 = Asia.

**Table 13 Impact of PDT Distribution on Overall Survival using Weighted Analyses by Regions –REGARD Study**

| Analysis | PDT Distribution by Region (Ram vs. Placebo) | mOS (Ram vs. Placebo) | Regional HR (95% CI) | Overall Study HR (95% CI) | Log-Rank p-Value |
|---|---|---|---|---|---|
| Primary analysis | R1: 32.1% vs. 45.0%, R2: 25.5% vs. 17.2%, R3: 27.8% vs. 37.5% | 5.2 vs. 3.8 | 0.896 (0.666, 1.205) 0.466 (0.266, 0.817) 0.694 (0.265, 1.818) | 0.776 (0.603, 0.998) | 0.0473 |
| Adjust PDT use within each region to regional average for both arms | R1: 36.3% vs. 36.3%, R2: 22.6% vs. 22.6%, R3: 30.8% vs. 30.8% | 5.3 vs. 3.7 | 0.771 (0.575, 1.035) 0.540 (0.309, 0.944) 0.666 (0.253, 1.753) | 0.712 (0.554, 0.915) | 0.0074 |

Additional subgroup analyses were submitted by the applicant showing results by baseline ECOG Performance Status (Table 13) and distribution of PDT use split by Performance status (Table 14).

**Table 14 Additional subgroup analyses by Performance Status (PS)-REGARD Study**

| REGARD: PFS and OS by baseline PS status | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Progression-Free Survival (months) | | | Overall Survival (months) | | |
| Baseline PS | | N | Ram | Placebo | HR (95%) | Ram | Placebo | HR (95%) |
| | | | | | | | | |
| PS=O | Overall | 93 | 2.8 | 1.7 | 0.622 (0.386, 1.002) | 6.2 | 6.8 | 0.995 (0.611,1.622) |
| | Region 1 | 67 | 2.7 | 1.5 | 0.782 (0.436, 1.404) | 5.4 | 9.4 | 1.589 (0.883,2.858) |
| | Region 2 | 17 | 4.7 | 1.2 | 0.367 (0.100, 1.349) | 3.5 | 3.0 | 0.431 (0.122,1.518) |
| | | | | | | | | |
| PS=1 | Overall | 257 | 1.6 | 1.3 | 0.441 (0.333, 0.585) | 4.6 | 2.9 | 0.678 (0.509, 0.902) |
| | Region 1 | 178 | 1.6 | 1.3 | 0.412 (0.293, 0.581) | 4.7 | 3.7 | 0.765 (0.545, 1.074) |
| | Region 2 | 67 | 1.9 | 1.3 | 0.425 (0.243, 0.745) | 4.3 | 2.6 | 0.453 (0.247, 0.830) |

Furthermore, data was provided showing the distribution of PDT use split by Performance status (Table 15).

**Table 15 Distribution of PDT use by PS-REGARD study**

| | | | PTD Use | | |
|---|---|---|---|---|---|
| Baseline PS | | Number of patients | Ramucirumab | Placebo | Overall |
| PS=0 | Overall | 98 | 37% | 61% | 45% |
| | Region 1 | 67 | 40% | 70% | 49% |
| | Region 2 | 17 | 18% | 33% | 24% |
| | | | | | |
| PS=1 | Overall | 257 | 27% | 29% | 28% |
| | Region 1 | 178 | 29% | 37% | 31% |
| | Region 2 | 67 | 27% | 13% | 22% |

Subgroup analyses for PFS are shown in figure 6.



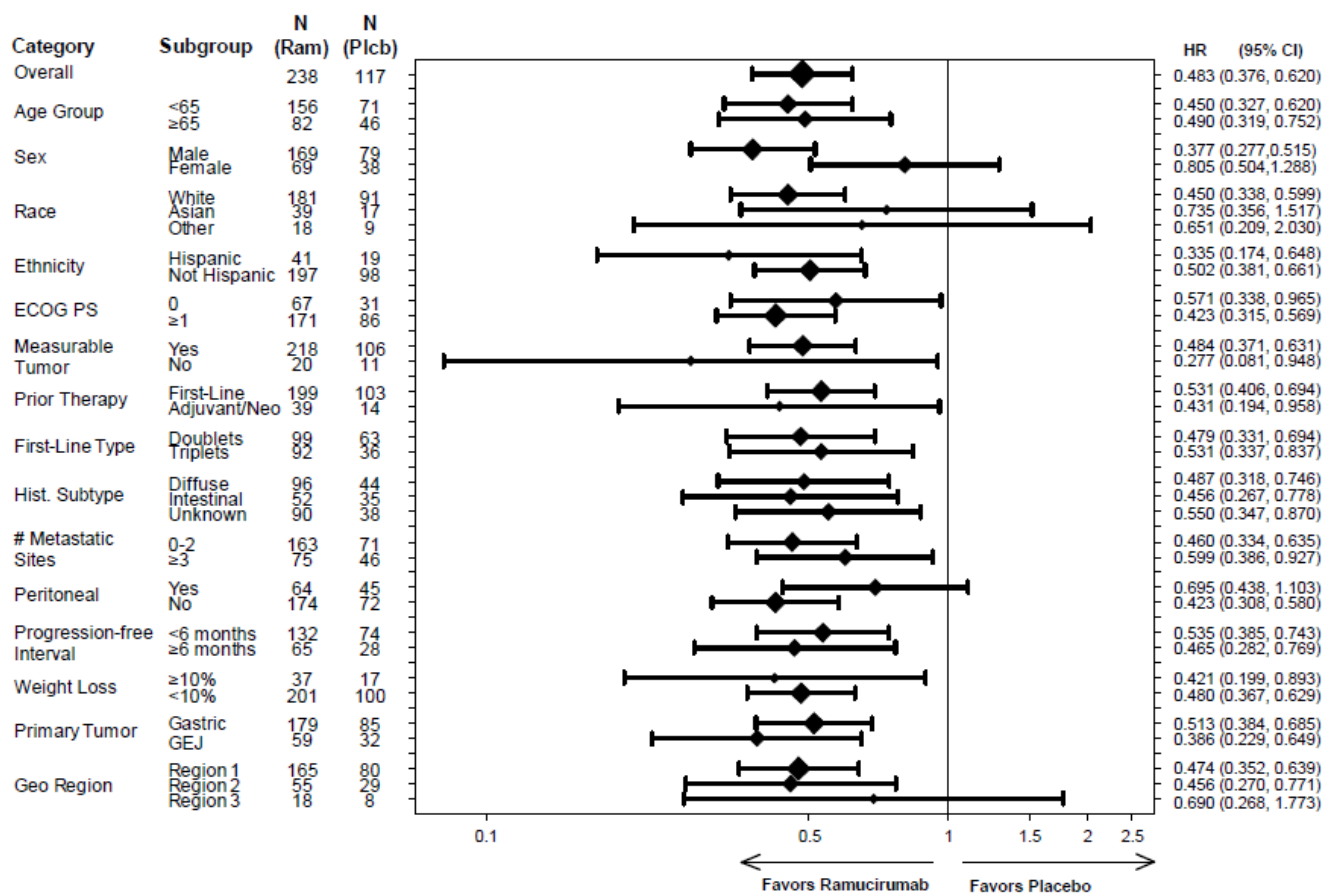| Category | Subgroup | N (Ram) | N (Plcb) | HR (95% CI) |
|---|---|---|---|---|
| Overall | | 238 | 117 | 0.483 (0.376, 0.620) |
| Age Group | <65 | 156 | 71 | 0.450 (0.327, 0.620) |
| | ≥65 | 82 | 46 | 0.490 (0.319, 0.752) |
| Sex | Male | 169 | 79 | 0.377 (0.277, 0.515) |
| | Female | 69 | 38 | 0.805 (0.504, 1.288) |
| Race | White | 181 | 91 | 0.450 (0.338, 0.599) |
| | Asian | 39 | 17 | 0.735 (0.356, 1.517) |
| | Other | 18 | 9 | 0.651 (0.209, 2.030) |
| Ethnicity | Hispanic | 41 | 19 | 0.335 (0.174, 0.648) |
| | Not Hispanic | 197 | 98 | 0.502 (0.381, 0.661) |
| ECOG PS | 0 | 67 | 31 | 0.571 (0.338, 0.965) |
| | ≥1 | 171 | 86 | 0.423 (0.315, 0.569) |
| Measurable Tumor | Yes | 218 | 106 | 0.484 (0.371, 0.631) |
| | No | 20 | 11 | 0.277 (0.081, 0.948) |
| Prior Therapy | First-Line | 199 | 103 | 0.531 (0.406, 0.694) |
| | Adjuvant/Neo | 39 | 14 | 0.431 (0.194, 0.958) |
| First-Line Type | Doublets | 99 | 63 | 0.479 (0.331, 0.694) |
| | Triplets | 92 | 36 | 0.531 (0.337, 0.837) |
| Hist. Subtype | Diffuse | 96 | 44 | 0.487 (0.318, 0.746) |
| | Intestinal | 52 | 35 | 0.456 (0.267, 0.778) |
| | Unknown | 90 | 38 | 0.550 (0.347, 0.870) |
| # Metastatic Sites | 0-2 | 163 | 71 | 0.460 (0.334, 0.635) |
| | ≥3 | 75 | 46 | 0.599 (0.386, 0.927) |
| Peritoneal | Yes | 64 | 45 | 0.695 (0.438, 1.103) |
| | No | 174 | 72 | 0.423 (0.308, 0.580) |
| Progression-free Interval | <6 months | 132 | 74 | 0.535 (0.385, 0.743) |
| | ≥6 months | 65 | 28 | 0.465 (0.282, 0.769) |
| Weight Loss | ≥10% | 37 | 17 | 0.421 (0.199, 0.893) |
| | <10% | 201 | 100 | 0.480 (0.367, 0.629) |
| Primary Tumor | Gastric | 179 | 85 | 0.513 (0.384, 0.685) |
| | GEJ | 59 | 32 | 0.386 (0.229, 0.649) |
| Geo Region | Region 1 | 165 | 80 | 0.474 (0.352, 0.639) |
| | Region 2 | 55 | 29 | 0.456 (0.270, 0.771) |
| | Region 3 | 18 | 8 | 0.690 (0.268, 1.773) |

Favors Ramucirumab ← | → Favors Placebo

**Figure 4 Forrest plot for subgroup analysis of PFS (stratified analysis) REGARD study**

**Study I4T-IE-JVBE (RAINBOW)**

*Methods*

Study RAINBOW (I4T-IE-JVBE) was a pivotal, global, multicentre, randomized, double-blind phase 3 study comparing the safety and efficacy of single-agent ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on first-line platinum- or fluoropyrimidine-containing combination therapy with or without anthracycline (epirubicin or doxorubicin).

*Study participants*

Main inclusion criteria included:

- Metastatic disease or locally advanced, unresectable disease.

- Disease progression during or within 4 months after the last dose of first-line therapy with any platinum or fluoropyrimidine doublet with or without anthracycline (epirubicin or doxorubicin).

- Age ≥ 18 years and an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-1 at study entry.

- Adequate organ function, defined as:

- Total bilirubin ≤ 1.5 mg/dL (25.65 $\mu$ mol/L), and aspartate transaminase and alanine transaminase ≤ 3.0 x the upper limit of normal (ULN) (or 5.0 x the ULN in the setting of liver metastases);

- Serum creatinine ≤ 1.5 x the ULN, or creatinine clearance (measured via 24-hour urine collection) ≥ 50 mL/minute;

- Urinary protein ≤ 1+ on dipstick or routine urinalysis (if urine dipstick or routine analysis was ≥ 2+, a 24-hour urine collection for protein was required to show <1000 mg of protein in 24 hours to allow participation in the study);

- Absolute neutrophil count ≥ $1.5 \times 10^9$/L, haemoglobin ≥ 9 g/dL (5.58 mmol/L), and platelets ≥ 100,000/$\mu$L; and

- International Normalized Ratio (INR) ≤ 1.5 and a partial thromboplastin time ≤ 5 seconds above the ULN (unless receiving anticoagulation therapy). Patients on full-dose anticoagulation were required to be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If receiving warfarin, the patient was required to have an INR ≤ 3.0 and no active bleeding or pathological condition present with a high risk of bleeding (for example, tumour involving major vessels or known varices).

Main exclusion criteria included:

- Squamous cell or undifferentiated gastric cancer.

- Any major surgery within 28 days prior to randomisation or central venous access device placement within 7 days prior to randomisation.

- Any chemotherapy other than platinum and fluoropyrimidine with or without anthracycline for advanced gastric or CEJ adenocarcinoma.

- History of deep vein thrombosis, pulmonary embolism, or any other thromboembolism during the 3 months prior to randomisation.

- Current anticoagulation therapy with warfarin, low molecular weight heparin or similar agents.

- History or evidence of known central nervous system metastases or carcinomatous meningitis.

- Any bleeding disorders or had a significant gastrointestinal bleeding within 3 months prior to randomization.

- Arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to randomization.

- On-going or active infection (HIV infection included), acquired immunodeficiency syndrome-related illness, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, uncontrolled thrombotic or haemorrhagic disorder, or any other serious uncontrolled medical disorders in the opinion of the investigator.

- Previous or concurrent malignancy except for basal or squamous cell skin cancer and /or in situ carcinoma of the cervix, or other solid tumours treated curatively and without the evidence of recurrence for at least 3 years prior to the study.

- Uncontrolled metabolic disorders or other non-malignant organ or systemic diseases or secondary effects of cancer.

- Bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection, Crohn's disease, ulcerative colitis, or chronic diarrhoea.

- Uncontrolled or poorly controlled hypertension despite standard medical management.

- Serious or non-healing wound, ulcer, or bone fracture within 28 days prior to randomization.

- Prior systemic therapy with an agent that directly inhibits VEGF or VEGF receptor activity. Other previous targeted therapies were permitted, if stopped at least 28 days prior to randomization.

- Current chronic therapy, with, non-steroidal anti-inflammatory agents (NSAIDs, such as indomethacin ibuprofen, naproxen, or similar agents), or other antiplatelet agents such as dipyridamole or clopidogrel, ticlopidine, anagrelide. Aspirin use (maximum dose 325 mg/day) was permitted.

- Patients who had a cumulative dose of >900mg/m$^2$ of epirubicin or >400mg/m$^2$ of doxorubicin.

- Pregnancy or breastfeeding.

- Concurrent active malignancy other than adequately-treated non-melanomatous skin cancer, other non-invasive carcinoma, or in situ neoplasm.

**Treatments**

Ramucirumab (8 mg/kg) was administered as an i.v. infusion on Days 1 and 15, in combination with paclitaxel (80mg/m2) administered on Days 1, 8, and 15 of a 28-day cycle. An equivalent volume of placebo was administered by i.v. on Days 1 and 15, in combination with paclitaxel (80mg/m2) administered on Days 1, 8, and 15 of a 28-day cycle.

**Objectives**

The primary objective of this study was to show efficacy in terms of prolonged survival time in patients treated with ramucirumab plus paclitaxel compared to patients treated with placebo plus paclitaxel as second-line treatment of advanced gastric or gastroesophageal (GEJ) adenocarcinoma after failure of any platinum and fluoropyrimidine doublet with or without anthracycline (epirubicin or doxorubicin). Secondary objectives included the evaluation of Progression Free Survival (PFS), time to progression (TTP), best overall response (BOR), objective response rate (ORR), the safety profile of ramucirumab in combination with paclitaxel, patient-reported outcome measures (European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 and EQ-5D, the pharmacodynamic profile of ramucirumab and to assess the immunonogenicity and pharmacokinetic (PK) parameters of ramucirumab.

**Outcomes/endpoints**

The primary study endpoint was overall survival (OS), defined as the interval between date of randomization and the date of death from any cause. Patients who were alive at the time of data cut off or who were lost to follow-up had data censored at the time they were last known to be alive.

Secondary endpoints included Progression-Free Survival (PFS) (defined as the time from the date of randomization until the date of objectively determined PD or death due to any cause, whichever was first)- Objective Response Rate (ORR) (defined as the proportion of patients achieving a best overall response of partial (PR) or complete response (CR)- Time to progression (TTP) [defined as the time from the date of randomization until the date of radiographic progression according to RECIST (Version 1.1)]- Best overall response (BOR) (defined as the best response across all time points from randomization until radiologically confirmed tumour progression)- Quality of life (QoL) as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30)-other secondary objectives aimed at evaluating the safety profile of ramucirumab in combination with paclitaxel, assessing the immunogenicity and pharmacokinetic parameters of ramucirumab.

**Sample size**

The sample size of this study was estimated to be 663 patients with 510 events based on the following assumptions:

- Accrual rate = 30 patients per month (including 5% drop-outs)

- 1:1 randomization

- Alpha = 0.025 (one-sided)

- Power = 90%

- HR = 0.75 [that is, median OS time of 7.0 months in the control group (placebo plus Paclitaxel) and 9.33 months in the test group (ramucirumab plus paclitaxel) assuming exponential distribution].

**Randomisation**

Patients were randomised to receive ramucirumab plus paclitaxel or placebo plus paclitaxel with a ratio of 1:1. Randomization was stratified by:

- Time to Progression (TTP) from the start of the first-line chemotherapy (<6 months vs. ≥6 months)

- Geographic region (North America, Europe (including Israel), Australia vs. South and Central America vs. Asia)

- Disease measurability (measurable versus non-measurable disease)

**Blinding**

This was a double-blinded study.

**Statistical methods**

The primary population for the efficacy analysis was the ITT population which included all randomized patients. The safety population included all patients who received any dose of an investigational product (ramucirumab, placebo or paclitaxel). The Per-Protocol (PP) population consisted of the randomized and treated patients who did not have a major protocol violation. The PP population was to be used for supportive efficacy analyses.

An interim futility analysis was to be conducted when 25% of the expected number of mortality events was observed.

## Results

### Participant flow



Abbreviations: ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category.
* Patients randomized but not treated for "other" reasons consisted of failure of inclusion/exclusion criteria (n=3) and 1 patient discontinued prior to administration of the first dose.
** Patient 137-0001 was randomized to the placebo plus paclitaxel arm; however, the patient received ramucirumab plus paclitaxel treatment. This patient is included in the placebo plus paclitaxel treatment arm for the ITT population, and is counted in the ramucirumab plus paclitaxel arm for the Safety population.
As of data cut-off date: 12 July 2013.

### Recruitment

Patients were enrolled between 23 December 2010 and 12 July 2013. A total of 170 centres in 27 countries were involved.

### Conduct of the study

The original protocol was issued on 01 June 2010. The protocol was amended 3 times, none of which included changes to the study design. No patients were enrolled under protocol amendments 1.1 through 3 inclusive. The major changes for amendments are described below:

Amendment 1.1 (dated 08 July 2010) contained administrative changes only.

Amendment 2 (dated 06 December 2010: The important changes included additional clarification of inclusion criteria regarding:  the age of patient (the patient had to be at least 18 years of age or of an acceptable age according to local regulations, whichever was older); the diagnosis of the disease (the patient had a histologically or cytologically confirmed diagnosis of gastric or GEJ adenocarcinoma); the disease progression [the patient had experienced documented objective radiographic or clinical disease progression that was confirmed by pathologic criteria (histology and/or cytology) if appropriate, during first-line therapy with any platinum/fluoropyrimidine doublet with or without anthracycline (epirubicin or

doxorubicin) for unresectable or metastatic disease]; and the reproductive status of female and male patients (female patients were surgically sterile, postmenopausal, or compliant with a highly effective contraceptive method (failure rate <1%) during and for 12 weeks after the treatment period; male patients were surgically sterile or compliant with a highly effective contraceptive regimen during and for 6 months after the treatment period. In addition, the frequency of radiographic assessments and the IDMC evaluations of safety data have been clarified.

Amendment 3 (dated 08 October 2012): The important changes included additional clarification of coagulation parameters in the inclusion/exclusion criteria; infusion times for study treatment; ramucirumab dose based on patient's body weight; complaint handling and dose modifications of investigational drug in response to Grade 3 and Grade 4 AEs.

**Baseline data**

Baseline demographic and disease characteristics are summarised in Table 16 and Table 17 respectively.

**Table 16 Patient demographic Characteristics at Baseline (ITT population)-RAINBOW study**

| Variable | Ramucirumab + Paclitaxel N = 330 | Placebo + Paclitaxel N = 335 | Total N = 665 |
|---|---|---|---|
| **Sex n (%)** | | | |
| Male | 229 (69.4) | 243 (72.5) | 472 (71.0) |
| Female | 101 (30.6) | 92 (27.5) | 193 (29.0) |
| **Age (years)** | | | |
| Median age (range) | 61 (25-83) | 61 (24-84) | 61 (24-84) |
| **Age group n (%)** | | | |
| Age <65 years | 204 (61.8) | 212 (63.3) | 416 (62.6) |
| Age ≥65 years | 126 (38.2) | 123 (36.7) | 249 (37.4) |
| **Race n (%)** | | | |
| White | 208 (63.0) | 199 (59.4) | 407 (61.2) |
| Asian | 110 (33.3) | 121 (36.1) | 231 (34.7) |
| Black | 6 (1.8) | 6 (1.8) | 12 (1.8) |
| Other[a] | 6 (1.8) | 9 (2.7) | 15 (2.4) |
| **Ethnicity n (%)** | | | |
| Hispanic or Latino | 31 (9.4) | 26 (7.8) | 57 (8.6) |
| Not Hispanic or Latino | 299 (90.6) | 309 (92.2) | 608 (91.4) |
| **ECOG PS n (%)** | | | |
| 0 | 117 (35.5) | 144 (43.0) | 261 (39.2) |
| 1 | 213 (64.5) | 191 (57.0) | 404 (60.8) |

**Table 17 Summary of Baseline Disease Characteristics -RAINBOW study**

| Variable | | Ramucirumab + Paclitaxel N = 330 n (%) | Placebo + Paclitaxel N = 335 n (%) | Total N = 665 n (%) |
|---|---|---|---|---|
| Histological Subtype | Intestinal Type | 145 (43.9) | 135 (40.3) | 280 (42.1) |
| | Diffuse Type | 115 (34.8) | 133 (39.7) | 248 (37.3) |
| | Mixed | 21 (6.4) | 14 (4.2) | 35 (5.3) |
| | Unknown/Missing | 49 (14.8) | 53 (15.8) | 102 (15.3) |
| Tumor Grade | Well differentiated | 28 (8.5) | 22 (6.6) | 50 (7.5) |
| | Moderately differentiated | 96 (29.1) | 106 (31.6) | 202 (30.4) |
| | Poorly differentiated | 186 (56.4) | 186 (55.5) | 372 (55.9) |
| | Unknown/Missing | 20 (6.1) | 21 (6.3) | 41 (6.2) |
| Primary Tumor Location | Gastric | 264 (80.0) | 264 (78.8) | 528 (79.4) |
| | GEJ | 66 (20.0) | 71 (21.2) | 137 (20.6) |
| Primary tumor present | Yes | 209 (63.3) | 209 (62.4) | 418 (62.9) |
| | No | 121 (36.7) | 126 (37.6) | 247 (37.1) |
| Extent of disease | Metastatic | 324 (98.2) | 324 (96.7) | 648 (97.4) |
| | Locally advanced | 6 (1.8) | 10 (3.0) | 16 (2.4) |
| Most common sites of metastasis[a] | Lymph Nodes | 215 (65.2) | 205 (61.2) | 420 (63.2) |
| | Peritoneal | 163 (49.4) | 152 (45.4) | 315 (47.4) |
| | Liver | 150 (45.5) | 138 (41.2) | 288 (43.3) |
| | Lung | 77 (23.3) | 70 (20.9) | 147 (22.1) |
| Number of metastatic sites[b] | 0 – 2 | 209 (63.3) | 232 (70.3) | 441 (66.3) |
| | ≥3 | 121 (36.7) | 103 (30.7) | 224 (33.7) |
| Weight loss over prior 3 months | ≥10% | 53 (16.1) | 47 (14.0) | 100 (15.0) |
| | <10% | 277 (83.9) | 286 (85.4) | 563 (84.7) |
| | Missing | 0 | 2 (0.6) | 2 (0.3) |
| Presence of ascites | Yes | 130 (39.4) | 107 (31.9) | 237 (35.6) |
| | No | 200 (60.6) | 228 (68.1) | 428 (64.4) |
| Disease Progression | During 1st Line Therapy | 227 (68.8) | 217 (64.8) | 444 (66.8) |
| | Within 4 months after Last 1st Line Dose | 94 (28.5) | 108 (32.2) | 202 (30.4) |
| | Missing | 9 (2.7) | 10 (3.0) | 19 (2.9) |

**Numbers analysed**

All 665 randomised patients were included in the intent-to-treat (ITT) population, the primary efficacy population. Of them, 4 patients randomised to the ramucirumab plus paclitaxel arm and 5 patients randomised to the placebo plus paclitaxel arm did not receive any treatment.

**Outcomes and estimation**

**Primary endpoint: Overall Survival (OS)**

The efficacy results in terms of the primary endpoint of Overall Survival (cut-off date 12 July 2013) are summarised in table 18 and figure 7.

**Table 18 Summary of OS (ITT population), RAINBOW study, cut-off 12 July 2013**

|  | Ramucirumab+Paclitaxel | Placebo+Paclitaxel |
|---|---|---|
| Patients randomised | 330 | 335 |
| Death | 256 (77.6%) | 260(77.6%) |
| Censored | 74 (22.4%) | 75(22.4%) |
| Overall Survival (months) | | |
| Median (95% CI) | 9.6 (8.5, 10.8) | 7.4 (6.3, 8.4) |
| Log-rank p-value (stratified) | 0.0169 | |
| Hazard ratio (95% CI) | 0.807 (0.678, 0.962) | |
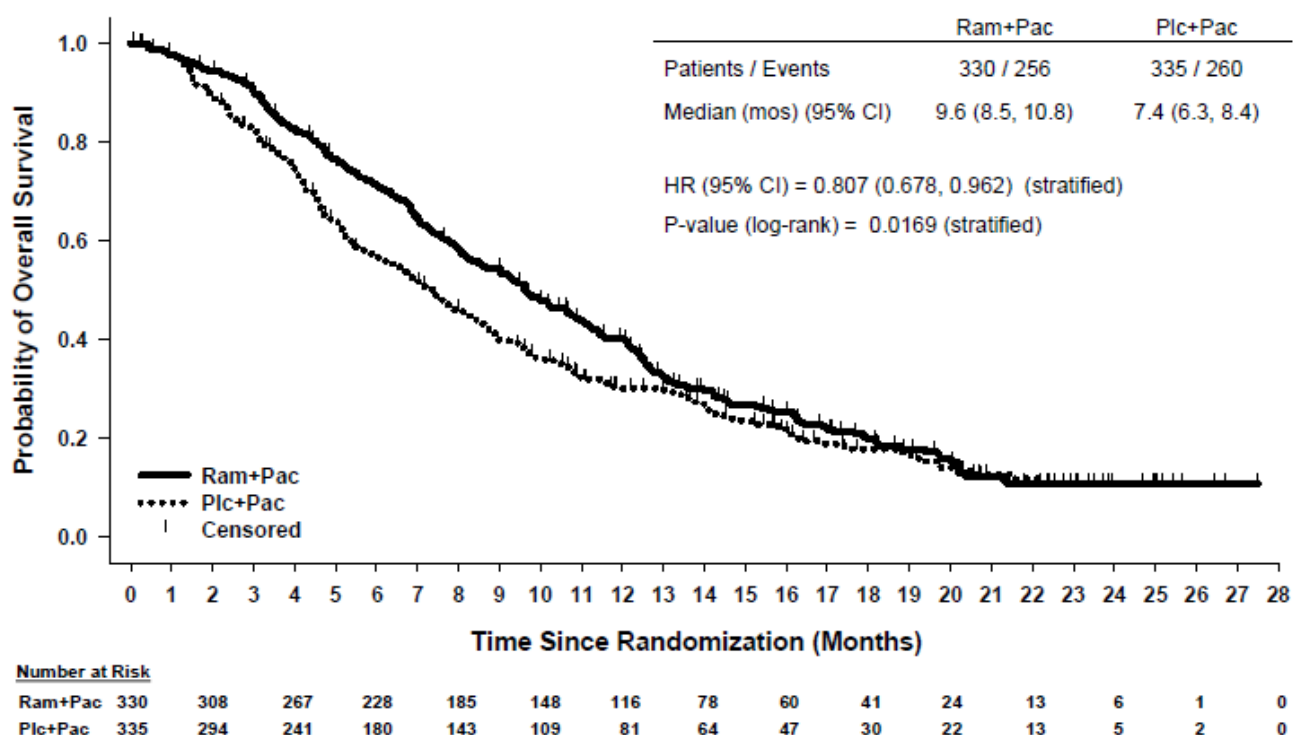


**Figure 5 Kaplan-Meier plot of OS (ITT population), RAINBOW study, cut-off 12 July 2013**

A summary of sensitivity analyses of OS is presented in table 19.

**Table 19 Summary of sensitivity analyses- RAINBOW study**

| Overall Survival | HR (95% CI) | p-Value |
|---|---|---|
| **Primary Analysis** IVRS strata – 516 events | 0.807 (0. 678, 0.962) | 0.0169 |
| **Pre-specified sensitivity analyses** | | |
| Unstratified analysis | 0.822 (0.691, 0.977) | 0.0256 |
| Stratified using CRF Strata | 0.792 (0.665, 0.943) | 0.0089 |
| Adjusted for prognostic factors using stepwise Cox regression[a] | 0.745 (0.626, 0.888) | 0.0010 |
| Per-protocol analysis (stratified) | 0.809 (0.676, 0.969) | 0.0210 |

**Key secondary endpoints**

**Progression Free Survival (PFS)**

Results in terms of the key secondary endpoints of PFS (cut-off date 12 July 2013) are summarised in table 20 and figure 8.

**Table 20 Summary of PFS (ITT Population), RAINBOW study, cut-off 12 July 2013**

|  | Ramucirumab+Paclitaxel | Placebo+Paclitaxel |
|---|---|---|
| Patients randomised | 330 | 335 |
| Progressive disease or died | 279 (84.5%) | 296 (88.4%) |
| Censored | 51 (15.5%) | 39 (11.6%) |
| Progression free survival (months) | | |
| Median (95% CI) | 4.4 (4.2, 5.3) | 2.9(2.8, 3.0) |
| Log-rank p-value (stratified) | <0.0001 | |
| Hazard ratio (95% CI) | 0.635 (0.536, 0.752) | |
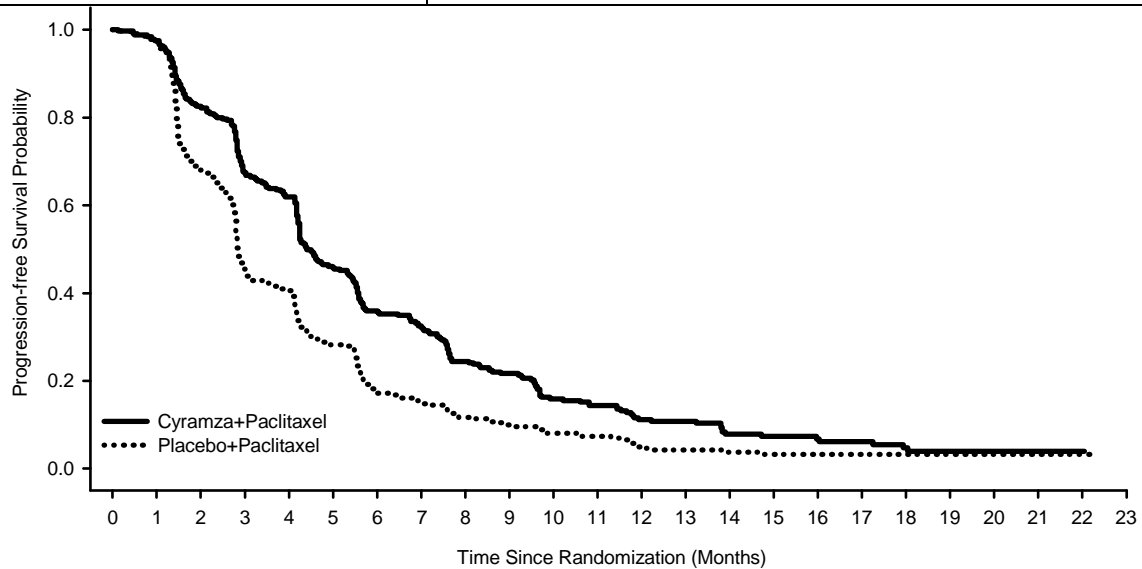


**Figure 6 Kaplan-Meier plot of PFS (ITT population) RAINBOW study, cut-off 12 July 2013**

**Other secondary endpoints**

The ORR in the ramucirumab arm plus paclitaxel was 27.9% (95% CI: 23.3, 33.0) versus 16.1 % (95% CI: 12.6, 20.4) in the placebo plus paclitaxel arm ((Odds ratio 2.140; 95% CI: 1.499, 3.160; p=0.0001).

More patients in the ramucirumab plus paclitaxel arm had improved or stable EORTC QLQ-C30 Global Health status compared to the placebo plus paclitaxel arm (Table 21) at each visit during the treatment. In contrast, a higher proportion in the placebo+paclitaxel arm had a stable or improved global health status by the end of treatment. The time to deterioration in EORTC QLQ-C30 subscales was better in the ramucirumab+paclitaxel arm for all subscales except for diarrhea (data not shown).

**Table 21 EORTC QLQ-C30 Global Health Status, ITT Population RAINBOW**

| | Ramucirumab + Paclitaxel N = 330 | | | | Placebo + Paclitaxel N = 335 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Visit | Improved | Stable | Deteriorated | No Data | Improved | Stable | Deteriorated | No Data | p-Value[a] |
| Cycle 2 Day 15 | 57 (17.3) | 118 (35.8) | 72 (21.8) | 83 (25.2) | 50 (14.9) | 116 (34.6) | 54 (16.1) | 115 (34.3) | 0.3937 |
| Cycle 4 Day 1 | 45 (13.6) | 74 (22.4) | 58 (17.6) | 153 (46.4) | 27 (8.1) | 65 (19.4) | 34 (10.1) | 209 (62.4) | 0.0196 |
| Cycle 5 Day 15 | 27 (8.2) | 53 (16.1) | 39 (11.8) | 211 (63.9) | 14 (4.2) | 38 (11.3) | 23 (6.9) | 260 (77.6) | 0.0063 |
| Cycle 7 Day 1 | 25 (7.6) | 23 (7.0) | 23 (7.0) | 259 (78.5) | 11 (3.3) | 19 (5.7) | 11 (3.3) | 294 (87.8) | 0.0298 |
| Cycle 8 Day 15 | 15 (4.5) | 24 (7.3) | 18 (5.5) | 273 (82.7) | 6 (1.8) | 12 (3.6) | 3 (0.9) | 314 (93.7) | 0.0034 |
| Cycle 10 Day 1 | 13 (3.9) | 12 (3.6) | 10 (3.0) | 295 (89.4) | 6 (1.8) | 7 (2.1) | 4 (1.2) | 318 (94.9) | 0.0453 |
| End of Treatment | 21 (6.4) | 80 (24.2) | 108 (32.7) | 121 (36.7) | 25 (7.5) | 86 (25.7) | 91 (27.2) | 133 (39.7) | 0.5062 |

Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Questionnaire-C30; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category.

a  2-sided p-value of Fisher's exact test for Not Deteriorated (Improved or Stable) versus Deteriorated/No Data comparing the treatment groups.

Note 1:  Assessment is based on a 6-week schedule.

Note 2:  Percentages are based on the number of patients in the ITT population in the corresponding treatment arm.

## Ancillary analyses

Subgroup analyses for OS are shown in figure 9.
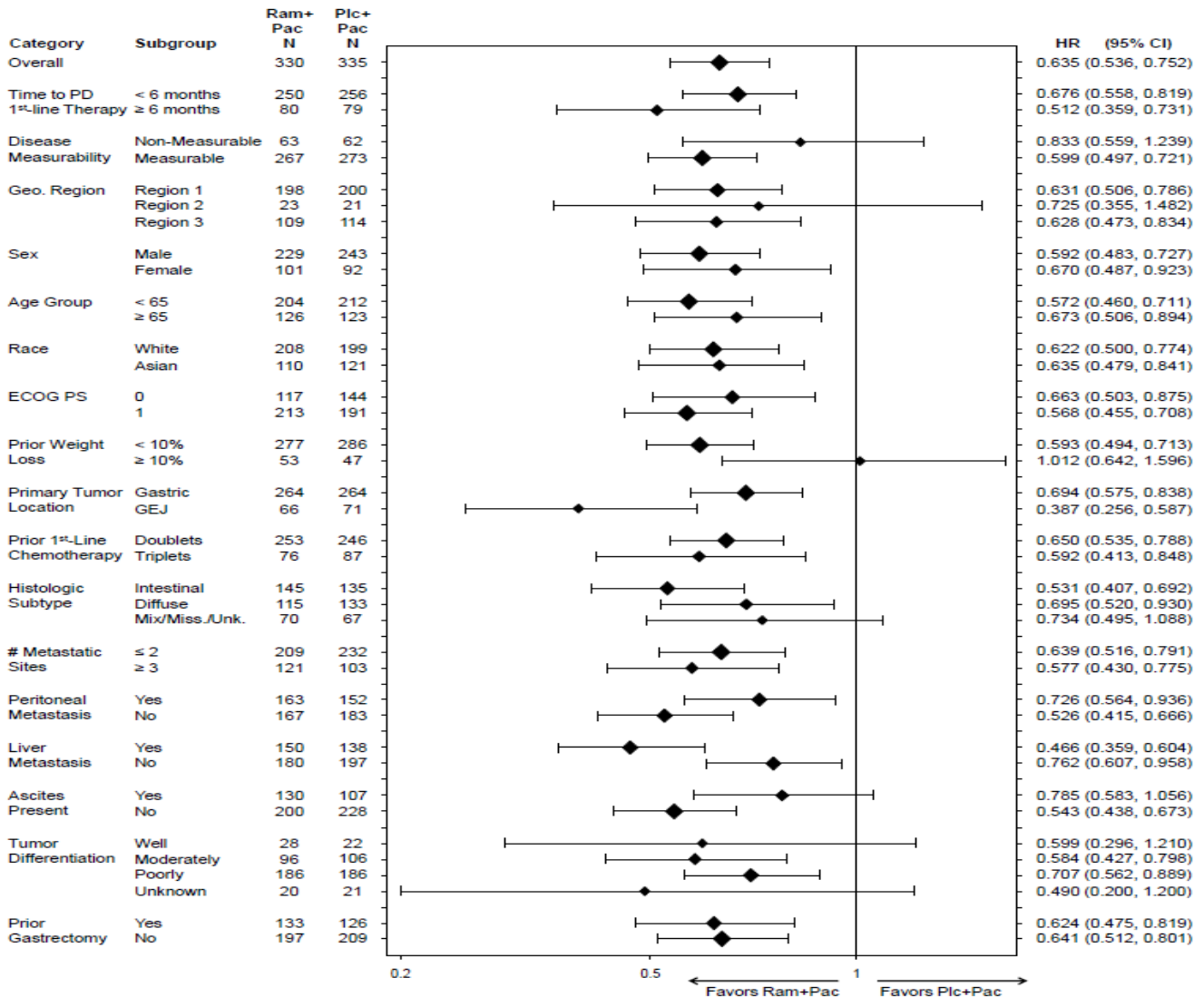


**Figure 7 Forest Plot of OS  by Subgroups - Stratified Analysis (ITT Population)- RAINBOW study**

Subgroup analyses for PFS are shown in figure 10.

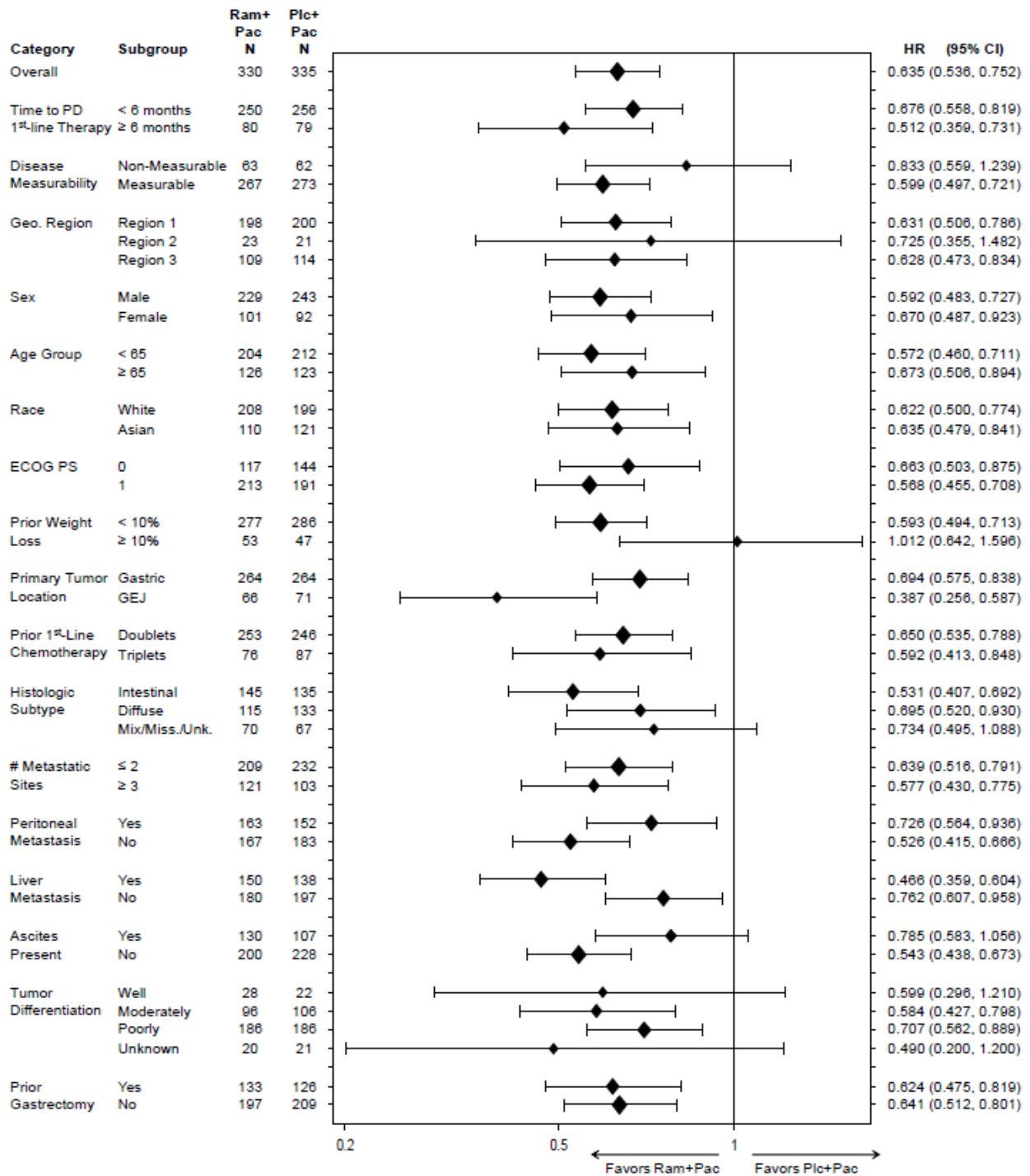| Category | Subgroup | Ram+ Pac N | Plc+ Pac N | | HR (95% CI) |
|---|---|---|---|---|---|
| Overall | | 330 | 335 | | 0.635 (0.536, 0.752) |
| Time to PD | < 6 months | 250 | 256 | | 0.676 (0.558, 0.819) |
| 1st-line Therapy | ≥ 6 months | 80 | 79 | | 0.512 (0.359, 0.731) |
| Disease | Non-Measurable | 63 | 62 | | 0.833 (0.559, 1.239) |
| Measurability | Measurable | 267 | 273 | | 0.599 (0.497, 0.721) |
| Geo. Region | Region 1 | 198 | 200 | | 0.631 (0.506, 0.786) |
| | Region 2 | 23 | 21 | | 0.725 (0.355, 1.482) |
| | Region 3 | 109 | 114 | | 0.628 (0.473, 0.834) |
| Sex | Male | 229 | 243 | | 0.592 (0.483, 0.727) |
| | Female | 101 | 92 | | 0.670 (0.487, 0.923) |
| Age Group | < 65 | 204 | 212 | | 0.572 (0.460, 0.711) |
| | ≥ 65 | 126 | 123 | | 0.673 (0.506, 0.894) |
| Race | White | 208 | 199 | | 0.622 (0.500, 0.774) |
| | Asian | 110 | 121 | | 0.635 (0.479, 0.841) |
| ECOG PS | 0 | 117 | 144 | | 0.663 (0.503, 0.875) |
| | 1 | 213 | 191 | | 0.568 (0.455, 0.708) |
| Prior Weight | < 10% | 277 | 286 | | 0.593 (0.494, 0.713) |
| Loss | ≥ 10% | 53 | 47 | | 1.012 (0.642, 1.596) |
| Primary Tumor | Gastric | 264 | 264 | | 0.694 (0.575, 0.838) |
| Location | GEJ | 66 | 71 | | 0.387 (0.256, 0.587) |
| Prior 1st-Line | Doublets | 253 | 246 | | 0.650 (0.535, 0.788) |
| Chemotherapy | Triplets | 76 | 87 | | 0.592 (0.413, 0.848) |
| Histologic | Intestinal | 145 | 135 | | 0.531 (0.407, 0.692) |
| Subtype | Diffuse | 115 | 133 | | 0.695 (0.520, 0.930) |
| | Mix/Miss./Unk. | 70 | 67 | | 0.734 (0.495, 1.088) |
| # Metastatic | ≤ 2 | 209 | 232 | | 0.639 (0.516, 0.791) |
| Sites | ≥ 3 | 121 | 103 | | 0.577 (0.430, 0.775) |
| Peritoneal | Yes | 163 | 152 | | 0.726 (0.564, 0.936) |
| Metastasis | No | 167 | 183 | | 0.526 (0.415, 0.666) |
| Liver | Yes | 150 | 138 | | 0.466 (0.359, 0.604) |
| Metastasis | No | 180 | 197 | | 0.762 (0.607, 0.958) |
| Ascites | Yes | 130 | 107 | | 0.785 (0.583, 1.056) |
| Present | No | 200 | 228 | | 0.543 (0.438, 0.673) |
| Tumor | Well | 28 | 22 | | 0.599 (0.296, 1.210) |
| Differentiation | Moderately | 96 | 106 | | 0.584 (0.427, 0.798) |
| | Poorly | 186 | 186 | | 0.707 (0.562, 0.889) |
| | Unknown | 20 | 21 | | 0.490 (0.200, 1.200) |
| Prior | Yes | 133 | 126 | | 0.624 (0.475, 0.819) |
| Gastrectomy | No | 197 | 209 | | 0.641 (0.512, 0.801) |

Favors Ram+Pac    Favors Plc+Pac

**Figure 8 Forest plot for subgroup analysis of PFS (stratified) RAINBOW study**

The Subgroup Analyses of OS and PFS by Region are presented in Table 22.

**Table 22 Subgroup Analyses of OS and PFS by Region- RAINBOW study**

| | Ramucirumab +Paclitaxel | | Placebo + Paclitaxel | | Hazard Ratio [a, b] |
|---|---|---|---|---|---|
| | N | Median – months (95%CI) | N | Median – months (95%CI) | (95%CI) |
| **Overall Survival** | | | | | |
| Region 1[c] | 198 | 8.6 (7.4, 9.8) | 200 | 5.9 (5.0, 7.1) | 0.726 (0.580, 0.909) |
| Region 2[c] | 23 | 7.1 (3.7, 16.2) | 21 | 8.1 (4.2, 9.6) | 0.797 (0.383, 1.660) |
| Region 3[c] | 109 | 12.1 (10.0, 13.3) | 114 | 10.5 (7.8, 14.1) | 0.986 (0.727, 1.337) |
| **Progression-Free Survival** | | | | | |
| Region 1[c] | 198 | 4.2 (3.9, 5.3) | 200 | 2.8 (2.6, 3.1) | 0.631 (0.506, 0.786) |
| Region 2[c] | 23 | 3.8 (1.54, 6.77) | 21 | 4.2 (2.3, 5.7) | 0.725 (0.355, 1.482) |
| Region 3[c] | 109 | 5.5 (4.2, 5.7) | 114 | 2.8 (2.8, 4.1) | 0.628 (0.473, 0.834) |

a Stratified by the randomization strata (Time to progression from the start of first-line therapy, and Disease measurability).
b Hazard ratio and 95% CI (Wald's) were estimated using the Cox model.
c Region 1 = Europe, Israel, United States, and Australia; Region 2 = Argentina, Brazil, Chile, and Mexico; Region 3 = Hong Kong, Japan, South Korea, Singapore, and Taiwan.

Information regarding the prior anticancer therapy, including targeted therapies, was also collected in RAINBOW. The OS, PFS, and ORR Subgroup Analysis by Prior Trastuzumab Therapy is presented in Table 23.

**Table 23 OS, PFS, and ORR Subgroup Analysis by Prior Trastuzumab Therapy, Unstratified Analysis- RAINBOW study**

| Efficacy Endpoint | Ramucirumab plus Paclitaxel (N = 330) | | | Placebo plus Paclitaxel (N = 335) | | | |
|---|---|---|---|---|---|---|---|
| | N | Events | Median (95% CI), months[a] | N | Events | Median (95% CI) months[a] | HR (95% CI)[b] |
| **Overall Survival** | | | | | | | |
| Previous Herceptin Therapy | | | | | | | |
| Yes | 20 | 14 | 11.4 (7.0, 17.9) | 19 | 16 | 7.0 (3.4, 14.6) | 0.679 (0.327, 1.410) |
| No | 310 | 242 | 9.6 (8.2, 10.8) | 316 | 244 | 7.4 (6.3, 8.4) | 0.835 (0.699, 0.998) |
| **Progression-Free Survival** | | | | | | | |
| Previous Herceptin Therapy | | | | | | | |
| Yes | 20 | 17 | 4.2(2.8, 7.6) | 19 | 19 | 2.7 (1.4, 3.0) | 0.399 (0.194, 0.822) |
| No | 310 | 262 | 4.4 (4.2, 5.4) | 316 | 277 | 2.9 (2.8, 3.1) | 0.657 (0.555, 0.779) |
| | N | Events (%) | 95% CI[c] | N | Events (%) | 95% CI[c] | |
| **Best Overall Response (CR+PR)** | | | | | | | |
| Previous Herceptin Therapy | | | | | | | |
| Yes | 20 | 9 (45.0) | 25.8, 65.8 | 19 | 2 (10.5) | 2.9, 31.4 | |
| No | 310 | 83 (26.8) | 22.2, 32.0 | 316 | 52 (16.5) | 12.8, 20.9 | |
| **Disease Control Rate (CR+PR+SD)** | | | | | | | |
| Previous Herceptin Therapy | | | | | | | |
| Yes | 20 | 16 (80.0) | 58.4, 91.9 | 19 | 11 (57.9) | 36.3, 76.9 | |
| No | 310 | 248 (80.0) | 75.2, 84.1 | 316 | 202 (63.9) | 58.5, 69.0 | |

Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; N = total number of patients; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; SD = stable disease.

[a] Estimated by the Kaplan-Meier method.

[b] Hazard ratio and 95% CI (Wald) were estimated using an unstratified Cox model.

[c] Estimated using Wilson method (recommended method of Altman et al. 2000).

## Summary of main studies

The following tables 24 and 25 summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 24 Summary of Efficacy for trial REGARD**

| | | | |
|---|---|---|---|
| **Title:** A Phase 3, Randomized, Double-Blinded Study of IMC-1121B and Best Supportive Care (BSC) Versus Placebo and BSC in the Treatment of Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy | | | |
| Study Identifier | I4T-IE-JVBD, IMCL CP12-0715, REGARD | | |
| Design | Phase 3, randomized, multicentre, placebo-controlled, double-blinded study | | |
| | Duration of Main phase: | | until progressive disease (PD), unacceptable toxicity, withdrawal of consent, or until other withdrawal criteria were met |
| Hypothesis | superiority | | |
| Treatment groups | Ramucirumab + BSC | 8 mg/kg intravenous over approximately 60 minutes administered every 2 weeks; 238 patients randomized. | |
| | Placebo + BSC | Equivalent volume of ramucirumab placebo (IV) over approximately 60 minutes administered every 2 weeks; 117 patients randomized. | |
| Endpoints and Definitions | Primary Endpoint | Overall Survival (OS) | Time from the date of randomization to the date of death from any cause. |
| | Secondary Endpoints | Progression free survival (PFS) | Time from the date of randomization until the date of objectively determined progressive disease (PD) or death due to any cause, whichever was first. |
| | | 12-week PFS Rate | The probability of being alive and progression-free 12 weeks after randomization |
| | | Objective response rate (ORR) | The proportion of patients achieving a best overall response of complete or partial response (CR + PR). |
| Database Lock: 26 September 2012 | | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | ITT population (cut-off date at 25 July 2012) (all randomized patients):355 | | |

| Descriptive statistics and estimate variability | Treatment group | Ramucirumab | Placebo |
|---|---|---|---|
| | Number of patients | 238 | 117 |
| | Median OS (months) | 5.2 | 3.8 |
| | 95% CI for median | (4.4 - 5.7) | (2.8 - 4.7) |
| | Median PFS (months) | 2.1 | 1.3 |
| | 95% CI for median | (1.5, 2.7) | (1.3, 1.4) |
| | 12-week PFS Rate (%) | 40.1 | 15.8 |
| | 95% CI | (33.6, 46.4) | (9.7, 23.3) |

| Effect estimate per comparison | Primary Endpoint (OS) | Comparison groups | Ramucirumab vs Placebo | |
|---|---|---|---|---|
| | | Hazard Ratio | 0.776 | |
| | | (95% CI) | (0.603 - 0.998) | |
| | | p-value | 0.0473 | |
| | Secondary Endpoint | Comparison groups | Ramucirumab vs Placebo | |
| | | Hazard Ratio | 0.483 | |

| | (PFS) | (95% CI) | (0.376, 0.620) |
|---|---|---|---|
| | | p-value | <0.0001 |
| | | 12-week PFS Rate %: (p-value) | <0.0001 |
| Notes | Stratification factors for the primary analysis (logrank): Weight loss (≥10% over the prior 3 months vs. <10%), Geographic region (North America, Europe, Australia, and New Zealand vs. South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia vs. Asia) and location of the primary tumour [gastric (including tumours of the gastric cardia that extend into the GEJ) vs. GEJ (including tumours of the distal oesophagus that extend into the GEJ, and tumours involving the GEJ when precise identification of the organ of origin was not possible)]. | | |

**Table 25 Summary of Efficacy for trial RAINBOW**

| **Title:** A Phase 3, Randomized, Double-Blinded Study of IMC-1121B and Paclitaxel Versus Placebo and Paclitaxel in the Treatment of Metastatic Gastric Adenocarcinoma, Refractory to or Progressive After First-Line Therapy with Platinum and Fluoropyrimidine | | | |
|---|---|---|---|
| Study identifier | I4T-IE-JVBE, (IMCL CP12-0922), RAINBOW | | |
| Design | Phase 3, randomized, multicentre, placebo-controlled, double-blinded study. | | |
| | Duration of Main phase: | Until progressive disease (PD), unacceptable toxicity, withdrawal of consent, or until other withdrawal criteria were met. | |
| Hypothesis | Superiority | | |
| Treatments groups | Ramucirumab+ Paclitaxel | Ramucirumab 8 mg/Kg + Paclitaxel 80 mg/m$^2$ intravenous over approximately 60 minutes administered on a 28-day cycle. 330 patients randomized. | |
| | Placebo+Paclitaxel | Placebo + Paclitaxel 80 mg/m$^2$ intravenous over approximately 60 minutes administered on a 28-day cycle. 335 patients randomized. | |
| Endpoints and definitions | Primary endpoint | Overall survival (OS) | The interval between date of randomization and the date of death from any cause. |
| | Secondary | Progression free survival (PFS) | The time from the date of randomization until the date of objectively determined PD (RECIST 1.0) or death due to any cause, whichever was first. |
| | Secondary | Overall response rate (ORR) | The proportion of patients achieving a best overall response of partial (PR) or complete response (CR). |
| Database lock | 31 December 2012 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | ITT (cut-off date at 12 July 2013)(all randomized patients):665 | | |
| Descriptive statistics and estimate variability | Treatment group | Ramucirumab+paclitaxel | Placebo+paclitaxel |
| | Number of patients | 330 | 335 |
| | Median OS (months) | 9.6 | 7.4 |
| | 95% CI for median | (8.5,10.8) | (6.3,8.4) |

| | | | | |
|---|---|---|---|---|
| | Median PFS (months) 95% CI for median | 4.4 (4.2,5.3) | 2.9 (2.8,3.0) | |
| | Objective Response Rate (%) 95% CI | 27.9% 23.3-33.0% | 16.1 12.6-20.4% | |
| Effect estimate per comparison | Primary Endpoint (OS) | Comparison groups | Ramucirumab vs Placebo | |
| | | Hazard Ratio (stratified) | 0.807 | |
| | | (95% CI) | (0.678 - 0.962) | |
| | | p-value | 0.0169 | |
| | Secondary Endpoint (PFS) | Comparison groups | Ramucirumab vs Placebo | |
| | | Hazard Ratio (stratified) | 0.635 | |
| | | (95% CI) | (0.536, 0.752) | |
| | | p-value | <0.0001 | |
| | Secondary Endpoint (ORR) | Comparison groups | Ramucirumab vs Placebo | |
| | | Odd Ratio | 2.140 | |
| | | (95% CI) | (1.449, 3.160) | |
| | | p-value (stratified) | 0.0001 | |
| **Notes** | Stratification factors for the primary analysis: time to Progression (TTP) from the start of the first-line chemotherapy (<6 months vs. ≥6 months), geographic region (North America, Europe (including Israel), Australia vs. South and Central America vs. Asia) and disease measurability (measurable vs no measurable disease) | | | |

**Analysis performed across trials (pooled analyses and meta-analysis)**

N/A

**Clinical studies in special populations**

N/A

**Supportive study**

No additional supportive efficacy data have been provided.

## 2.5.2. Discussion on clinical efficacy

**Design and conduct of clinical studies**

*Ramucirumab+paclitaxel combination therapy*

RAINBOW, a global, randomised, double-blind, study of Cyramza plus paclitaxel versus placebo plus paclitaxel, was conducted in 665 patients with locally recurrent and unresectable or metastatic gastric cancer (including GEJ adenocarcinoma) following platinum- and fluoropyrimidine-containing chemotherapy, with or without anthracycline (see SmPC, section 5.1).

Patients were randomised in a 1:1 ratio to receive Cyramza plus paclitaxel (n=330) or placebo plus paclitaxel (n=335). Randomisation was stratified by geographic region, time to progression from the start of first-line therapy (<6 months versus ≥ 6 months) and disease measurability (see SmPC, section 5.1).

No notable inbalances in pretreatment characteristics were observed between the two treatment groups.


*Ramucirumab monotherapy*

REGARD, a multinational, randomised, double-blind study of Cyramza plus BSC versus placebo plus BSC, was conducted in 355 patients with locally recurrent and unresectable, or metastatic gastric cancer (including GEJ adenocarcinoma) following platinum- or fluoropyrimidine-containing chemotherapy (see SmPC, section 5.1).

Patients were randomised in a 2:1 ratio to receive an intravenous infusion of Cyramza 8 mg/kg (n= 238) or placebo (n= 117) every 2 weeks. Randomisation was stratified by weight loss over the prior 3 months (≥ 10% versus < 10%), geographic region, and location of the primary tumour (gastric versus GEJ) (see SmPC, section 5.1).  Although these stratification factors are considered acceptable, it is noted that no stratification was applied by VEGFR2 expression in tumours, thus precluding the possible finding of differential effects by VEGFR2 expression.

Randomization resulted in several imbalances, patients in the ramucirumab arm presenting with a more favourable distribution of several baseline characteristics known to be of prognostic value (lower no. of metastases, higher proportion of patients with a progression free interval≥6 months, higher proportion of patients receiving chemotherapy in the adjuvant setting, higher proportion of patients with tumours of intestinal type). The applicant conducted a number of sensitivity analyses to assess the impact of the observed imbalances of prognostic factors. In all sensitivity analyses, a significant effect on overall survival remained, and the effect size did not change notably.

Selection of the 8 mg/kg dose every other week for the monotherapy treatment may not be optimal since a higher dose of ramucirumab in monotherapy may be more efficacious while remaining tolerable. There may be an opportunity to further optimise the benefit/risk profile in the monotherapy setting given the exposure-efficacy relationship and overall safety profile observed in the REGARD study. Given the mild safety profile of ramucirumab in the monotherapy, and the considerable higher MTD of 13 mg/kg QW, exploration of an alternative dosing regimen is warranted. To further investigate this, the Applicant will submit the results of a dose-response study (see conclusions on clinical efficacy).

After first-line treatment of gastric cancer, no second-line treatment for metastatic gastric cancer had been approved in Europe at the time of conducting the studies. The comparators used in the studies are considered acceptable.


**Efficacy data and additional analyses**

*Ramucirumab+paclitaxel combination therapy*

In the RAINBOW study, ramucirumab in combination with paclitaxel reduced the risk of death in this population by 19% (HR = 0.807; 95% CI: 0.678, 0.962; p=0.0169), with a 2.4 months longer median survival in the ramucirumab plus paclitaxel arm (9.6 versus 7.4 months). The effect of ramucirumab+paclitaxel was apparent in all pre-specified subgroups, except for the subgroup of patients with non-measurable disease.

In addition, in contrast to region 1 (Western population), no beneficial effect of adding ramucirumab to paclitaxel was observed in region 3 (HR 0.986; CI 0.727-1.337). This may be related to the higher use of PDT in region 3 (Asia). A notably higher percentage of patients in Region 3 (67.3%) received PDT

compared with Region 1 (37.2%). This higher use of PDT is likely to have contributed to the longer median survival time in Region 3 in the control arm (10.5 months compared with 5.6 months in Region 1, in the control arm).

Treatment with ramucirumab plus paclitaxel significantly reduced the risk of disease progression or death (HR = 0.635; 95% CI: 0.536, 0.752; p<0.0001), with a 1.5 months longer median PFS in the ramucirumab plus paclitaxel arm compared with the placebo plus paclitaxel arm (4.4 months vs. 2.9 months). The robustness of the main PFS analysis results was supported by pre-specified sensitivity analyses, as demonstrated by consistent HRs between 0.599 and 0.649 with p<0.0001. In all subgroups the stratified HR numerically favoured the ramucirumab plus paclitaxel arm, except for the subgroup of patients with weight loss greater than or equal to 10% in the 3 months prior to randomization.

Objective response rate (complete response [CR] + partial response [PR]) was significantly improved in patients receiving Cyramza plus paclitaxel compared with those receiving placebo plus paclitaxel (Odds ratio 2.140; 95% CI: 1.499 to 3.160; p=0.0001). The ORR in the Cyramza plus paclitaxel arm was 27.9% and in the placebo plus paclitaxel arm was 16.1% (SmPC, section 5.1).

More patients in the ramucirumab plus paclitaxel arm had improved or stable EORTC QLQ-C30 Global Health status compared to the placebo plus paclitaxel arm at each visit during the treatment however a higher proportion in the placebo+paclitaxel arm had a stable or improved global health status by the end of treatment.

*Ramucirumab monotherapy*

In the pivotal study REGARD, ramucirumab as single-agent was associated with a HR for OS of 0.776 (95% CI [0.603; 0.998]; p=0.0473), with 5.3 months of median OS in the ramucirumab arm compared to 3.8 months in the placebo arm.

During the initial evaluation, the CHMP raised a major objection about the differential OS outcome: the benefit on OS was most pronounced in region 2 (Latin America and Middle East (HR: region 1: 0.896; region 2: 0.464; region 3: 0.694)). The higher use of PDT in the ramucirumab arm (25.5%) in region 2 compared to the placebo arm (17.2%) was unexpected when considering absence of efficacy in the placebo arm and not in line with the distribution of PDT in the other regions. In response, the applicant argued that the majority of patients in the REGARD study (67.3%) did not receive PDT and that patients who did receive PDT in region 2 only amounted to 19 patients. A post hoc subgroup analysis by PDT use was conducted, showing a significant result in patients not receiving PDT, but not in patients receiving PDT. The CHMP acknowledged that is not possible to disentangle the effects of better prognosis in patients receiving post discontinuation therapy (PDT) from the possible effects of PDT on survival. The observed OS effects seen in RAINBOW study in region 1 (HR 0.726) and the poor relative results in region 3 (HR 0.986) could be related to the more frequent use of PDT in region 3 (67% vs. 47%), but is more likely to reflect better prognosis, as the median OS is 3.5 months longer in region 3 than in region 1 (12.1 vs 8.6 months). In the REGARD study the opposite OS results in region 1 (HR 0.896) vs. region 2 (HR 0.464), could reflect the more frequent use of PDT in region 1 (32.1%), but more likely better prognosis. Therefore this deviant distribution of PDT could be explained by a worse clinical condition of patients in the placebo group. However, based on the larger effect size observed in the RAINBOW study, ramucirumab monotherapy should be indicated for patients for whom treatment with ramucirumab in combination with paclitaxel is not appropriate (see discussion on benefit-risk).

Inconsistency was also observed regarding gender (ramucirumab effective in men, but potentially detrimental in women) and histological subtype (large effect in diffuse type, no effect in intestinal or unknown subtype). A potential pathophysiological mechanism responsible for this inconsistency is not known. The influence of expression of VEGFR-2 and other biomarkers was not investigated. Therefore, it is unknown whether the observed inconsistency is attributable to differences in expression between the

two treatment arms. The CHMP recommended the applicant to submit the assay results for VEGF-C and VEGF-D from the RAINBOW study which includes correlations with efficacy measures (if applicable) by the end of 2Q 2015. The RAINBOW study results for sVEGFR2 will be submitted by the end of 4Q 2015, when the assay is validated.

In general, ramucirumab was not associated with a deterioration of QoL. However, the extent of QoL data was limited by the rapid progression characteristic of advanced, treatment-resistant gastric cancer and by the absence of QoL evaluation at the end of therapy.

## 2.5.3.  Conclusions on the clinical efficacy

The RAINBOW study has provided convincing evidence of clinical efficacy of the combination of ramucirumab plus paclitaxel in terms of the primary endpoint OS, compared to placebo plus paxlitaxel in patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. The REGARD study has provided convincing evidence of clinical efficacy of the monotherapy in terms of the primary endpoint OS, compared to placebo in patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy for whom treatment in combination with paclitaxel is not appropriate.

The CHMP considers the following measures necessary to address issues related to the dosing regimen for the monotherapy setting:

The MAH shall submit results from the randomised dose ranging pharmacokinetics (PK) and safety study of ramucirumab monotherapy (14T-MC-JVDB). This phase 2 study will evaluate the PK and safety of various schedules of ramucirumab, including an exploration of higher doses than the approved dose of 8mg/kg every 2 weeks in second line gastric adenocarcinoma.

## 2.6.  Clinical safety

### Study 14T-IE-JVBD (REGARD)

### Patient exposure
Of 355 randomized patients, 351 received at least 1 dose of study therapy, including 236 in the ramucirumab group and 115 in the placebo group. Four patients were randomized and not treated (2 in each arm). One of these 4 died subsequent to randomization and prior to administration of the first dose; the other 3 experienced symptoms that made them unsuitable for dosing in the opinion of the investigator (performance status decline, brain metastases, and laboratory abnormalities, respectively).

Patients continued treatment until there was evidence of progressive disease or unacceptable toxicity. The ramucirumab dose regimen used in REGARD was 8 mg/kg every 2 weeks.

The median duration of therapy was 8 weeks for the ramucirumab arm (median 4 cycles) and 6 weeks for the placebo arm (median 3 cycles) (Table 26). The median relative dose intensity was 99.6% for the ramucirumab arm, with 91.5% of patients receiving doses ≥ 90% of the 8 mg/kg protocol-stipulated dose level. The cumulative number of patient-years exposure was 57.5 and 17.4 years for ramucirumab and placebo respectively.

**Table 26 Extent of exposure in the REGARD study (Safety Population)**

|  | Ramucirumab<br>N = 236 | Placebo<br>N = 115 |
|---|---|---|
| **Duration of Therapy (Weeks)** | | |
| Median | 8.0 | 6.0 |
| Mean (SD) | 12.7 (11.7) | 7.9 (7.7) |
| Range | 2 – 72 | 2 - 60 |
| **Total Number of Cycles Received** | | |
| Median | 4.0 | 3.0 |
| Mean (SD) | 6.1 (5.6) | 3.9 (3.8) |
| Range | 1 – 34 | 1 – 30 |
| **Dose Intensity (mg/kg/wk)[a]** | | |
| Median | 3.98 | 4.00 |
| Mean (SD) | 3.90 (0.32) | 3.93 (0.28) |
| Range | 2.4 – 4.6 | 2.6 – 4.4 |
| **Relative Dose Intensity (%)[a]** | | |
| Median | 99.6 | 100.0 |
| Mean (SD) | 97.52 (7.95) | 98.25 (7.03) |
| Range | 59.8 – 114.5 | 65.7 – 110.7 |

More patients on the ramucirumab arm (versus the placebo arm) had any dose delay ≥ 7 days (5.1% vs. 1.7%), dose omitted (20.3% vs. 10.4%), infusion rate modification (6.4% vs. 1.7%), or infusion interruption (1.3% vs. 0%). Three patients in the ramucirumab arm (1.3 %) and 1 patient (0.9%) in the placebo arm required dose reductions, each due to an AE. The most frequent TEAEs leading to dose modification and delays were asthenia (n = 5; 2.1%), abdominal pain (n = 4; 1.7%), and anaemia (n = 3; 1.3%) in the ramucirumab arm, and asthenia and vomiting (each, n = 2; 1.7%) in the placebo arm.

**Adverse events**

An overview of treatment-emergent adverse events is presented in table 27.

**Table 27 Overview of treatment-emergent adverse events in the REGARD study**

| Adverse Event[a] | Ramucirumab<br>N = 236<br>n (%) | Placebo<br>N = 115<br>n (%) |
|---|---|---|
| Patients with ≥1 TEAE | 223 (94.5) | 101 (87.8) |
| Patients with ≥1 treatment-emergent SAE | 106 (44.9) | 51 (44.3) |
| Patients with ≥1 TEAE Grade ≥3 | 134 (56.8) | 67 (58.3) |
| Discontinuations due to an AE[b] | 25 (10.5) | 7 (6.0) |
| Deaths due to an AE[b] | 22 (9.3) | 15 (13.0) |

Abbreviations: AE = adverse event; N = number of treated patients; n = number of patients in category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Patients may be counted in more than 1 category.

[b] Based on patient disposition (End of Treatment or Report of Patient Death).

A total of 223 patients in the ramucirumab group (94.5%) and 101 patients in the placebo group (87.8%) experienced at least 1 TEAE.

Preferred terms for very common AEs (≥ 10% incidence) observed at a higher incidence among patients receiving ramucirumab than among patients receiving placebo included hypertension (15.3% vs. 7.8%), diarrhoea (14.4% vs. 8.7%), and abdominal pain upper (11.4% vs. 4.3%).

Preferred terms for any-grade AEs (≥ 5% and < 10% incidence) observed with at least twice the incidence rate among patients receiving ramucirumab than among patients receiving placebo were headache (9.3% vs. 3.5%) and hyponatremia (5.5% vs. 1.7%).

Preferred terms for less common AEs (≥1% and <5% incidence) observed with at least twice the incidence rate among patients receiving ramucirumab than among patients receiving placebo included epistaxis (4.7% vs. 0.9%), pain (4.2% vs. 0.9%), neutropenia (3.8% vs. 0.9%), mucosal inflammation (3.8% vs. 0.9%), rash (3.8% vs. 0.9%), and intestinal obstruction (2.1% vs. 0%).

The relationship between TEAES and exposure to ramucirumab was determined by the investigator and were reported at a similar rate in both arms (53.0% in the ramucirumab arm and 50.4% in the placebo arm).

The frequency of individual Grade ≥3 TEAE was <10% for all events in both ramucirumab and placebo group. The overall incidence of Grade ≥3 TEAEs was 56.8% in the ramucirumab arm and 58.3 % placebo arms. The most common Grade ≥3 TEAE occurred at 7.2% in the ramucirumab arm and 2.6 % in the placebo arm; no Grade >3 hypertension was observed.

**Adverse Drug Reactions (ADRs)**

Events meeting either of the below criteria in REGARD were evaluated as potential ADRs ("Incidence" means the percentage of patients experiencing the event):

- The ramucirumab incidence was ≥ 10% AND the ramucirumab incidence was greater than or equal to the placebo incidence.

- The ramucirumab incidence was between 1% and 10%, AND ramucirumab incidence was ≥ 2 times the placebo incidence, AND the number of patients experiencing the event on the ramucirumab arm was ≥ 4.

Clinically relevant ADRs reported in ≥ 1% and < 5% of the ramucirumab treated patients in REGARD were: neutropenia, arterial thromboembolic events, intestinal obstruction, epistaxis and rash (see Table 28).

**Table 28 Adverse Drug Reactions in ≥1 and <5% of Ramucirumab-Treated Patients All Treated Patients REGARD**

| System Organ Class | Event[a] | Ramucirumab (N=236) | | Placebo (N=115) | |
|---|---|---|---|---|---|
| | | All Grades Toxicity (%) | Grade ≥3 Toxicity (%) | All Grades Toxicity (%) | Grade ≥3 Toxicity (%) |
| Blood and Lymphatic System Disorders | Neutropenia[b] | 4.7 | 2.1 | 0.9 | 0 |
| Cardiac Disorders/Nervous System Disorders | Arterial Thromboembolic Events (ATEs)[c] | 1.7 | 1.3 | 0 | 0 |
| Gastrointestinal Disorders | Intestinal Obstruction | 2.1 | 1.7[d] | 0 | 0 |
| Respiratory, Thoracic and Mediastinal Disorders | Epistaxis | 4.7 | 0 | 0.9 | 0 |
| Skin and Subcutaneous Tissue Disorders | Rash[e] | 4.2 | 0 | 1.7 | 0 |

Abbreviations: ATE = arterial thromboembolic events; MedDRA = Medical Dictionary for Regulatory Activities.

[a] MedDRA preferred term (Version 15.0).

[b] MedDRA preferred terms included are: neutropenia and neutrophil count decreased. Grade 4 neutropenia was reported in 1 ramucirumab-treated patient.

[c] MedDRA preferred terms included are: angina pectoris, cardiac arrest, cerebral ischaemia, cerebrovascular accident, myocardial infarction, and myocardial ischaemia. A Grade 4 ATE was reported in 1 ramucirumab-treated patient, and Grade 5 ATEs were reported in 2 ramucirumab-treated patients.

[d] Grade 4 intestinal obstruction was reported in 1 ramucirumab-treated patient, and Grade 5 intestinal obstruction was reported in 1 ramucirumab-treated patient.

[e] MedDRA preferred terms included are: rash and rash papular.

The ADRs reported in ≥ 5 % of ramucirumab treated patients in REGARD study are presented in Table 29.

**Table 29 Adverse Drug Reactions in ≥5% of Ramucirumab-Treated Patients All Treated Patients REGARD**

| System Organ Class | Frequency[a] | Event[b,c] | Ramucirumab (N=236) | | Placebo (N=115) | |
|---|---|---|---|---|---|---|
| | | | All Grades Toxicity (%) | Grade 3-4 Toxicity (%) | All Grades Toxicity (%) | Grade 3-4 Toxicity (%) |
| Gastrointestinal Disorders | Very Common | Abdominal Pain[d] | 28.8 | 5.9 | 27.8 | 2.6 |
| | Very Common | Diarrhea | 14.4 | 0.8 | 8.7 | 1.7 |
| Metabolism and Nutrition Disorders | Common | Hypokalemia[e] | 5.9 | 2.1 | 5.2 | 0.9 |
| | Common | Hyponatremia | 5.5 | 3.4 | 1.7 | 0.9 |
| Nervous System Disorders | Common | Headache | 9.3 | 0 | 3.5 | 0 |
| Vascular Disorders | Very Common | Hypertension[f] | 16.1 | 7.6 | 7.8 | 2.6 |

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of treated patients.

[a] Very common - ≥10%; Common ≥1% and <10%. Refer to National Cancer Institute Common Terminology Criteria for Adverse Events criteria (Version 4.0) for each grade of toxicity.

[b] MedDRA preferred term (Version 15.0).

[c] For ramucirumab, none of the ADRs listed above occurred at a CTCAE grade of 5; the only ADRs listed that occurred at a CTCAE grade of 4 were hyponatremia in 1 ramucirumab-treated patient and hypokalemia in 1 ramucirumab-treated patient.

[d] MedDRA preferred terms included are abdominal pain, abdominal pain lower, abdominal pain upper, and hepatic pain.

[e] MedDRA preferred terms included are: blood potassium decreased and hypokalemia.

[f] MedDRA preferred terms included are: blood pressure increased and hypertension.

## Adverse events of special interest (AESI)

AEs of special interest (AESI) included infusion related reactions (IRRs), hypertension, proteinuria, venous and arterial thromboembolic events, bleeding/haemorrhagic events, GI perforation, congestive heart failure, wound-healing complications, fistula, liver failure / liver injury and reversible posterior leukoencephalopathy syndrome (RPLS).

*Infusion related reactions (IRRs)*

IRRs were observed in 11.5% of patients in the ramucirumab phase II trials. In the phase III pivotal trial IRRs one patient with grade 1 IRR in the ramucirumab arm and 2 patients in the placebo arm were observed. Six patients (JVBO: 2 [4.0%], JVBQ: 4 [9.5%]) experienced Grade 3 IRR events and 1 (2.0%) patient in Study JVBO experienced a Grade 4 IRR event. The majority of events occurred during or following a first or second ramucirumab infusion. Symptoms included rigors/tremors, back-pain/spasms, chest pain and/or tightness, chills, flushing, dyspnoea, wheezing, hypoxia, and paraesthesia. In severe cases symptoms included bronchospasm, supraventricular tachycardia, and hypotension.

*Hypertension*

In the pivotal phase III study, hypertension reported as follows: all grades at 16.8% and grade 3 at 7.6% of patients in the ramucirumab arm. Antihypertensive therapy was administered to patients as needed throughout the study. Four patients required dose delay and/or modification for hypertension.

Subjects in the phase II single agent ramucirumab studies experienced hypertension as follows: there were 17 patients with Grade 3 events (JVBO: 7 [14.0%], JVBP: 3 [7.7%], JVBQ: 5 [11.9%], JVBR: 2 [3.3%]) and 2 patients with Grade ≥4 events (JVBP: 1 [2.6%], JVBQ: 1 [2.4%]). Two patients experienced a grade 4 hypertension event that resulted in discontinuation of ramucirumab.

*Proteinuria*

In the pivotal study, proteinuria was observed at 3.0% of patients treated with ramucirumab. One patient experienced grade 3 proteinuria.

In the 4 different phase II studies, 11.0% of patients experienced events of proteinuria that were considered at least possibly related to ramucirumab (as assessed by the investigator); this includes 2 patients with grade 3 proteinuria in studies JVBO and JVBQ, respectively, and 1 patient with a Grade 4 event of proteinuria in Study JVBO that resulted in discontinuation of ramucirumab.

*Thromboembolic events*

Arterial thromboembolic events (ATE) were observed in 1.7% (all grades) of patients treated with ramicurimuab in the pivotal trial. Of these four patients, one experienced a grade 4 and two experienced a grade 5 thromboembolic event, of which two were possibly attributed to exposure to ramucirumab. A total of seven patients across 3 of the single-agent ramucirumab arms phase II experienced ATEs. Grade 3 ATE in two patients and grade 4 ATE in two patients enrolled in the melanoma study were considered related to ramucirumab.

In the phase III REGARD trial venous thrombo-embolic events were observed in 3.8% of patients treated with ramicurimuab. In the ramucirumab arm, there were 3 VTEs of Grade 3 (all events of pulmonary embolism). Across the phase II studies, two patients experienced a grade 3 VTE.

*Bleeding/haemorrhage events*

In the REGARD study, the incidence of bleeding events (any grade) was 12.7% in the ramucirumab arm. Epistaxis was the most frequently reported bleeding event in the ramucirumab arm (4.7%, vs. 0.9% in the placebo arm). The incidence of severe bleeding was 3.4%.

Across the 4 phase II studies, bleeding was reported in 30.4% patients receiving single-agent ramucirumab arms. The majority of events were Grade 1-2, and 3 patients in the HCC trial experienced grade 3-4 events and 3 patients in ovarian cancer experienced Grade 3 events. Gastrointestinal bleeding was most frequently observed in the HCC trial (all grades: 9.4; grade 3 4.8 and grade 4: 2.4%).

*Gastrointestinal perforation*

Two fatal cases in the ramucirumab were reported in the REGARD study. In the phase II ovarian cancer trial, two patients experienced grade 3 and grade 4-5 GI perforation respectively.

*Congestive heart failure*

In the pivotal REGARD III study, one case of grade 1 heart failure was observed in the ramucirumab arm, more than 30 days after the first dose of ramucirumab was administered. One patient in the phase II study JVBP experienced a Grade 2 event of congestive heart failure (left ventricular systolic dysfunction), which was possible related to ramucirumab.

*Wound-healing complications*

No wound-healing complications were observed in either the REGARD or in phase II single-agent ramucirumab trials.

*Fistula*

One grade 3 enterocutaneous fistula was observed in the ramucirumab arm of the REGARD trial and was possibly related to ramucirumab.

In phase II study JVBR (ovarian cancer), one grade1 anal fistula was observed, which resolved during continuation of ramucirumab. One grade 4 genital fistula was observed 25 days after the last dose of ramucirumab in a patient with progression of disease and was not considered related to the study drug.

*Liver failure, liver injury*

Liver toxicity is described under Laboratory findings section below.

*Reversible posterior leuko-encephalopathy syndrome (RPLS)*

In the pivotal phase III REGARD trial and across the 4 supportive phase 2 single-agent ramucirumab studies, no events of RPLS were observed.

*QTc prolongation*

Study JVBK was a multicenter, open-label, evaluated the relationship between ramucirumab (monotherapy 10mg/kg Q 3 weeks for 9 weeks) and corrected QT interval changes in patients with advanced cancer (n=68).

During Cycle 3 the upper limit of the 2-sided 90% CI of the least square means of change from baseline for QTcF was less than 10 msec at all postdose time points. Categorical outlier analysis for Cycle 3 showed 2 patients (3 time points) with a QTcF value >450 msec and ≤ 480 msec. No patient had a QTcF value >480 msec or QT, QTcB, or QTcF value ≥ 500 msec in this population.

An increase in QTcF of >30 msec and ≤ 60 msec was seen in 3 patients (5 time points) in Cycle 3 and an increase of >60 msec was observed in one patient. This patient had the shortest baseline QTcF value (347 msec) among all patients participating in the study. The absolute QTcF values at these visits were 412 msec at Cycle 3, Day 1/Week 1, 03:15 hour and 431 msec at Cycle 3, Day 1/Week 1, 04:15 hour. None of these QTc values exceeded 450 msec.

**Serious adverse event/deaths/other significant events**

**Serious Adverse Events (SAEs)**

An overview of the Treatment-Emergent SAEs occurring in ≥ 2% of patients on the ramucirumab arm is presented in Table 30.

**Table 30 Treatment-Emergent Serious Adverse Events Occurring in ≥2% of Patients on the Ramucirumab Arm, by MedDRA Preferred Term-REGARD Study**

| System Organ Class / Preferred Term[a] | Ramucirumab N = 236 n (%) | | Placebo N = 115 n (%) | |
|---|---|---|---|---|
| | All Events | Related[b] | All Events | Related[b] |
| Patients with any AE | 106 (44.9) | 31 (13.1) | 51 (44.3) | 15 (13.0) |
| **Gastrointestinal Disorders** | | | | |
| Abdominal pain | 10 ( 4.2) | 2 (0.8) | 3 ( 2.6) | 0 |
| Ascites | 6 ( 2.5) | 0 | 3 ( 2.6) | 0 |
| Vomiting | 6 ( 2.5) | 3 (1.3) | 5 ( 4.3) | 1 (0.9) |
| Intestinal obstruction | 5 ( 2.1) | 0 | 0 | 0 |
| Dysphagia | 5 ( 2.1) | 0 | 3 ( 2.6) | 1 (0.9) |
| **General Disorders and Administration Site Conditions** | | | | |
| Disease Progression | 10 (4.2) | 1 (0.4) | 7 (6.1) | 1 (0.9) |
| Multi-organ failure | 6 (2.5) | 0 | 1 ( 0.9) | 0 |
| **Blood and Lymphatic System Disorders** | | | | |
| Anemia | 9 ( 3.8) | 1 (0.4) | 2 ( 1.7) | 0 |
| **Injury, Poisoning and Procedural Complications** | | | | |
| Medication error[c] | 7 ( 3.0) | 3 (1.3) | 1 ( 0.9) | 0 |

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of treated patients; n = number of patients in category.

a MedDRA Version 15.0.

b Relationship as classified by the investigator.

c Medication errors were reported per the protocol procedures. No safety issues were associated with medication errors.

**Deaths**

Among the 78 patients who died while on treatment or within 30 days of the last dose of study therapy, a total of 37 died due to an AE [22 (9.3%) in the ramucirumab arm and 15 (13.0%) in the placebo arm]. Five such deaths in the ramucirumab arm (2.1%) and 2 deaths in the placebo arm (1.7%) were attributable to AEs considered by the investigator related to study therapy. Three patients in the ramucirumab arm (and none in the placebo arm) died due to an AE more than 30 days after the last dose of study therapy; in 2 of the 3 cases the AE that resulted in death developed within 30 days after the last dose of study therapy, but none of the events was considered related to study therapy by the investigator.

In addition to the total of 40 patients who died due to an AE, 16 patients (11 in the ramucirumab arm and 5 in the placebo arm) had TEAEs with an outcome of death (where the primary cause of death was not the adverse event). These were all cases in which disease progression, multi-organ failure, or symptomatic deterioration was recorded as AEs. One of these cases (in the ramucirumab arm) was reported as related to study therapy by the investigator; the event was disease progression. TEAEs with a worst grade of Grade 4 occurred in 16 (6.8%) of ramucirumab-treated patients and 9 (7.8%) of placebo-treated patients. TEAEs with a worst grade of Grade 5 (death) occurred in 35 (14.8%) of ramucirumab-treated patients and 19 (16.5%) of placebo-treated patients.

**Table 31 Summary of deaths-REGARD Study**

|  | Ramucirumab N = 236 n (%) | Placebo N = 115 n (%) |
|---|---|---|
| **All Deaths (%)** | 177 (75.0) | 98 (85.2) |
| Due to Disease Progression[a] | 148 (62.7) | 74 (64.3) |
| Due to an Adverse Event[a] | 25 (10.6) | 15 (13.0) |
| Due to Other Causes[a,b] | 4 (1.7) | 9 (7.8) |
| **Deaths on Treatment or Within 30 Days of Last Dose (%)** | 48 (20.3) | 30 (26.1) |
| Due to Disease Progression[a] | 26 (11.0) | 15 (13.0) |
| Due to an Adverse Event[a] | 22 (9.3) | 15 (13.0) |

**Laboratory findings**

Clinical liver toxicity and abnormal laboratory findings, was reported in 10.2% of patients treated with ramucirumab in the pivotal REGARD study (see Table 32). All liver failure / liver injury events considered at least possibly related to study drug.

**Table 32 Liver Failure/Liver Injury REGARD Safety Population**

| | Ramucirumab Arm N = 236 | | | Placebo Arm N = 115 | | |
|---|---|---|---|---|---|---|
| | **All** | **Gr. 3-4** | **Gr. 5** | **All** | **Gr. 3-4** | **Gr. 5** |
| **All Events[a] (%)** | **24 (10.2)** | **10 (4.2)** | **1 (0.4)** | **9 (7.8)** | **5 (4.3)** | **0** |
| ≥1 clinical term | 12 (5.1) | 5 (2.1) | 1 (0.4) | 4 (3.5) | 1 (0.9) | 0 |
| ≥1 laboratory term | 17 (7.2) | 8 (3.4) | 0 | 6 (5.2) | 5 (4.3) | 0 |
| Only laboratory term | 12 (5.1) | 1 (0.4) | 0 | 5 (4.3) | 3 (2.6) | 0 |
| **Clinical Term** | | | | | | |
| Cholestasis | 1 (0.4) | 0 | 1 (0.4) | 1 (0.9) | 1 (0.9) | 0 |
| Hepatic Failure | 1 (0.4) | 1 (0.4) | 0 | 0 | 0 | 0 |
| Hepatic Function Abnormal | 1 (0.4) | 0 | 0 | 0 | 0 | 0 |
| Hepatic Pain | 0 | 0 | 0 | 1 (0.9) | 0 | 0 |
| Hepatomegaly | 2 (0.8) | 1 (0.4) | 0 | 0 | 0 | 0 |
| Jaundice | 4 (1.7) | 1 (0.4) | 0 | 1 (0.9) | 0 | 0 |
| Jaundice Choleostatic | 1 (0.4) | 1 (0.4) | 0 | 1 (0.9) | 0 | 0 |
| Liver Disorder | 2 (0.8) | 1 (0.4) | 0 | 0 | 0 | 0 |
| **Laboratory Term** | | | | | | |
| Alanine Aminotransferase Increased | 9 (3.8) | 3 (1.3) | 0 | 2 (1.7) | 1 (0.9) | 0 |
| Aspartate Aminotransferase Increased | 9 (3.8) | 3 (1.3) | 0 | 2 (1.7) | 2 (1.7) | 0 |
| Bilirubin Conjugated Increased | 1 (0.4) | 1 (0.4) | 0 | 0 | 0 | 0 |
| Blood Bilirubin Increased | 6 (2.5) | 3 (1.3) | 0 | 1 (0.9) | 1 (0.9) | 0 |
| Gamma-Glutamyltransferase Increased | 1 (0.4) | 0 | 0 | 1 (0.9) | 1 (0.9) | 0 |
| Hepatic Enzyme Increased | 2 (0.8) | 1 (0.4) | 0 | 0 | 0 | 0 |
| Hyperammonemia | 1 (0.4) | 0 | 0 | 0 | 0 | 0 |
| Hyperbilirubinemia | 3 (1.3) | 1 (0.4) | 0 | 3 (2.6) | 3 (2.6) | 0 |
| Transaminase Increased | 0 | 0 | 0 | 1 (0.9) | 0 | 0 |

Abbreviations:  Gr. = Grade; N = number of randomized patients.

a   Patients may have experienced more than 1 event term.

Source:  t_14_03_10_05_ae_liv_saf.rtf.

In the single-arm ramucirumab phase II studies, there were 3 fatal cases of liver failure, all related to the underlying disease. Liver events were highest in the HCC JVBQ study (all grades 26.2%; grade 3 or higher: 16.7%) and in the ovarian cancer JVBO phase II study (15.0% all grades; 6.7% grade 3 or higher).

In the pivotal phase III REGARD study, neutropenia was observed with a higher any-grade (3.8 vs 0.8%) and Grade ≥3 (0.9 and 0%) incidence in the ramucirumab arm compared with the placebo arm respectively.

Any grade hyponatraemia was more frequently observed in the ramucirumab group (5.5%) compared to the placebo group (1.7%), even like grade 3 hyponatraemia events (3.4 vs 0.9%)

Hypokalaemia was observed with a higher Grade ≥3 incidence in the ramucirumab arm (2.1%) compared with the placebo arm (0.9%). However, laboratory shift tables for potassium did not indicate any imbalance between treatment arms.

There were no differences observed in the occurrence of hypoalbumenia in the ramucirumab (5.1%) vs. the placebo group (5.2%).

**Safety in special populations**

No studies were conducted.

**Safety related to drug-drug interactions and other interactions**

No specific safety issues related to possible drug-drug interaction were identified (see also discussion on clinical pharmacology).

**Discontinuation due to adverse events**

Twenty-five subjects in the ramucirumab group (10.5%) of the pivotal REGARD study compared to 7 (6.0%) subjects in the placebo arm discontinued treatment due to AEs. Eleven of these discontinuations in the ramucirumab and 2 in the placebo group were considered at least possibly related to treatment by the investigator.

In the 4 supportive Phase 2 single-agent ramucirumab studies, a total of 32 (16.8%) patients across the studies experienced at least 1 TEAE that led to discontinuation of study drug and included IRR (observed in 5 patients across 2 studies), proteinuria (1 patient each in 3 studies), GI haemorrhage (2 patients in 1 study), intestinal perforation (2 patients in 1 study), and hypertension (1 patient each in 2 studies).

**Post marketing experience**

Not applicable.

**Study I4T-IE-JVBE (RAINBOW)**

**Patient exposure**

The median duration of therapy in the RAINBOW study was 18.9 weeks for the ramucirumab plus paclitaxel arm and 12.1 weeks for the placebo plus paclitaxel arm. Of the 665 patients randomized to treatment, 656 received at least 1 dose of study drug.

The median relative dose intensity of paclitaxel was 87.7% in the ramucirumab plus paclitaxel arm compared to 93.2% in the placebo plus paclitaxel arm and the median cumulative dose of ramucirumab in the ramucirumab plus paclitaxel arm was 70.0 mg/kg compared to 49.0 mg/kg of placebo in the placebo plus paclitaxel arm. Patients in the ramucirumab plus paclitaxel arm had a longer median duration of treatment.

In the ramucirumab plus paclitaxel arm 48.9% of patients had dose delays compared to 28.0% of patients in the placebo plus paclitaxel arm. For the ramucirumab plus paclitaxel arm, the percentage of dose delays was 40.1% for ramucirumab and 38.8% for paclitaxel. A higher percentage of patients had dose modifications of any study drug in the ramucirumab plus paclitaxel arm than in the placebo plus paclitaxel arm. Irrespective of treatment arm, dose modifications of any study drug were primarily due to AEs.

Dose level reductions and dose omissions occurred more frequently in the ramucirumab arm compared to the placebo arm (25.4% versus 7.9% and 50.2% versus 32.8% respectively).

**Table 33 Extent of exposure in the RAINBOW study (Safety Population)**

| | Ramucirumab + Paclitaxel (N = 327) | | Placebo + Paclitaxel (N = 329) | |
|---|---|---|---|---|
| **Any Study Drug** | | | | |
| **Duration of Therapy (Weeks)** | | | | |
| Median | 18.9 | | 12.1 | |
| Mean (SD) | 23.5 (18.6) | | 17.1 (14.7) | |
| Range | 2 - 102 | | 2 - 103 | |
| **Total Number of 28-Day Cycles Received[a]** | | | | |
| Median | 5.0 | | 3.0 | |
| Mean (SD) | 5.7 (4.3) | | 4.3 (3.5) | |
| Range | 1 - 22 | | 1 - 24 | |
| | **Ramucirumab[b]** | **Paclitaxel[c]** | **Placebo[b]** | **Paclitaxel[c]** |
| **Duration of Therapy (Weeks)** | | | | |
| Median | 18.0 | 17.7 | 12.0 | 12.0 |
| Mean (SD) | 23.0 (18.5) | 21.7 (16.7) | 16.4 (13.8) | 16.5 (14.4) |
| Range | 2 - 102 | 2 - 94 | 2 - 101 | 2 - 103 |
| **Total Number of 28-Day Cycles Received[a]** | | | | |
| Median | 4.0 | 4.0 | 3.0 | 3.0 |
| Mean (SD) | 5.7 (4.3) | 5.4 (3.9) | 4.2 (3.3) | 4.2 (3.4) |
| Range | 1 - 22 | 1 - 20 | 1 - 24 | 1 - 24 |
| **Cumulative Dose** | | | | |
| Median | $70.0 \ (mg/kg)^b$ | $813.0 \ mg/m^{2c}$ | $49.0 \ (mg/kg)^b$ | $714.0 \ mg/m^{2c}$ |
| Mean (SD) | 87.8 (68.5) | 1067.9 (815.2) | 64.3 (54.0) | 898.0 (787.4) |
| Range | 8-420 | 79-4399 | 8-363 | 64-5330 |
| **Dose Intensity** | | | | |
| Median | 4.0 $(mg/kg/week)^b$ | 52.6 $(mg/m^2/week)^c$ | 4.0 $(mg/kg/week)^b$ | 55.9 $(mg/m^2/week)^c$ |
| Mean (SD) | 3.9 (0.3) | 50.2 (8.9) | 3.9 (0.25) | 53.7 (7.2) |
| Range | 2.5 - 4.6 | 26.8 - 62.1 | 2.3 - 4.5 | 22.7 - 64.2 |
| **Relative Dose Intensity (%)** | | | | |
| Median | $98.6^b$ | $87.7^c$ | $99.6^b$ | $93.2^c$ |
| Mean (SD) | 96.7 (8.0) | 83.6 (14.8) | 98.4 (6.2) | 89.6 (12.0) |
| Range | 63.5 - 113.9 | 44.6 - 103.6 | 58.7 - 111.7 | 37.9 - 107.0 |

a. Number of cycles received. Patients counted only once using the maximum number of cycles received.
b Based on last available weight prior to each infusion.
c Based on last available body surface area prior to each infusion.


**Adverse events**

An overview of treatment-emergent adverse events is presented in table 34.

**Table 34 Overview of Treatment-Emergent Adverse Events in the RAINBOW study**

| Adverse Event[a] | Ramucirumab plus Paclitaxel N = 327 n (%) | Placebo plus Paclitaxel N = 329 n (%) |
|---|---|---|
| Patients with ≥1 TEAE | 324 (99.1) | 322 (97.9) |
| Patients with ≥1 TE-SAE | 153 ( 46.8) | 139 ( 42.2) |
| Patients with ≥1 TEAE Grade ≥3 | 267 ( 81.7) | 206 ( 62.6) |
| Patients with ≥1 TEAE leading to discontinuation of any study drug[b] | 102 ( 31.2) | 80 ( 24.3) |
|    Patients with ≥1 TEAE leading to discontinuation of ramucirumab/placebo | 68 ( 20.8) | 68 ( 20.7) |
|    Patients with ≥1 TEAE leading to discontinuation of paclitaxel | 91 ( 27.8) | 76 ( 23.1) |
| Patients with a TEAE leading to death | 39 ( 11.9) | 51 ( 15.5) |

Abbreviations: N = total number of treated patients; n = number of patients in category; SAE = serious adverse event; TE = treatment-emergent; TEAE = treatment-emergent adverse event.

a   Patients may be counted in more than 1 category.

b   Any study drug = ramucirumab/placebo or paclitaxel.

Treatment-emergent AE was observed in 99.1% in the ramucirumab plus paclitaxel arm and in 97.9% in the placebo plus paclitaxel arm. A Grade ≥ 3 TEAEs was observed in 81.7% of patients in the ramucirumab plus paclitaxel arm compared to 62.6% of patients in the placebo plus paclitaxel arm. In the ramucirumab plus paclitaxel arm 27.8% of patients discontinued treatment compared to 23.1% of patients in the placebo plus paclitaxel arm. Ramucirumab discontinuation was observed in 20.8% of patients and placebo discontinuation was observed in 20.7% due to TEAEs.

The most frequently reported TEAEs, by preferred terms (at least 20% incidence, regardless of grade), observed at a higher incidence (with at least 5 percentage point difference) in the ramucirumab plus paclitaxel arm than in the placebo plus paclitaxel arm were neutropenia (54.4% vs. 31.0%), decreased appetite (40.1% vs. 31.9%), fatigue (39.8% vs.32.2%), leukopenia (33.9% vs. 21.0%), diarrhea (32.4% vs. 23.1%), abdominal pain (30.9% vs. 20.4%), epistaxis (30.6% vs. 7.0%), vomiting (26.9% vs. 20.7%), oedema peripheral (25.1% vs. 13.7%), hypertension (23.9% vs. 4.9%), and asthenia (21.1% vs. 13.7%).

Grade ≥3 TEAEs occurring in more than 10% of patients in either arm were neutropenia, anemia, leukopenia, hypertension, and malignant neoplasm progression.

Independent of treatment arm, the incidence any-grade neutropenia was higher in Asian patients (77.1% versus 44.5%) than in White patients (43.7% versus 23.5%), whereas the incidence of Grade 3 neutropenia in the ramucirumab plus paclitaxel arm was similar in Asian (22.0% versus 21.8%) and White patients (21.8% versus 11.2%).The incidence of Grade 4 neutropenia was higher in Asian patients (37.6% versus 4.2%) than in White patients (9.7% versus 3.1%) in the ramucirumab plus paclitaxel arm. The incidences of neutropenic infectious complications and febrile neutropenia were similar between White and Asian patients [febrile neutropenia 4 (3.7%) versus (3.4%)]. Thrombocytopenia of any grade was observed in 13.1% of the ramucirumab plus paclitaxel arm patients compared to 6.1% of placebo plus paclitaxel arm patients.

**Adverse Drug Reactions (ADRs)**

Events meeting either of the below criteria in RAINBOW were evaluated as potential ADRs for ramucirumab in combination with paclitaxel in the treatment of advanced gastric cancer:

- The AE incidence in the ramucirumab plus paclitaxel arm was ≥ 10% AND the ramucirumab plus paclitaxel incidence was ≥ the placebo plus paclitaxel incidence.

- The AE incidence in the ramucirumab plus paclitaxel arm was between 1% and 10%, AND ramucirumab plus paclitaxel incidence was ≥ 2 times the placebo plus paclitaxel incidence, AND the number of patients experiencing the event on the ramucirumab plus paclitaxel arm was ≥ 4.

The most common adverse reactions observed in ramucirumab-treated patients are: fatigue/asthenia, neutropenia, leukopenia, diarrhoea, epistaxis, and hypertension (SmPC, section 4.8). An overview of Adverse Drug Reactions occurring in ≥5% of patients is presented in Table 35.

**Table 35 Adverse Drug Reactions in ≥5% of Ramucirumab plus Paclitaxel treated Patients (RAINBOW study)**

| System Organ Class | Frequency[a] | Event[b,c] | Ramucirumab plus Paclitaxel (N=327) | | Placebo plus Paclitaxel (N=329) | |
|---|---|---|---|---|---|---|
| | | | All Grades Toxicity (%) | Grade ≥3 Toxicity (%) | All Grades Toxicity (%) | Grade ≥3 Toxicity (%) |
| Blood and Lymphatic System Disorders | Very Common | Leukopenia[d] | 33.9 | 17.4 | 21.0 | 6.7 |
| | Very Common | Neutropenia[e] | 54.4 | 40.7 | 31.0 | 18.8 |
| | Very Common | Thrombocytopenia | 13.1 | 1.5 | 6.1 | 1.8 |
| Gastrointestinal Disorders | Very Common | Diarrhea | 32.4 | 3.7 | 23.1 | 1.5 |
| | Very Common | Gastrointestinal hemorrhage events[f] | 10.1 | 3.7 | 6.1 | 1.5 |
| | Very Common | Stomatitis | 19.6 | 0.6 | 7.3 | 0.6 |
| General Disorders and Administration Site Disorders | Very Common | Fatigue[g] | 56.9 | 11.9 | 43.8 | 5.5 |
| | Very Common | Peripheral Edema | 25.1 | 1.5 | 13.7 | 0.6 |
| Metabolism and Nutrition Disorders | Very Common | Hypoalbuminemia[h] | 11.0 | 1.2 | 4.9 | 0.9 |
| Renal and Urinary Disorders | Very Common | Proteinuria[i] | 16.8 | 1.2 | 6.1 | 0.0 |
| Respiratory, Thoracic, and Mediastinal Disorders | Very Common | Epistaxis | 30.6 | 0.0 | 7.0 | 0.0 |
| Vascular Disorders | Very Common | Hypertension[j] | 25.1 | 14.7 | 5.8 | 2.7 |

Abbreviations: ADR = adverse drug reaction; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities; N = number of treated patients.

[a] Very common ≥10%. Refer to National Cancer Institute CTCAE (Version 4.02) for each grade of toxicity.
[b] MedDRA preferred term (Version 16.0).
[c] Two patients had Grade 5 GI hemorrhage (1 in each treatment arm) and 1 patient in the placebo plus paclitaxel arm had a Grade 5 hypoalbuminemia event. Among the ADRs listed in the event column, those that occurred at CTCAE Grade 4 were leukopenia (5 patients in the ramucirumab plus paclitaxel arm and 3 patients in the placebo plus paclitaxel arm), neutropenia (62 patients in the ramucirumab plus paclitaxel arm and 11 patients in the placebo plus paclitaxel arm), and GI hemorrhage (1 patient in each arm).
[d] MedDRA preferred terms included leukopenia and white blood cell count decreased.
[e] MedDRA preferred terms included neutropenia and neutrophil count decreased.
[f] MedDRA preferred terms included anal hemorrhage, diarrhea hemorrhage, gastric hemorrhage, gastrointestinal hemorrhage, hematemesis, hematochezia, hemorrhoidal hemorrhage, Mallory-weiss syndrome, melena, esophageal hemorrhage, rectal hemorrhage, and upper gastrointestinal hemorrhage.

**Adverse events of special interest (AESI)**

Adverse events of special interest (AESI) included infusion related reactions (IRR), hypertension, proteinuria, arterial and venous thromboembolic events, bleeding/haermorrhagic events, GI perforation, and congestive heart failure, wound healing complications, fistula, liver failure/liver injury and reversible posterior leukoencephalopathy syndrome (RPLS).

*Infusion related reactions (IRR)*

Any-grade IRR was reported for 5.8% of patients in the ramucirumab plus paclitaxel arm and 3.6% of patients in the placebo plus paclitaxel arm. Grade 3 IRR events were experienced by 0.6% of patients in the ramucirumab plus paclitaxel arm; there was no Grade 3 IRR events observed in the placebo plus paclitaxel arm. There was no Grade 4 or Grade 5 IRR events observed in either treatment arm. In the Phase 2 combination studies including ramucirumab plus paclitaxel, IRRs were observed in Study JVBJ but not in Study JVCA. Of 40 patients in Study JVBJ, 9 (22.5%) had IRRs. The majority of these events were Grade 1 (n=3) or Grade 2 (n=4). One patient (2.5%) had a Grade 3 IRR and 1 patient (2.5%) had a Grade 4 anaphylactic reaction that, per investigator assessment, was related to carboplatin.

The majority of events occurred during or following a first or second ramucirumab infusion. Symptoms included rigors/tremors, back-pain/spasms, chest pain and/or tightness, chills, flushing, dyspnoea, wheezing, hypoxia, and paraesthesia. In severe cases symptoms included bronchospasm, supraventricular tachycardia, and hypotension (SmPC, section 4.4).

*Hypertension*

Hypertension of any grade was observed in 25.1% of patients receiving ramucirumab plus paclitaxel and in 5.8% of patients receiving placebo plus paclitaxel. The incidence of Grade 3 hypertension was observed in 14.7% of patients in the ramucirumab plus paclitaxel arm and in 2.7% of patients in placebo plus paclitaxel arm. There were no Grade 4 or Grade 5 events in either arm. Hypertension resulted in the discontinuation of any study drug for 0.6% of patients in the ramucirumab plus paclitaxel arm, a ramucirumab dose omission for 1.2% of patients in the ramucirumab plus paclitaxel arm and paclitaxel dose omission for 0.6% ofv patients in the ramucirumab plus paclitaxel arm. In the Phase 2 combination studies including ramucirumab plus paclitaxel, hypertensive events were observed in two studies. In Study JVBJ patients received ramucirumab plus paclitaxel plus carboplatin, 6 (15%) of 40 patients had hypertensive events of all grades. the majority being grade 1 or 2. One patient (2.6%) had a Grade 3 hypertensive event. In Study JVCA patients received ramucirumab plus paclitaxel, 5 (16.1%) of 31 patients had hypertensive events of all grades with the majority being Grade 1 or Grade 2. Two (6.5%) patients had a Grade 3 hypertensive event. No Grade 4 or Grade 5 hypertensive events were reported in either Study JVBJ or Study JVCA.

*Proteinuria*

Proteinuria of any grade occurred in 16.8% of patients in the ramucirumab plus paclitaxel arm compared to 6.1% in the placebo plus paclitaxel arm. Grade 3 proteinuria was observed in 1.2% of patients in the ramucirumab plus paclitaxel arm compared to 0 patients in the placebo plus paclitaxel arm. A total of 1.2% of patients in the ramucirumab plus paclitaxel arm experienced proteinuria that led to the discontinuation of any study therapy. In Study JVBJ, 4 patients (10%) out of 40 had proteinuria (3 Grade 1 proteinuria and 1 Grade 2 proteinuria). Per investigator assessment, 3 events were related to ramucirumab. Information on relationship between TEAE and chemotherapy was not collected on the JVBJ TEAE CRF. In Study JVCA, no patients had proteinuria of any grade.

*Thromboembolic events*

Arterial thromboembolic events (ATE) of any grade were observed in 1.8% of patients in the ramucirumab plus paclitaxel arm compared to 1.5% in the placebo plus paclitaxel arm. Grade 3 ATE was observed in 0.3% of patients in the ramucirumab plus paclitaxel arm compared to 0.6% in the placebo plus paclitaxel arm. Grade 4 ATEs were observed in 0.3% of patients in the ramucirumab plus paclitaxel arm. There were no grade 5 ATEs reported in the ramucirumab plus paclitaxel arm. In phase II Study JVBJ, 2 (5%) of 40 patients had ATEs, none of which were Grade ≥3. In 1 case, the ATE was a Grade 2 cerebral ischemia event, assessed by investigator as possibly related to ramucirumab. The other ATE was a Grade 1 angina pectoris event, assessed by investigator as unrelated to ramucirumab. In Study JVCA, no patients had an ATE of any grade.

Venous thromboembolic events (VTEs) occurred in 4.0% of patients in the ramucirumab plus paclitaxel arm and in 5.5% of patients in the placebo plus paclitaxel arm. Grade 3 VTEs were observed in 2.1% of patients in the ramucirumab plus paclitaxel arm and in 2.4% of patients in the placebo plus paclitaxel arm. No Grade 4 VTEs occurred in the ramucirumab plus paclitaxel arm. Grade 5 was observed in 0.3% of patients in the ramucirumab plus paclitaxel. In Study JVBJ, 2 (5%) of 40 patients had VTEs. Both patients in Study JVBJ with VTEs had Grade 4 pulmonary embolism. Per investigator assessment, both events were possibly related to ramucirumab. In Study JVCA, 1 (3.2%) of 31 patients had a VTE, which was a Grade 3 pulmonary embolism. Per investigator assessment, the event was possibly related to ramucirumab. The patient was hospitalized. The event was considered ongoing at PDBL date. No action was taken with respect to ramucirumab administration.

*Bleeding/haemorrhage events*

The incidence of bleeding events of any grade was observed in 41.9% of patients in the ramucirumab plus paclitaxel arm compared to 17.9% of patients in the placebo plus paclitaxel arm. Epistaxis was the most frequently reported bleeding event of bleeding in the ramucirumab plus paclitaxel arm (30.6% vs. 7.0% in the placebo plus paclitaxel arm). The incidence of severe bleeding events (Grade ≥3) was observed in 4.3% of patients in the ramucirumab plus paclitaxel arm and in 2.4% of patients in the placebo plus paclitaxel arm. Gastrointestinal bleeding was the most frequently observed bleeding event (all grade GI bleeding events 10.1% in ramucirumab plus paclitaxel arm patients compared to 6.1% in the placebo plus paclitaxel arm patients). In Study JVBJ, 18 (45%) of 40 patients had bleeding/haemorrhage events that included epistaxis, gingival bleeding, haemoptysis, contusion, blood blister, conjunctival hemorrhage, diarrhea haemorrhagic, hematemesis, petechiae, and vessel puncture site hematoma. The majority of these bleeding/haemorrhage events were Grade 1 or Grade 2 epistaxis (12 of 18 patients with bleeding events). No bleeding/haemorrhage events were Grade ≥3. Per investigator assessment, 10 of the 18 bleeding/haemorrhage events in Study JVBJ were possibly related to ramucirumab. One patient in Study JVBJ had a GI haemorrhage event reported as Grade 1 diarrhea haemorrhage, assessed by investigator as unrelated to ramucirumab. In Study JVCA, 11 (35.5%) of 31 patients had bleeding/haemorrhage events that included epistaxis, haemoptysis, and contusion. The vast majority of these bleeding/haemorrhage events were Grade 1 or Grade 2 epistaxis (10 of 11 patients with bleeding events). No bleeding/haemorrhage events were Grade ≥3. Per investigator assessment, 10 of the 11 bleeding/haemorrhage events in Study JVCA were possibly related to ramucirumab. No bleeding/haemorrhage events were Grade ≥3 in study JVCA.

*Gastrointestinal perforation*

Any grade gastrointestinal perforation (GI) event was observed in 1.2% of patients in the ramucirumab plus paclitaxel arm and in 0.3% of patients in the placebo plus paclitaxel arm. In the Phase 2 combination studies including ramucirumab plus paclitaxel, no GI perforation events were observed.

*Congestive Heart Failure*

All grades Congestive heart failure (CHF) events were observed in 2.4% of patients in the ramucirumab plus paclitaxel arm compared to 1.2% of patients in the placebo plus paclitaxel arm. Grade 3 CHF was observed in 0.6% of patients in the ramucirumab plus paclitaxel arm compared to 0.3% of patients in the placebo plus paclitaxel arm. In the Phase 2 combination studies (JVBJ and JVCA) including ramucirumab plus paclitaxel, no CHF events occurred.

*Wound healing complications*

In RAINBOW and in the Phase 2 combination studies including ramucirumab plus paclitaxel, no wound-healing complications were observed.

*Fistula*

In RAINBOW and in the Phase 2 combination studies including ramucirumab plus paclitaxel, no fistula events occurred.

*Liver failure, liver injury*

In RAINBOW study, the incidence of any-grade liver failure / liver injury events, including clinical and laboratory events, in the ramucirumab plus paclitaxel arm was 16.5% ( see Laboratory findings section below).

In study JVBJ no patient had liver failure/liver injury events. In Study JVCA, 3 (9.7%) patients had liver failure/liver injury events identified by laboratory terms (without clinical symptoms) of ALT increased and AST increased, all of which were Grade 1. Per investigator assessment, 3 of the 4 laboratory term events (1 ALT increased and 2 AST increased) were possibly related to ramucirumab.

*Reversible Posterior Leukoencephalopathy Syndrome (RPLS)*

In RAINBOW and in the Phase 2 combination studies including ramucirumab plus paclitaxel, no events of RPLS were observed.

**Serious adverse events/deaths/other significant events**

**Serious Adverse Events (SAEs)**

An overview of the Treatment-Emergent SAEs occurring in ≥2% of patients on the ramucirumab plus paclitaxel arm is presented in Table 36.

**Table 36 Treatment-Emergent Serious Adverse Events Occurring in ≥2% of Patients in the Ramucirumab plus Paclitaxel Arm, by MedDRA Preferred Term- RAINBOW Study**

| Preferred Term[a] | Ramucirumab plus Paclitaxel N = 327 n (%) | | Placebo plus Paclitaxel N = 329 n (%) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| **Patients with any TE-SAE** | **153 (46.8)** | **139 (42.5)** | **139 (42.2)** | **122 (37.1)** |
| Malignant Neoplasm Progression | 40 (12.2) | 39 (11.9) | 45 (13.7) | 45 (13.7) |
| Neutropenia | 12 (3.7) | 12 (3.7) | 3 (0.9) | 3 (0.9) |
| Abdominal Pain | 8 (2.4) | 7 (2.1) | 10 (3.0) | 7 (2.1) |
| Febrile Neutropenia | 8 (2.4) | 8 (2.4) | 4 (1.2) | 4 (1.2) |
| General Physical Health Deterioration | 8 (2.4) | 7 (2.1) | 9 (2.7) | 7 (2.1) |
| Anemia | 7 (2.1) | 6 (1.8) | 6 (1.8) | 5 (1.5) |
| Pyrexia | 7 (2.1) | 2 (0.6) | 6 (1.8) | 0 |
| Vomiting | 7 (2.1) | 4 (1.2) | 9 (2.7) | 8 (2.4) |

**Deaths**

Of the 89 patients who died while on treatment or within 30 days of the last dose of study treatment, 25 died due to an AE [11 (3.4%) in the ramucirumab plus paclitaxel arm and 14 (4.3%) in the placebo plus paclitaxel arm]; 8% of the patients in the ramucirumab plus paclitaxel arm died due to progressive disease compared to 11.6% of patients in the placebo plus paclitaxel arm. Additionally, 2 patients in the ramucirumab plus paclitaxel arm and 1 patient in the placebo plus paclitaxel arm died due to an AE more than 30 days after the last dose of study treatment. For all 3 patients, the onset of the AEs that resulted in death was within 30 days after the last dose of study treatment. The AEs were malabsorption/anorexia and elevated serum creatinine/carbamid (urea) level from the ramucirumab plus paclitaxel arm, and paralytic ileus from the placebo plus paclitaxel treatment arm. Among these Grade 5 AEs that occurred more than 30 days after last dose of study treatment, only the AE of malabsorption was considered related to ramucirumab by the investigator.

**Table 37 Summary of deaths —Safety population- RAINBOW study**

| | Ramucirumab + Paclitaxel N = 327 n (%) | Placebo + Paclitaxel N = 329 n (%) |
|---|---|---|
| **All Deaths[a]** | 255 (78.0) | 256 (77.8) |
| Disease Progression | 236 (72.2) | 233 (70.8) |
| Adverse Event | 13 (4.0) | 15 (4.6) |
| Other | 6 (1.8) | 8 (2.4) |
| **Deaths on treatment or within 30 days of last dose [a]** | 37 (11.3) | 52 (15.8) |
| Disease Progression | 26 (8.0) | 38 (11.6) |
| Adverse Event | 11 (3.4) | 14 (4.3) |

a Cause of death as classified by the investigator.

### Laboratory findings

The incidence of any-grade liver failure/liver injury events, including clinical and laboratory events, in the ramucirumab plus paclitaxel arm was 16.5%. Table 38 summarises events of liver failure/liver injury, including liver infection.

**Table 38 Liver Failure/Liver Injury RAINBOW Safety Population**

| | Ramucirumab + Paclitaxel Arm N = 327 n (%) | | | Placebo + Paclitaxel Arm N = 329 n (%) | | |
|---|---|---|---|---|---|---|
| | All | Gr. 3 | Gr. 4 | All | Gr. 3 | Gr. 4 |
| **All Events (%)[a]** | 54 (16.5) | 12 (3.7) | 3 (0.9) | 41 (12.5) | 11 (3.3) | 2 (0.6) |
| ≥1 clinical term | 6 (1.8) | 1 (0.3) | 0 | 9 (2.7) | 2 (0.6) | 0 |
| ≥1 laboratory term | 52 (15.9) | 11 (3.4) | 3 (0.9) | 38 (11.6) | 10 (3.0) | 2 (0.6) |
| Only laboratory term[b] | 48 (14.7) | 10 (3.1) | 2 (0.6) | 32 (9.7) | 6 (1.8) | 2 (0.6) |
| **Clinical Term** | | | | | | |
| Cholestasis | 2 (0.6) | 0 | 0 | 1 (0.3) | 0 | 0 |
| Hepatic Function Abnormal | 0 | 0 | 0 | 2 (0.6) | 0 | 0 |
| Hepatocellular injury | 0 | 0 | 0 | 1 (0.3) | 0 | 0 |
| Hepatomegaly | 2 (0.6) | 0 | 0 | 1 (0.3) | 0 | 0 |
| Jaundice | 3 (0.9) | 1 (0.3) | 0 | 3 (0.9) | 1 (0.3) | 0 |
| Jaundice Choleostatic | 0 | 0 | 0 | 2 (0.6) | 1 (0.3) | 0 |
| Ocular icterus | 1 (0.3) | 0 | 0 | 0 | 0 | 0 |
| **Laboratory Term** | | | | | | |
| Alanine Aminotransferase Increased | 20 (6.1) | 4 (1.2) | 0 | 18 (5.5) | 2 (0.6) | 1 (0.3) |
| Aspartate Aminotransferase Increased | 27 (8.3) | 6 (1.8) | 0 | 17 (5.2) | 5 (1.5) | 0 |
| Blood Bilirubin Increased | 16 (4.9) | 3 (0.9) | 0 | 11 (3.3) | 5 (1.5) | 0 |
| Gamma-Glutamyltransferase Increased | 11 (3.4) | 1 (0.3) | 2 (0.6) | 6 (1.8) | 2 (0.6) | 1 (0.3) |
| Hepatic Enzyme Increased | 3 (0.9) | 3 (0.9) | 0 | 1 (0.3) | 0 | 0 |
| Hyperammonemia | 1 (0.3) | 0 | 0 | 0 | 0 | 0 |
| Hyperbilirubinemia | 7 (2.1) | 1 (0.3) | 0 | 7 (2.1) | 2 (0.6) | 0 |
| Hypertransaminasaemia | 2 (0.6) | 1 (0.3) | 0 | 0 | 0 | 0 |
| Liver Function Test Abnormal | 2 (0.6) | 1 (0.3) | 1 (0.3) | 1 (0.3) | 0 | 0 |
| Transaminases Increased | 0 | 0 | 0 | 2 (0.6) | 0 | 0 |
| Liver Infection | 0 | 0 | 0 | 0 | 0 | 0 |

### Safety in special populations

No studies were conducted.

**Safety related to drug-drug interactions and other interactions**

No specific safety issues related to possible drug-drug interaction were identified (see also discussion on clinical pharmacology).

**Discontinuation due to adverse events**

In each arm, the same percentage of patients experienced TEAEs leading to discontinuation (20.8% in the ramucirumab plus paclitaxel arm versus 20.7% in the placebo plus paclitaxel arm). TEAEs were observed in 27.8% of patients in the ramucirumab plus paclitaxel arm compared to 23.1% in the placebo plus paclitaxel arm.

TEAEs leading to the discontinuation of ramucirumab or placebo, respectively, included malignant neoplasm progression (4.0% vs. 4.6%), fatigue (1.8% vs. 0.9%), general physical health deterioration (1.8% vs. 1.5%), ascites (1.2% vs. 0.6%), and proteinuria (1.2% vs. 0). The most frequent (at least 2% incidence in the ramucirumab plus paclitaxel arm) TEAEs leading to the discontinuation of paclitaxel were neutropenia (4.0% vs. 0.3%), malignant neoplasm progression (3.4% vs. 4.6%), thrombocytopenia (2.8% vs. 0), and neuropathy peripheral (2.1% vs. 0.6%).

**Post marketing experience**

Not applicable.

## 2.6.1. Discussion on clinical safety

Clinically relevant ADRs reported in ≥ 1% and < 5% of the ramucirumab plus paclitaxel-treated patients in RAINBOW were gastrointestinal perforation (1.2% ramucirumab plus paclitaxel versus 0.3% for placebo plus paclitaxel) and sepsis (3.1% ramucirumab plus paclitaxel versus 1.8% placebo plus paclitaxel) (see SmPC, section 4.8).

Clinically relevant ADRs reported in ≥ 1% and < 5% of the ramucirumab treated patients in REGARD were: neutropenia, arterial thromboembolic events, intestinal obstruction, epistaxis, and rash (see SmPC, section 4.8).

Clinically relevant reactions (including Grade ≥ 3) associated with antiangiogenic therapy observed in ramucirumab-treated patients across clinical studies were: arterial thromboembolic events, infusion-related reactions and proteinuria (see SmPC, section 4.8).

Grade ≥3 TEAEs occurring in more than 10% of patients in either arm were neutropenia, anaemia, leukopenia, hypertension, and malignant neoplasm progression.

A similar percentage of patients in both treatment arms had any-grade TE-SAEs (46.8% [ramucirumab plus paclitaxel arm] versus 42.2% [placebo plus paclitaxel arm]), while a higher percentage of patients in the ramucirumab plus paclitaxel arm than in the placebo plus paclitaxel arm had Grade ≥ 3 TE-SAEs (42.5% versus 37.1%, respectively).

The most frequently reported TE-SAE with a higher incidence in the ramucirumab plus paclitaxel arm (54.4%) was neutropenia .This event did not result in the death of any patient however it  did not result in an increased incidence of neutropenic fever which was low and similar in both treatments. Neutropenia is considered an identified risk in the Risk Management Plan.

Infusion-related reactions (IRRs) were reported in clinical studies with ramucirumab. The infusion rate of ramucirumab should be reduced by 50 % for the duration of the infusion and all subsequent infusions if the patient experiences a grade 1 or 2 infusion-related reaction. Ramucirumab should be immediately and permanently discontinued in the event of a grade 3 or 4 infusion-related reaction (see SmPC, section 4.2). Infusion-related reactions are considered an identified risk in the Risk Management Plan.

An increased incidence of severe hypertension was reported in patients receiving ramucirumab as compared to placebo. In most cases hypertension was managed using standard antihypertensive treatment. Patients with uncontrolled hypertension were excluded from the trials: ramucirumab treatment should not be initiated in such patients until and unless their pre-existing hypertension is controlled. Patients who are treated with ramucirumab should have their blood pressure monitored. Ramucirumab should be temporarily discontinued for severe hypertension until controlled with medical management. Ramucirumab should be permanently discontinued if medically significant hypertension cannot be controlled with antihypertensive therapy (see SmPC, sections 4.2 and 4.4). In general hypertension could be adequately managed with concurrent use of (combinational) antihypertensives. Hypertension is considered an identified risk in the Risk Management Plan.

The incidence of proteinuria is low except for Asian patients in whom a higher incidence was observed, especially when ramucirumab was combined with paclitaxel. However, the clinical relevance of proteinuria in patients with a poor prognosis is questionable.  Proteinuria was not related to arterial hypertension neither to the length of exposure to ramucirumab.

Patients should be monitored for the development or worsening of proteinuria during ramucirumab therapy. If the urine protein is ≥ 2+ on a dipstick, a 24 hour urine collection should be performed. Ramucirumab therapy should be temporarily discontinued if the urine protein level is ≥ 2 g/24 hours. Once the urine protein level returns to <2 g/24 hours, treatment should be resumed at a reduced dose level (6 mg/kg every 2 weeks). A second dose reduction (to 5 mg/kg every 2 weeks) is recommended if a urine protein level ≥ 2 g/24 hours reoccurs (see SmPC, sections 4.4 and 4.2). Ramucirumab therapy should be permanently discontinued if the urine protein level is >3 g/24 hours or in the event of nephrotic syndrome (see SmPC, section 4.2).  Proteinuria is considered an identified risk in the Risk Management Plan.

The observed higher frequency of arterial thromboembolic events is in line with the pharmacological inhibition of VEGFR2 by ramucirumab. Discontinuation of ramucirumab has been advised in patients experiencing a severe ATE (see SmPC, section 4.4). Arterial thromboembolic events are considered an identified risk in the Risk Management Plan.

Ramucirumab is an antiangiogenic therapy and has the potential to increase the risk of severe bleeding. Ramucirumab should be permanently discontinued in patients who experience severe bleeding: NCI CTCAE Grade 3 or 4 bleeding (see SmPC, section 4.2). Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. Severe gastrointestinal haemorrhage, including fatal events, was reported in patients with gastric cancer treated with ramucirumab in combination with paclitaxel (see SmPC, section 4.4). Bleeding/Haemorrhagic Events are considered an identified risk in the Risk Management Plan.

The occurrence of GI perforation is in line with the pharmacological inhibition of VEGFR2 by ramucirumab leading to inhibition of angiogenesis. Therefore, the two fatal cases of GI perforation in the ramucirumab arm are considered possibly related to the use of ramucirumab. Gastrointestinal perforation is considered an identified risk in the Risk Management Plan.

Ramucirumab should be permanently discontinued in patients who experience gastrointestinal perforations (see SmPC, sections 4.2 and 4.4).

Although the overall observed frequency of fistulas was low in the REGARD and phase II trials is not increased for the ramucirumab arm compared to placebo, the occurrence of fistula might be in line with the pharmacological inhibition of VEGFR2 by ramucirumab leading to inhibition of angiogenesis, rendering tissues more susceptible for fistula formation. For several anti-antiangiogenic agents, GI perforation has been associated with longer term use of these agents. Since exposure to ramucirumab in the REGARD trial is only 8 weeks, exposure to ramucirumab in the REGARD study might have been too short for patients to develop this serious ADR and incidence of GI perforation might have been underestimated. Fistula formation is considered an identified risk in the Risk Management Plan.

Patients may be at increased risk for the development of fistula when treated with Cyramza. Ramucirumab treatment should be discontinued in patients who develop fistula (see SmPC, sections 4.2 and 4.4).

In phase II JVBQ study among hepatocellular carcinoma patients, liver events were more common than in other patient populations. Therefore, pre-existing liver disease, like cirrhosis and/or hepatorenal syndrome (frequently observed in these patients), might negatively impact the safety of ramucirumab. Liver failure/liver injury is considered an identified risk in the Risk Management Plan.

Ramucirumab should be used with caution in patients with severe liver cirrhosis (Child-Pugh B or C), cirrhosis with hepatic encephalopathy, clinically significant ascites due to cirrhosis, or hepatorenal syndrome. In these patients, ramucirumab should only be used if the potential benefits of treatment are judged to outweigh the potential risk of progressive hepatic failure (see SmPC, section 4.4).

The impact of ramucirumab has not been evaluated in patients with serious or non-healing wounds. In a study conducted in animals, ramucirumab did not impair wound healing. However, since ramucirumab is an antiangiogenic therapy and may have the potential to adversely affect wound healing, ramucirumab treatment should be withheld for at least 4 weeks prior to scheduled surgery. The decision to resume ramucirumab following surgical intervention should be based on clinical judgment of adequate wound healing (see section 4.4). If a patient develops wound healing complications during therapy, ramucirumab should be discontinued until the wound is fully healed (see section 4.2). Impaired wound healing is considered an identified risk in the Risk Management Plan.

In the pivotal REGARD study, one case of grade 1 CHF was observed in the ramucirumab arm, more than 30 days after the first dose of ramucirumab was administered. One patient in the phase II study JVBP experienced a Grade 2 event of congestive heart failure (left ventricular systolic dysfunction), which was possible related to ramucirumab. All grades CHF events were observed in 2.4% of patients in the ramucirumab plus paclitaxel arm compared to 1.2% of patients in the placebo plus paclitaxel arm. Grade 3 CHF was observed in 0.6% of patients in the ramucirumab plus paclitaxel arm compared to 0.3% of patients in the placebo plus paclitaxel arm. Congestive heart failure is considered an identified risk in the Risk Management Plan.

Anaemia has been reported with some anti-angiogenic agents and has been observed in ramucirumab studies, including some Grade 3 and Grade 4 events. Anaemia has been categorized as a potential risk (see Risk Management Plan).

Abdominal pain is a very common symptom in gastric cancer patients. Increased risk of abdominal pain has been associated with anti-angiogenic therapeutic agents. The majority of events have been reported as Grade 1 or Grade 2. Abdominal pain has been categorized as a potential risk (see Risk Management Plan).

Two cases of Reversible Posterior Leukoencephalopathy Syndrome have been reported in a blinded study. As study therapy remains blinded and the case swere confounded by combination therapy, including 5-fluorouracil (5-FU), for which RPLS is expected, the safety of study subjects is not considered to be affected by continuation of therapy with ramucirumab. Considering the potential severity of this rare usually reversible event, RPLS has been categorized as a potential risk (see Risk Management Plan).

Venous thrombo-embolic events (VTEs) were more frequently reported in the placebo (7.0%) than in the ramucirumab arm (3.8%) of the phase III REGARD trial. In the ramucirumab arm, there were 3 VTEs of Grade 3 (all events of pulmonary embolism). Across the phase II studies, two patients experienced a grade 3 VTE. In Rainbow study, VTEs occurred in 4.0% of patients in the ramucirumab plus paclitaxel arm. Grade 3 VTEs were observed in 2.1% of patients in the ramucirumab plus paclitaxel arm. No Grade 4 VTEs occurred in the ramucirumab plus paclitaxel arm. Grade 5 was observed in 0.3% of patients in the ramucirumab plus paclitaxel. Venous thrombo-embolic events have been categorized as a potential risk (see Risk Management Plan).

Cyramza has no known influence on the ability to drive and use machines. If patients experience symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides (see SmPC, section 4.7).

There is no data on overdose in humans. Cyramza has been administered in a Phase 1 study up to 10 mg/kg every two weeks without reaching a maximum tolerated dose. In case of overdose, supportive therapy should be used (see SmPC, section 4.9).

From the safety database,  a summary of ADRs reported in ≥  5 % of ramucirumab treated patients in RAINBOW and REGARD study  have been included in the Summary of Product Characteristics (see SmPC, section 4.8).

## 2.6.2. Conclusions on the clinical safety

The safety profile of ramucirumab is generally acceptable and in line with other agents targeting inhibition of the VEGF/VEGFR axis, with fatigue/asthenia, neutropenia, leukopenia, diarrhoea, epistaxis and hypertension being the most common adverse reactions observed in ramucirumab-treated patients.

## 2.7. Pharmacovigilance

**Detailed description of the pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

## 2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

**PRAC Advice**

Based on the PRAC review of the Risk Management Plan version 3.0, the PRAC considers by consensus that the risk management system for ramucirumab (Cyramza) for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy in combination with paclitaxel and  for the treatment of adult patients (monotherapy) with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

**Table 39 Summary of the Safety Concerns**

| Summary of safety concerns | |
|---|---|
| **Important Identified Risks** | Arterial thromboembolic events |
| | Hypertension |
| | Infusion-related reaction |
| | Proteinuria |
| | GI perforation |
| | Bleeding/Haemorrhagic events |
| | Impaired wound healing |
| | Neutropenia |
| | Fistula formation |
| | Liver failure / liver injury |
| | Congestive heart failure |
| **Important Potential Risks** | Reversible Posterior Leukoencephalopathy Syndrome |
| | Anaemia |
| | Abdominal pain |
| | Reproductive and developmental toxicity |
| | VTE |
| **Missing Information** | Carcinogenicity |
| | Genotoxicity |

The PRAC agreed.

- **Pharmacovigilance plans**

**Table 40 On-going and planned studies in the PhV development plan**

| Activity/Study title (category 1-3) | Objectives | Safety concerns addressed | Status Planned, started, | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| **PASS/Registry:**<br><br>**I4T-MC-JVDD:** Safety and Effectiveness of Ramucirumab in Patients with Advanced Gastric Cancer in the European Union and North America: A Prospective Observational Registry<br><br>**Category 3** | **Primary objective**:<br>To evaluate 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<br><br>**Secondary objective:**<br>To evaluate 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 | Potential safety signals in special populations, such as elderly, patients with cardiac comorbidities, hepatic impairment and renal impairment | Planned | Final study report estimated for completion Q4 2021 |

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

- **Risk minimisation measures**

**Table 41: Summary table of Risk Minimisation Measures**

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| **Important identified risks** | | |
| Arterial Thromboembolic Events | Proposed text in SmPC | None proposed |
| Hypertension | Proposed text in SmPC | None proposed |
| Infusion-Related Reactions | Proposed text in SmPC | None proposed |
| Proteinuria | Proposed text in SmPC | None proposed |
| Gastrointestinal perforation | Proposed text in SmPC | None proposed |
| Bleeding/Haemorrhagic events | Proposed text in SmPC | None proposed |
| Impaired wound healing | Proposed text in SmPC | None proposed |
| Neutropenia | Proposed text in SmPC | None proposed |
| Fistula formation | Proposed text in SmPC | None proposed |
| Liver failure/liver injury | Proposed text in SmPC | None proposed |
| Congestive heart failure | Not applicable | None proposed |
| **Important potential risks** | | |
| Reversible Posterior Leukoencephalopathy Syndrome | Not applicable | None proposed |
| Anaemia | Proposed text in SmPC | None proposed |
| Abdominal pain | Proposed text in SmPC | None proposed |
| Reproductive and developmental toxicity | Proposed text in SmPC | None proposed |
| Venous Thromboembolic Events | Not applicable | None proposed |
| **Missing Information** | | |
| Carcinogenicity, genotoxicity | Proposed text in SmPC | None proposed |

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

## 2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

# 3. Benefit-Risk Balance

### *Benefits*

**Beneficial effects**

*Ramucirumab+paclitaxel combination therapy*

The results of RAIBOW study, has provided convincing evidence of clinical efficacy of ramucirumab plus paclitaxel compared to paclitaxel alone in terms of the primary endpoint OS (HR 0.807, 95%: CI 0.678, 0.962, p=0.0169), with a gain in median OS of 2.2 months in favour of ramucirumab + paclitaxel (median OS 9.6 months vs 7.4 months, respectively). The effect on OS was observed in several subgroups of the population.

Treatment with ramucirumab plus paclitaxel significantly reduced the risk of disease progression or death by 37% (HR = 0.635; 95% CI: 0.536, 0.752; p<0.0001), representing a 52% (1.5 months) longer median PFS in the ramucirumab plus paclitaxel arm compared with the placebo plus paclitaxel arm (4.4 months vs. 2.9 months). The robustness of the main PFS analysis results was supported by pre-specified sensitivity analyses, as demonstrated by consistent HRs between 0.599 and 0.649 with p<0.0001.

More patients in the ramucirumab plus paclitaxel arm had improved or stable EORTC QLQ-C30 Global Health status at each visit during the treatment compared to the placebo plus paclitaxel arm.

*Ramucirumab monotherapy*

Ramucirumab monotherapy was associated with a statistically significant improvement in the primary endpoint of OS for ramucirumab plus BSC versus placebo plus BSC (HR = 0.776; 95% CI: 0.603, 0.998; p=0.0473), with gain of 1.4 months of median OS in favour of RAMUCIRUMAB (median OS 5.2 months vs 3.8 months, respectively).

Treatment with ramucirumab significantly reduced the risk of disease progression or death by 52% (HR = 0.483; 95% CI: 0.376, 0.620; p<0.0001), resulting in a 62% longer median time to disease progression in the ramucirumab arm. Progression free survival at 12 weeks was 40.1% in the ramucirumab arm versus 15.8% in the placebo arm (p<0.0001). Improvements in PFS were observed with ramucirumab across all subgroups.

**Uncertainty in the knowledge about the beneficial effects**

*Ramucirumab+paclitaxel combination therapy*

Tumour tissue of patients included in the RAINBOW study was not tested for HER2 overexpression. Based on limited data from REGARD patients with HER2 positive gastric or GEJ adenocarcinoma and patients previously treated with trastuzumab (in RAINBOW), it is considered unlikely that Cyramza has a detrimental effect or that it has no effect on patients with HER2 positive gastric cancer (see SmPC section 5.1).

*Ramucirumab monotherapy*

One remaining uncertainty is whether the dose selection in the monotherapy indication has been optimal. Although there was some evidence for ramucirumab activity there was no clear dose effect relation in the dose finding studies (2-20 mg/kg). Evaluation of every-2-week (6 to 10 mg/kg) and every-3-week (15 to 20 mg/kg) dose regimens did not result in a maximum tolerated dose. All dose regimens were well tolerated. No phase 2 study in gastric cancer was conducted to support the dose selection. Additional follow-up will further investigate the optimal dose (see discussion on clinical efficacy).

*Risks*

**Unfavourable effects**

Overall, the safety profile of ramucirumab was consistent across studies and in line with other agents targeting inhibition of the VEGFR: the most common adverse reactions associated with ramucirumab treatment (as a single agent or in combination with paclitaxel) were fatigue/asthenia, neutropenia, leukopenia, diarrhoea, epistaxis, and hypertension.

In combination treatment (RAINBOW study), the most frequently reported adverse drug reactions with a higher incidence in the ramucirumab plus paclitaxel arm was neutropenia (54.4% *v.* 31.0). This event did not result in the death of any patient and did not result in an increased incidence of neutropenic fever which was low and similar in both treatments. Adverse drug reactions of grade $\geqslant$ 3 higher with combination treatment included neutropenia (40.7% vs. 18.8%), leukopenia (17.4% vs. 6.7%), hypertension (14.7% vs. 2.7%) and fatigue (11.9% vs. 5.0%). However, the percentage of patients experiencing TEAEs leading to discontinuation was similar between treatment groups (20.8% in the ramucirumab plus paclitaxel arm versus 20.7% in the placebo plus paclitaxel arm). The proportion of deaths considered by the investigator related to study therapy was similar between treatment groups (3.4% v. 4.3% for ramucirmab+paclitaxel v. placebo+paclitaxel, respectively).

In monotherapy (REGARD study), hypertension (16.1% vs. 7.6%), diarrhea (14.4% v. 8.7%), and headache (9.3% v. 3.5%) were more frequent in the ramucirumab group. Adverse drug reactions of grade $\geqslant$ 3 higher more frequently associated with monotherapy treatment included hypertension (7.6% v. 2.6%) and abdominal pain (5.9% v. 2.6%). The proportion of deaths considered by the investigator related to study therapy was similar between treatment groups (2.1% v. 1.7% for ramucirmab v. placebo, respectively).

**Uncertainty in the knowledge about the unfavourable effects**

No specific uncertainties about the unfavourable effects raised concerns outside those mentioned in the RMP (see discussion on clinical safety and RMP).

*Benefit-risk balance*

**Importance of favourable and unfavourable effects**

In combination with paclitaxel, the OS benefit is considered clinically relevant and robustly demonstrated (difference in median OS of 2.2 months). Results in key secondary endpoints supported the observed improvement in overall survival. Furthermore, measures of EORTC QLQ-C30 Global Health status also tended to favour ramucirumab + paclitaxel treated patients over placebo+paclitaxel ones. The results are considered to be mature, consistent and of clinical relevance.

The benefit in terms of OS when ramucirumab is administered as monotherapy in patients with progressive advanced gastric cancer or gastro-oesophageal adenocarcinoma previously treated with 5FU and/or platinum containing chemotherapy, although less pronounced compared to the combination therapy (difference in median OS of 1.4 months compared to 2.2 months), is considered clinical relevant. The results obtained for the secondary endpoint, PFS, are in line with the effect on OS.

The toxicity associated with ramucirumab was expected based on the mechanism of action. The incidence of adverse drug reactions was higher for the combination treatment of ramucirumab+paclitaxel compared to placebo+paclitaxel but did not result in a higher proportion of treatment-related deaths or treatment discontinuation. In monotherapy, hypertension, diarrhea, and headache were more frequent with ramucirumab compared to placebo but the differences in grade 3 or higher adverse drug reactions were small. The proportion of treatment-related deaths was also similar between groups.

**Benefit-risk balance**

For the ramucirumab and paclitaxel combination, the observed improvement in overall survival has clearly been shown. In view of the reasonably well tolerated toxicity, the benefit/risk balance for the combination of ramucirumab +paclitaxel therapy is therefore considered positive.

Similarly, the benefit/risk balance for the monotherapy is considered positive based on the improvement in overall survival and the tolerable toxicity. However, the effect size associated with monotherapy was of small magnitude and the benefits were considered to outweigh the risks by a relatively smaller amount (see discussion on the benefit-risk balance).

*Discussion on the benefit-risk balance*

The data presented have shown convincing evidence of efficacy of ramucirumab in combination with paclitaxel in patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. The effect in terms of overall survival is clinically relevant in this condition, which is associated with a very poor prognosis.

There may be an opportunity to further optimise the benefit/risk profile in the monotherapy setting given the exposure-efficacy relationship and overall safety profile observed in the REGARD study. Given the mild safety profile of ramucirumab in the monotherapy, and the considerable higher MTD of 13 mg/kg QW, an alternative dosing regimen may be explored. To explore this further, the applicant will submit the results of a of a phase II dose-response study investigating three alternative ramucirumab monotherapy dosing regimens.

Although the benefit-risk balance is overall considered to be favourable for the single-agent regimen as well, the effect size in terms of overall survival was larger for the combination regimen (albeit from an indirect comparison). Therefore, the balance of benefits and risks for monotherapy was carefully considered. A minority of CHMP members considered that the effect associated with ramucirumab as single agent was too marginal and possibly even inferior to single-agent chemotherapy that are used in this setting. However, according to the prevalent CHMP view, the benefits outweighed the risks and although the effect on OS was relatively small, this could still represent a useful therapeutic option in this second-line setting, when chemotherapy in combination with ramucirumab is not the preferred option. Thus, the CHMP concluded that single-agent treatment in this second-line setting should be restricted to patients for whom treatment with ramucirumab in combination with paclitaxel is not appropriate (see SmPC section 4.1).

The CHMP also assessed the generalizability of results, in view of the fact that the pivotal clinical trials only recruited patients with good performance status (ECOG PS 0 or 1), and assessed whether a restriction of the indication to good performance status patients was necessary. The CHMP concluded that although there is some uncertainty on whether similar efficacy and safety results could be observed in patients with poor performance status, it is common for clinical trials to recruit good prognosis patients. Furthermore, in view of the relatively tolerable safety profile, the CHMP considered that this uncertainty raised no major concerns in terms of safety. Thus, in the absence of clear signals against the generalizability of results, the CHMP concluded against a restriction of the indication to patients with good performance status. However, the CHMP agreed that attention should be drawn (see SmPC section 4.1)

to information about the population recruited in the clinical studies and the efficacy results observed in the different regimens as described in the SmPC section 5.1.

# 4. Recommendations

*Outcome*

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of ramucirumab in combination with paclitaxel for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy and the risk-benefit balance of ramucirumab monotherapy for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate are favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

### Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

### Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

### Conditions or restrictions with regard to the safe and effective use of the medicinal product
- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

| Description | Due date |
|---|---|
| The MAH shall submit results from the randomised dose ranging pharmacokinetics (PK) and safety study of ramucirumab monotherapy (14T-MC-JVDB). This phase 2 study will evaluate the PK and safety of various schedules of ramucirumab, including higher doses than the approved dose of 8mg/kg every 2 weeks in second line gastric adenocarcinoma. | 01/04/2017 ( PK results)<br><br>01/04/2018 (Final CSR and safety results) |

***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.***

Not applicable.

## CHMP divergent position

Divergent position to the majority recommendation are appended to this report.

### New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that ramucirumab is qualified as a new active substance.

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# Appendix 1

**DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS**

**Some members of the CHMP expressed a divergent position as follows:**

**Monotherapy Indication**

The MAA presented the REGARD study to support the use of Cyramza as monotherapy in second line gastric cancer.

The Applicant justified the placebo control by the fact that chemotherapy was not an accepted standard in this setting when the study was initiated. Patients were not selected on their non-eligibility to any treatment. Indeed, at progression, 33% of patients received chemotherapy (third line) when disease progression is expected to have further lowered the acceptability of chemotherapy.

This may indicate that much more than one third of enrolled patients would have been amenable to an active treatment on second line, at time of randomization and were thus under-treated with placebo. This considerably weakens the evidence brought by the REGARD to show a benefit with Cyramza monotherapy in the whole included population. In addition, any conclusion limited to patients not eligible to chemotherapy would be hazardous since the exact representation of this subgroup in the REGARD study is unknown and necessarily inferior to 66%.

In contrast, the RAINBOW study demonstrated a modest benefit over chemotherapy when Cyramza is combined with paclitaxel. These results cannot be extrapolated to Cyramza monotherapy. There is no evidence that, when the combination is not appropriate, a monotherapy with Cyramza is superior to chemotherapy. It is even impossible to exclude that Cyramza monotherapy is inferior to chemotherapy.

For all these reasons, the monotherapy indication granted to Cyramza which potentially includes patient candidates for chemotherapy appears to extrapolate and is not based on demonstrative evidence.

# Divergent opinion

————————————————————
**Pierre Demolis**

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**Ján Mazag**

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**Juris Pokrotnieks**

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**Concepcion Prieto Yerro**

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**Sol Ruiz**

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