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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name (Proposed) Trade Name	Ramucirumab/IMC-1211 Cyramza
Therapeutic Class	Monoclonal antibody targeting VEGFR-2
Applicant	Eli Lilly
Formulation(s)	1- 100 mg/10 mL single use vial 2- 500 mg/50 mL single use vial
Dosing Regimen Indication(s)	8 mg/kg IV every 2 weeks Treatment of patients with advanced gastric or gastroesophageal junction adenocarcinoma after prior chemotherapy.
Intended Population(s)	Previously treated patients with advanced or metastatic gastric or

gastroesophageal cancer.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended for the use of ramucirumab for the treatment of patients with advanced or metastatic gastric/gastroesophageal junction carcinoma that is resistant to or has progressed after a fluoropyrimidine- and/or platinum- containing regimen. Approval is contingent upon reaching agreement with Lilly on product labeling and upon reaching agreement on any PMCs or PMRs deemed necessary by other disciplines. Approval is also contingent upon satisfactory reviews of ramucirumab performed by other FDA disciplines.

The Applicant provided data establishing the safety and effectiveness of the product for the proposed indication as described under 21 CFR 314.70 and 21 CFR 601.2.

1.2 Risk Benefit Assessment

Analysis of condition
Summary of evidence Ramucirumab is proposed as a treatment for patients with locally advanced or metastatic gastric adenocarcinoma (including GEJ adenocarcinoma) whose disease progressed after or during first line treatment with a cisplatin/fluoropyrimidine regimen. Advanced and metastatic gastric adenocarcinoma is considered incurable (median overall survival of with chemotherapy is 8-12 months) and the aim of therapy is to prolong survival and improve quality of life. When relapse occurs after first line chemotherapy, median survival with supportive care is 3-4 months. Small clinical trials with irinotecan and docetaxel suggest that a second line chemotherapy improves survival, but there is no current standard of care for the second line treatment.
Conclusion Advanced and metastatic gastric and GEJ adenocarcinoma is a progressive disease with a fatal outcome. Median survival after diagnosis of the disease is approximately 8-12 months.
Unmet medical need In the Western world, first-line therapy for patients with advanced or metastatic gastric/GEJ carcinoma usually consists of the administration of a fluoropyrimidine in combination with platinum (with or without a third drug, usually an anthracycline). Patients whose tumors express HER-2 are candidates to receive, in addition to the above mentioned chemotherapy, trastuzumab. Upon recurrence or lack of response, survival is short and patients rapidly deteriorate. There is no consensus or approved therapy for the second-line treatment of patients with gastric/JEG

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Conclusion

Relapsed/refractory advanced or metastatic gastric/GEJ carcinoma is condition with a poor outcome for which there are no approved therapies and no uniform recommendation for treatment.

Clinical benefit

Summary of evidence

The efficacy of ramucirumab in the treatment of locally advanced or metastatic gastric or gastroesophageal junction (GEJ) carcinoma that has progressed after one line of treatment with a platinum- and fluoropyrimidine- based therapy (for advanced/metastatic disease or in the adjuvant setting if progressed during treatment or within 4 months after treatment) was demonstrated in one well conducted clinical trial, IMCL CP12-0715 (I4T-IE-JBVD or REGARD), 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 Adenocarcinoma (GEJ) Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy. This improvement in overall survival was confirmed by the high-level results of a second trial in the same setting, study I4E-IE-JVBE (CP12-0922; RAINBOW, entitled A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase 3 Study of Weekly Paclitaxel with or without Ramucirumab in Patients with Metastatic Gastric Adenocarcinoma, Refractory to or Progressive After First-Line Therapy with Platinum and Fluoropyrimidine).

The primary objective of Study I4T-IE-JBVD was to demonstrate improvement in overall survival (OS). The secondary objectives were to compare PFS, response rate (both as per RECIST 1.1 criteria) between the two treatment arms, to evaluate the safety profile in the two treatment arms, to assess immunogenicity of IV ramucirumab, and to assess pharmacokinetics of IV ramucirumab.

Treatment consisted of either ramucirumab or placebo at 8 mg/kg on Day 1 every 2 weeks in combination with best supportive care (which excluded chemotherapy, immunotherapy, and other investigational drugs). This type of design isolated the effect of the investigational drug and allowed for a direct comparison of the efficacy and toxicity between the active treatment and placebo. The blinded nature of this study also reduced the chance of bias in the conduct and analysis of the trial.

Patients were randomized (using either an electronic data capture system or by accessing a call-in Interactive Voice Response System [IVRS] or Interactive Web Response System [IWRS]) on a 2:1 basis to receive either ramucirumab or placebo, respectively. Randomization was stratified by weight loss ($\geq 10\%$ over the prior 3 months versus $< 10\%$), geographic region (North America, Europe, Australia, and New Zealand versus South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia versus Asia), and location of the primary tumor [gastric (including tumors of the gastric cardia that extend into the GEJ) versus GEJ (including

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tumors of the distal esophagus that extend into the GEJ, and tumors involving the GEJ when precise identification of the organ of origin is not possible)].

Patients received treatment until disease progression, unacceptable toxicity, or patient's refusal. Following documentation of progressive disease, patients were followed for survival status until death or withdrawal of patient consent or until cutoff date for final analysis.

Response and disease status were assessed every 6 weeks during study treatment, and at the end of study treatment.

The first patient was enrolled on October 6, 2009 and the last patient was enrolled on January 10, 2012. A total of 355 patients were randomized, 238 patients randomized to the ramucirumab arm and 117 patients to the placebo arm. Two patients in each treatment arm were not treated. At the time of data cut-off, 14 patients (5.8%) in the ramucirumab arm and 1 patient (0.8%) in the placebo arm were still receiving study treatment.

Patient demographic characteristics were balanced between the two treatment arms. Median age at randomization was 60 years in the ramucirumab arm and 61 years in the placebo arm; there was a slight imbalance in the proportion of patients 65 years of age or older (34% in the ramucirumab arm and 39% in the placebo arm). Most patients were men (71% and 68% in the ramucirumab and placebo arms respectively) and White (76% and 78% in the ramucirumab and placebo arms respectively). Initial disease characteristics were generally similar and balanced between treatment arms. All patients had a diagnosis of adenocarcinoma.

The most frequent primary site was the stomach (75% in the ramucirumab arm and 74% in the placebo arm). All patients received prior anti-cancer treatment. The majority of patients enrolled in the study received prior platinum/fluoropyrimidine combination therapy (84% and 75% in the ramucirumab and placebo arms respectively). Study arms were balanced regarding response to prior therapy and duration of response.

At the time of the data cut-off, 94% patients in the ramucirumab arm and 97% patients in the placebo arm had discontinued treatment. The main reason for treatment discontinuation was disease progression [126 patients (53%) in the ramucirumab arm and 73 patients (62%) in the placebo arm].

The analysis of OS was performed on the ITT population, 238 patients in the ramucirumab arm and 117 patients in the placebo arm. At the time of the data cut-off for the final analysis (July 25, 2012), the median follow-up time (i.e., time from randomization to the time of death or censoring) was 4.9 months in the ramucirumab arm and 3.7 months in the placebo arm. The survival analysis was based on a total of 278 deaths: 179 events (75%) reported in the ramucirumab arm and 99 events (85%) reported in the placebo arm. Survival estimates using the Kaplan Meier method were compared using a log-rank test (Cox method) stratified by factors specified at the time of randomization. The addition of ramucirumab to standard of care resulted in a survival benefit, with a statistically significant log rank test with a p-value of 0.0473 and an

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estimated hazard ratio of 0.776 (95% CI: 0.603 to 0.998). The use of ramucirumab in addition to standard of care resulted in a risk of death reduction of 22% when compared to placebo and standard of care. Median overall survival (95% CI) in the ramucirumab arm was 5.2 months (4.4 to 5.7), compared to 3.8 months (2.8 to 4.7) in the placebo arm.

Treatment with ramucirumab reduced the risk of disease progression or death by 52% (HR = 0.483; 95% CI: 0.376, 0.620; p<0.0001). Median time to disease progression in the ramucirumab arm was 2.1 (95% CI 1.5; 2.7) months and 1.3 (95% CI 1.3; 1.4) months. Type I error for evaluation of PFS as a secondary endpoint was controlled using gate keeping methodology. Because the curves appeared to separate around the median (likely based on the timing of tumor assessments), the HR may be the better estimate for the treatment effect on PFS.

The protocol was overall well conducted, and protocol violations were minimal and did not impact the integrity of the data.

Although statistically significant, FDA had the following concerns regarding the study results: modest magnitude of effect, borderline significance and whether the results would be reproducible for this NME, and the potential for a detrimental treatment effect in women.. Eli Lilly addressed these concerns by submitting the high level results of a second study, RAINBOW, a Phase 3 randomized study comparing ramucirumab/paclitaxel vs. placebo/paclitaxel for the second line treatment of gastric/GEJ adenocarcinoma. A total of 665 patients (330 patients in the ramucirumab/paclitaxel arm and 335 patients in the placebo/paclitaxel arm) were enrolled in the RAINBOW study. Generally speaking, patients in the RAINBOW study were similar to patients in the REGARD study, with the exception of race and histology, as there were more Asian patients in the RAINBOW study (Asian patients constituted 16% of patients in REGARD).

The primary endpoint for the RAINBOW study was OS. Ramucirumab in combination with paclitaxel reduced the risk of death in this population by 19% (stratified log rank test HR = 0.807; 95% CI 0.678, 0.962; p=0.0169), prolonging median survival time (9.63 months [95% CI: 8.48, 10.81] in the ramucirumab arm vs. 7.36 months [95% CI: 6.31, 8.38] in the placebo arm, a 2.27 months difference). One hundred and ninety three women (101 and 92 in the ramucirumab/paclitaxel and placebo/paclitaxel arms respectively) enrolled in this study, and they appeared to benefit from ramucirumab treatment at least as much as in the general study population with a median HR of 0.672 (0.483; 0.935, nominal p= 0.01740). In addition, in the RAINBOW study, there was a (nominally) statistically significant improvement in OS in Region 1, which included the US and Europe (HR=0.726, 95% CI 0.580; 0.909 and a nominal p=0.0050). These data support the hypothesis that the subgroup analysis results in the REGARD study are likely related to the small sample and random effects.

In conclusion, data from the REGARD study (supported by the high-level results of the RAINBOW study) support the conclusion that the addition of ramucirumab to the second line treatment of gastric/GEJ carcinoma results in clinical benefit.

Conclusion

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There are no drugs approved for the second-line treatment of patients with relapsed/refractory advanced or metastatic gastric/GEJ adenocarcinoma. REGARD was a well conducted study that showed that the addition of ramucirumab to best supportive care resulted in a modest survival benefit, with a statistical significant log rank test with a p value of 0.0473 and an estimated HR of 0.776 (95% CI: 0.603 to 0.998). Median overall survival (95% CI) in the ramucirumab arm was 5.2 months (4.4 to 5.7), compared to 3.8 months (2.8 to 4.7) in the placebo arm. This benefit was supported by an increased median PFS and the high level results of a second study, RAINBOW, comparing ramucirumab in combination with paclitaxel vs. placebo/paclitaxel. Ramucirumab in combination with paclitaxel reduced the risk of death in this population by 19% (stratified log rank test HR = 0.807; 95% CI 0.678, 0.962; p=0.0169), prolonging median survival time (9.63 months [95% CI: 8.48, 10.81] in the ramucirumab arm vs. 7.36 months [95% CI: 6.31, 8.38] in the placebo arm, a 2.27 months difference).

The results of these two studies support the efficacy of ramucirumab in the second line treatment of gastric/GEJ carcinoma.

Risk

Summary of evidence

The main safety analyses were performed on JVBD/REGARD, the pivotal study for the proposed indication (236 patients exposed to ramucirumab). Additionally, data from 334 patients treated with ramucirumab monotherapy from Phase 1 dose-escalation and Phase 2 studies were analyzed to evaluate the toxicity profile of ramucirumab.

A total of 351 patients received either ramucirumab or placebo in the JVBD trial (constituting the safety analysis dataset). At the time of data cut-off, 96% of these patients discontinued ramucirumab or placebo. Main reason for treatment discontinuation was disease progression, which occurred with greater frequency in the placebo arm (62%) than in the ramucirumab arm (53%). Adverse events leading to treatment discontinuation (including adverse events with an outcome of treatment discontinuation) occurred with higher frequency in the ramucirumab arm (14%) than in the placebo arm (7%).

Patients in the placebo arm received a median of 3 infusions (6 weeks of placebo). Patients treated in the ramucirumab arm received a median of 4 infusions (8 weeks of treatment). Median relative dose intensity for both arms was greater than 99% (only 3 patients in the ramucirumab arm and 1 patient in the placebo arm required dose reduction) in both arms.

Almost all patients in both arms of the JVBD study experienced adverse events. Grade 3-4 AEs were more frequently observed in the ramucirumab arm (55%) than in the placebo arm (51%). The incidence of non-fatal serious adverse events (SAEs) was 38% in both arms. At the SOC (MedDRA System Organ Class) level, the most frequently affected systems ($\geq 25\%$ incidence) were gastrointestinal (ramucirumab arm 69%, placebo arm 64%), general disorders and administration site conditions (ramucirumab arm 54%, placebo arm 56%), metabolism and nutrition disorders (ramucirumab arm 38%, placebo arm 42%), investigations (ramucirumab arm 39%, placebo arm 18%), and respiratory, thoracic, and mediastinal disorders (ramucirumab arm

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25%, placebo arm 27%).

At the preferred term level, the most frequently reported events (incidence $\geq 20\%$) were fatigue (ramucirumab arm 25%, placebo arm 24%), decreased appetite (ramucirumab arm 24%, placebo arm 23%), vomiting (ramucirumab arm 20%, placebo arm 25%), nausea (ramucirumab arm 19%, placebo arm 26%), abdominal pain (ramucirumab arm 19%, placebo arm 25%), and constipation (ramucirumab arm 15%, placebo arm 23%). With the exception of fatigue and decreased appetite (where the incidence rates were similar), in all these events the incidence in the placebo arm was at least 5% higher than in the ramucirumab arm.

Grade 3-4 events (preferred term analysis) were more frequently observed in the placebo arm (ramucirumab arm 51%, placebo arm 55%). Events occurring with $\geq 2\%$ difference in the ramucirumab arm were pain (2% vs. none in the ramucirumab and placebo arms, respectively), hyponatremia (3% versus 1% in the ramucirumab and placebo arms, respectively), abdominal pain (5% versus 3% in the ramucirumab and placebo arms, respectively), and hypertension (7% versus 3% in the ramucirumab and placebo arms, respectively). Events occurring with $\geq 2\%$ difference in the placebo arm were asthenia (2% versus 7% in the ramucirumab and placebo arms respectively), dysphagia (2% versus 4% in the ramucirumab and placebo arms, respectively), and anemia (6% versus 8% in the ramucirumab and placebo arms, respectively).

Most patients (64% in the placebo arm and 63% in the ramucirumab arm) died because of progression of disease. There were 54 deaths that occurred secondary to an adverse event with a start date within 30 days of the last dose of study treatment. However, if the events of disease progression, gastric cancer, and neoplasm are removed from this population, there were 26 patients (11% patients in the ramucirumab arm) and 12 patients (10% patients in the placebo arm) who experienced an adverse event with a fatal outcome. Treatment related deaths were more frequent in the ramucirumab arm, and although only four events were attributed by the investigators as treatment-related, it is not possible to rule out the contribution of the treatment to other events such as hemorrhage, perforations, etc.

Regarding adverse events of special interest (VEGF/R inhibition-related and assessed by combining multiple preferred terms), these events were observed, as expected, more frequently in patients in the ramucirumab arm. The incidence of hypertension was 17% in the ramucirumab arm and 8% in the placebo arm (Grades 3 incidence rates were 8% and 3% in the ramucirumab and placebo arms, respectively). There were no Grade 4 hypertensive events.

The incidence of proteinuria was similar (3.0% in the ramucirumab arm and 2.6% in the placebo arm), with a single Grade 3 event in the ramucirumab arm. However, in 18 (8%) patients in the ramucirumab arm and 4 (3%) patients in the placebo arm, the urine analysis for proteinuria was considered “positive” or “+++” (presumably dipstick).

No arterial thromboembolic events were observed in the placebo arm. There were 4 patients in the ramucirumab arm who experienced 6 arterial thromboembolic events. Although the role of ramucirumab could not be ruled out, there were co-morbid factors (prior history of hypertension,

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concomitant sepsis, etc.) that have contributed. Eight subjects (7%) in the placebo arm and 9 subjects (4%) in the ramucirumab arm experienced venous thromboembolic events.

Bleeding/hemorrhagic events were more frequent in the ramucirumab arm (13% per-patient incidence) than in the placebo arm (11%). There was one event of fatal gastric/gastrointestinal hemorrhage per arm. The majority of events were Grade 1-2; the incidence of Grade 1-2 bleeding/hemorrhagic events in the ramucirumab arm was 10% versus 9% in the placebo arm. In the JVBD study, as expected, subjects in the ramucirumab arm experienced more hemorrhagic events than patients in the placebo arm; however, the incidence of serious, life-threatening or fatal events of hemorrhages was not increased.

In summary, treatment with ramucirumab in the JVBD study resulted in the increased incidence of certain VEGF/R inhibition-related toxicities; however, most patients tolerated ramucirumab without requiring dose reductions.

Supportive data:

In addition to patients enrolled in the REGARD trial, Eli Lilly submitted safety data and a high level overview from 334 patients treated with ramucirumab as a single agent in Phase 1 and 2 clinical studies. Because this population was heterogeneous, marked differences in the toxicity profiles were observed when evaluated in different disease settings (i.e., patients with ovarian carcinoma experienced more AEs than other patients, patients with renal cell carcinoma experienced more renal and urinary complications, etc).

In this pooled population, the overall incidence of bleeding/hemorrhagic events was 48%, and the incidence of \geq Grade 3 events was 4%. Thirty one (16%) patients experienced epistaxis and in all but one case, these were Grade 1-2 in severity.

The overall incidence of hypertension (PTs included: hypertension, hypertensive crisis, blood pressure diastolic increased, and blood pressure increased) in the pooled phase 2 (n=191) population was 29%, and 10% of the pooled population had an event of Grade 3-4 hypertension. There were two Grade 4 events, one in a patient with renal cell carcinoma and another in a patient with HCC. Although not observed in the monotherapy studies nor the pivotal study, there was an event of RPLS in the metastatic colorectal cancer study when ramucirumab was used in combination with FOLFIRI.

Proteinuria was observed in 15% of patients in the pooled phase 2 population (n=191), and 2% experienced Grade 3-4 proteinuria. There was one event of nephrotic syndrome in a patient with melanoma.

The following arterial thromboembolic events were observed in the pooled population: acute coronary syndrome, angina pectoris, cerebral ischemia, myocardial infarction (all these events were Grade 3-4), and Grade 2 femoral artery occlusion and coronary artery disease.

In summary, the supportive data from Phase 1-2 single-arm studies was generally consistent with

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the safety data from the pivotal study, JVBD. The safety database was adequate and allowed for the characterization of the toxicity profile of ramucirumab.

Conclusion

The analysis of the database shows that ramucirumab toxicity is within the range (both in the type of events and the incidence rates) of bevacizumab and aflibercept, the only other approved biologics inhibiting the VEGF pathway. There were no new or unexpected safety signals when compared with bevacizumab and aflibercept.

Ramucirumab monotherapy was well tolerated for the second line treatment of gastric/GEJ carcinoma.

Risk management

The risks of ramucirumab use in the treatment of relapsed/refractory advanced gastric/GEJ carcinoma whose disease had progressed after a first-line treatment with a fluoropyrimidine- and platinum- containing regimen will be managed through product labeling. The risks are also managed in that this drug will be administered by oncologists who have specific training in the administration of anti-neoplastic drugs and in the management of toxicities related to these drugs.

Benefit-risk summary and assessment

Relapsed or refractory advanced or metastatic gastric/GEJ cancer is an incurable disease and the standard of care is generally palliative treatment. A recently published Phase 3 study (Ford H., 2013) in this same setting compared docetaxel versus best supportive care in 168 patients (median follow-up of 12 months and 161 deaths, 80 in the docetaxel group and 81 in the active symptom control group), showed a median overall survival in the docetaxel group of 5.2 months (95% CI 4.1–5.9) versus 3.6 months (3.3–4.4) in the active symptom control group (hazard ratio 0·67, 95% CI 0.49; 0.92; p=0·01).

Metastatic advanced gastric/GEJ carcinoma is a progressive disease with a fatal outcome. Median survival after diagnosis of the disease is approximately 8-12 months. There is no standard of care or approved drugs for the second line treatment, and docetaxel and irinotecan are some of the drugs used frequently in this setting, although no uniform consensus or recommendation exists.

The efficacy and safety of ramucirumab was studied in a Phase 3 trial, REGARD. REGARD was a prospective, multinational, randomized (2:1), double-blind, parallel-arm study of ramucirumab versus placebo plus best supportive care in patients with relapsed/refractory advanced or metastatic gastric/GEJ carcinoma after first-line treatment with a fluoropyrimidine- platinum-containing regimen. REGARD was a well conducted study that randomized 355 patients (238 in the ramucirumab arm and 117 in the placebo arm). The addition of ramucirumab to best supportive care resulted in a survival benefit, with a statistical significant log rank test with a p value of 0.0473 and an estimated HR of 0.776 (95% CI: 0.603 to 0.998). Median overall survival (95% CI) in the ramucirumab arm was 5.2 months (4.4 to 5.7), compared to 3.8 months (2.8 to 4.7) in the placebo arm. This benefit was supported by an increased median PFS and

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(more importantly) the high level results of a second study, RAINBOW, comparing ramucirumab in combination with paclitaxel vs. placebo/paclitaxel. Ramucirumab in combination with paclitaxel reduced the risk of death in this population by 19% (stratified log rank test HR = 0.807; 95% CI 0.678, 0.962; p=0.0169), prolonging median survival time (9.63 months [95% CI: 8.48, 10.81] in the ramucirumab arm vs. 7.36 months [95% CI: 6.31, 8.38] in the placebo arm, a 2.27 months difference).

The results of these two studies support the efficacy of single-agent ramucirumab in the second-line treatment of gastric/GEJ carcinoma.

The analysis of the safety database (including 334 patients from monotherapy Phase 1 and 2 studies) shows that ramucirumab toxicity is within the range (both in the type of events and the incidence rates) of bevacizumab and afibbercept, the only other approved biologic products targeting the VEGF pathway. Ramucirumab was well tolerated, and there were no new or unexpected safety signals.

In summary, the approval is recommended based on a prolongation of overall survival with an acceptable toxicity profile for which the oncology community has experience in its management. The study effects were supported by the PFS results and the high level results of a second study, RAINBOW, showing a larger magnitude of effect in overall survival in the same disease setting.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Eli Lilly will be required to provide progress reports as described in 21 CFR 600.80.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no clinical recommendations for PMC/PMRs.

2 Introduction and Regulatory Background

The Applicant seeks approval for the following indication: "Ramucirumab is for the treatment of patients with gastric or gastroesophageal junction previously treated with a cisplatin-containing regimen." The application was submitted on August 23 2013 and the PDUFA goal date is April 23 2014. The clinical module was submitted on April 30 2013 (rolling submission).

This review will describe the efficacy and safety data supporting ramucirumab for the second-line treatment of gastric or GEJ carcinoma and the recommendation of the clinical reviewer.

2.1 Product Information

Ramucirumab is a recombinant human monoclonal antibody of the IgG1 class that specifically binds to vascular endothelial growth factor receptor 2 (VEGFR-2) and blocks the activation of this receptor. Ramucirumab has an approximate molecular weight of 146.8 kDa and it is produced in murine NS0 cells by recombinant DNA technology.

Ramucirumab is a sterile, clear to slightly opalescent and colorless to slightly yellow solution at a pH of 6.0 for intravenous infusion following dilution and preparation. Ramucirumab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. Ramucirumab is formulated in a preservative-free solution in an aqueous solution which contains 0.65 mg histidine, 1.22 mg histidine monohydrochloride, 4.383 mg sodium chloride, 9.98 mg glycine, 0.1 mg polysorbate 80, and Water for Injection, USP.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently no drugs approved for the second-line treatment of advanced and/or metastatic gastric carcinoma and GEJ cancer. First and second-line treatments are selected based on the patient's health status and preferences, medical co-morbidities, HER-2 status, etc. Older drugs approved for the treatment of gastric cancer include fluorouracil, doxorubicin, and mitomycin C. In the last decade, docetaxel and trastuzumab labels have been expanded to include an indication in gastric cancer (first-line treatment).

Docetaxel in combination with cisplatin and fluorouracil was approved (2006) for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease (Taxotere USPI). This approval was supported by TAX325, a multicenter, open-label, randomized trial that randomized 445 patients to receive docetaxel (75 mg/m^2 on day 1) in combination with cisplatin (75 mg/m^2 on day 1) and fluorouracil (750 mg/m^2 per day for 5 days) or cisplatin (100 mg/m^2 on day 1) and fluorouracil (1000 mg/m^2 per day for 5 days). The length of a treatment cycle was 3 weeks for the investigational arm and 4 weeks for the cisplatin-5FU arm. The demographic characteristics were balanced between the two treatment arms. The median age was 55 years, 71% were men, 71% were White, 24% were 65 years of age or older, 19% had a prior curative surgery, and 12% had palliative surgery. The median number of cycles administered per patient was 6 (with a range of 1-16) for the docetaxel arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint and was defined as time from randomization to disease progression or death from any cause within 12 weeks of the last evaluable tumor assessment or within 12 weeks of the first infusion of study drugs for patients with no evaluable tumor assessment after randomization. The hazard ratio (HR) for TTP was 1.47 (CF/TCF, 95% CI: 1.19-1.83) with a significantly longer TTP ($p=0.0004$) in the TCF arm. Approximately 75% of patients had died at the time of this analysis. Overall survival was significantly longer ($p=0.0201$) in the TCF arm with a HR of 1.29 (95% CI: 1.04-1.61; mOS in the docetaxel arm was 9.2 months vs. 8.6 months in the CF arm).

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Trastuzumab (Herceptin) was approved in 2010 for the treatment, in combination with cisplatin and capecitabine or 5-fluorouracil of patients with HER2 over expressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease (Herceptin USPI). This indication was supported by the results of the ToGA study, an open-label, multi-center trial, where 776 patients were randomized 1:1 to receive trastuzumab in combination with cisplatin and a fluoropyrimidine or chemotherapy alone. All patients were either HER2 gene amplified (FISH+) or HER2 over expressing (IHC 3+). On both study arms cisplatin was administered at a dose of 80 mg/m² Day 1 every 3 weeks for 6 cycles and capecitabine was administered at 1000 mg/m² orally twice daily for 14 days of each 21 day cycle for 6 cycles. The median age of the study population was 60 years (range: 21–83); 76% were men; 53% were Asian, 38% White; 91% had ECOG PS of 0 or 1; 82% had primary gastric cancer, and 18% had primary gastroesophageal adenocarcinoma. The main outcome measure of ToGa was OS, analyzed by the unstratified log rank test. Median OS was 11 (9.4;12.5) months in the chemotherapy arm and 13.5 (11.;15.7) months in the trastuzumab arm (HR 0.73, 95% CI 0.60;0.91, p=0.0038).

In the NCCN guidelines for the first-line treatment, cisplatin-fluoropyrimidine regimens are preferred over three-drug regimens because of toxicity concerns. Recommended two- or three-drugs regimens in first line are CF (cisplatin and fluoropyrimidine), DCF (docetaxel, cisplatin, fluoropyrimidine) and its variants (oxaliplatin or carboplatin), ECF (epirubicin, cisplatin, fluoropyrimidine), irinotecan/fluoropyrimidine, paclitaxel/cisplatin/fluoropyrimidine, and docetaxel/cisplatin. For second line treatment, NCCN guidelines recommend treatment with docetaxel, paclitaxel, irinotecan, irinotecan/cisplatin or irinotecan/fluoropyrimidine. With the exception of cisplatin/fluoropyrimidine, DCF, and ECF (Category 1, based on randomized controlled clinical trials), there is no consensus regarding these recommendations (Category 2 for all other combinations). Treatment of advanced or metastatic gastric cancer is summarized with more detail in Section 2.6.1 of this review. Table 1 summarizes the results of some of the studies supporting NCCN recommendations

Table 1 - Phase 3 trials of first-line chemotherapy in advanced/metastatic gastric cancer

Study	Treatment	N	Median OS (months)	P value
ML17032 (Okines A. et al 2009)	CF	137	9.3	NS
	CX	139	10.5	
REAL-2 (Okines A. et al 2009)	ECF	249	9.9	0.02
	ECX	241	9.9	
	EOF	235	9.3	
	EOX	239	11.2	
V325 (Van Cutsem E. et al, 2006)	DCF	221	9.2	0.02
	CF	224	8.6	
ToGA (Bang YK et al, 2010)	CX/CF + trastuzumab	294	13.8	0.0046
	CX/CF	290	11.1	

C: cisplatin; F: 5-FU; X: capecitabine; E: epirubicin; O: oxaliplatin; D: docetaxel;

2.3 Availability of Proposed Active Ingredient in the United States

Ramucirumab is a new molecular entity (NME), available only for investigational use under
INDs 11856, [REDACTED] (b) (4)

(b) (4)

2.4 Important Safety Issues With Consideration to Related Drugs

Interference with the VEGF pathway induces a characteristic pattern of toxicity observed in approved and experimental drugs targeting this pathway. Hypertension, gastrointestinal toxicity, proteinuria, thromboembolic events, hemorrhage, reversible posterior leukoencephalopathy (RPLS) and wound healing are consistently observed across clinical trials and in the post marketing setting following the administration of both biologic and small molecules anti-VEGF and anti-VEGFR agents (approved and investigational). The spectrum of adverse events in individual patients and different disease settings is variable and may reflect several factors: dose of the VEGF inhibitor, specificity of the inhibition of the pathway, disease factors, co-morbidities, co-targeting of other pathways, and use of concomitant chemotherapy treatment.

This section of the review will focus on the safety issues observed primarily with bevacizumab, the biologic drug that directly targets VEGF, with no direct actions on tyrosine kinases involved in the VEGF pathway. The box warning in the Avastin label describes gastrointestinal perforations, surgery and wound healing complications, and hemorrhage. In addition to these adverse reactions, the Warnings and Precautions section describes non-gastrointestinal fistula formation, arterial thromboembolic events, hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), and infusion reactions.

VEGFR-2 signaling generates nitric oxide and prostaglandin I2, which induces vasodilatation in arterioles and venules, the component of vasculature that has the most impact on blood pressure. Blockage of VEGF leads to vasoconstriction. Vascular rarefaction, a phenomenon observed in patients with hypertension, has also been postulated as a mechanism for hypertension in patients receiving VEGF inhibitors.

As described in Dr. Chen's and Dr. Cleck's comprehensive review of adverse events related to inhibition of the VEGF pathway (Chen H., 2009), the effect of anti-VEGF agents on blood pressure is dose-dependent. In a Phase 2 study in patients with renal-cell carcinoma (RCC) treated with placebo 3 mg/kg bevacizumab or 10 mg/kg bevacizumab, the rate of hypertension was significantly higher in the high-dose group (36%) compared with the low dose group (3%). This dose dependency has also been observed with small-molecule VEGF TKIs. Patients with pre-existing hypertension are generally more likely to develop further elevation in blood pressure when receiving anti-VEGF therapy.

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The risk of hypertension may be also related to indication or concomitant chemotherapy (although differences in data collection or monitoring between trials may also cause differences in hypertension rates. As described in Dr. Chen's paper, the highest rate of hypertension (36%) occurred in a renal cell cancer trial (10 mg dose) compared to a reported rate (all Grades) of 24% in a trial in patients with breast cancer (AVF2119g).

In a recent meta-analysis (Rampura, 2010) of 20 randomized controlled trials that included 12,526 patients, bevacizumab was associated with a significantly increased risk of Grade 3-4 hypertension, with an incidence of 7.9% (95% CI: 6.1–10.2) and a RR of 5.28 (95% CI: 4.15–6.71). The risk of high-grade hypertension associated with bevacizumab significantly increased in patients with renal cell carcinoma (RR: 8.99, 95% CI: 2.72–29.72), non-small cell lung cancer (RR: 7.06; 95% CI: 3.66–13.62), pancreatic cancer (RR: 5.52; 95% CI: 2.12–14.35), and colorectal cancer (RR: 5.24, 95% CI: 3.89–7.05).

In most cases, hypertension can be controlled with oral hypertensive agents. However, a patient may develop uncontrolled hypertension, hypertensive crisis, or RPLS with life-threatening complications.

Reversible posterior leukoencephalopathy syndrome (RPLS) is a severe condition that since the original description by Hinchey in 1996, has been associated with hypertensive encephalopathy, pre-eclampsia, eclampsia, LES, vasculitis, tumor lysis syndrome, infection, sepsis, shock, and exposure to cytotoxic agents (particularly platinum compounds), bevacizumab, other anti-VEGF/R inhibitory molecules, and biologic or immunosuppressive agents.

Clinically, RPLS causes a variety of acute to subacute neurologic symptoms that include headache, nausea, vomiting, altered mental status, seizures, stupor, and visual disturbances (from blurred vision to cortical blindness).

Radiological findings of RPLS include vasogenic edema that primarily affects the white matter and generally involves the bilateral parietal-occipital lobes and occasionally the basal ganglia, brainstem, or cerebellum; the edema may be asymmetrical. MRI with diffusion weighted imaging is the preferred diagnostic test. Vasogenic edema is best seen on T2 weighted images using fluid-attenuated inversion recovery (FLAIR) sequencing.

Disorders that cause hypertension can lead to RPLS. Prior history of hypertension may provide a degree of protection. At any given increased blood pressure, preexisting chronic hypertension may lower the probability of RPLS because of adaptive vascular changes as opposed to patients who develop new onset acute hypertension (Mukherjee P., 2001). Controversy exists over the RPLS mechanism. The initial Hinchey hypothesis of hypertension leading to failed auto regulation followed by capillary permeability damage cannot explain the approximately 20%-40% of RPLS cases with no documented hypertension. A more complex mechanism may exist involving direct endothelial damage/dysfunction. For some drugs associated with RPLS, like cyclosporine and tacrolimus, there is some evidence that they can cause perturbation of the

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blood-brain barrier. Cyclosporine also has been reported to have direct toxic effects on vascular endothelial cells.

RPLS is described in the adverse reactions sections of the labels for VEGF inhibitor drugs bevacizumab, axitinib, and sunitinib. In all drugs, the observed incidence was less than 1%.

Scappaticci et al. (Scappaticci, 2007) performed a meta-analysis on the increased risk of thromboembolic events in patients receiving bevacizumab in clinical trials. Data were pooled from five randomized controlled trials that included a total of 1745 patients with metastatic colorectal, breast, or non-small-cell lung carcinoma. Combined treatment with bevacizumab and chemotherapy, compared with chemotherapy alone, was associated with an increased risk of arterial thromboembolic events (HR = 2.0, 95% confidence interval [CI] = 1.05 to 3.75; p = .031) but not for a venous thromboembolic event (HR = 0.89, 95% CI = 0.66 to 1.20; p = .44). The absolute rate of developing an arterial thromboembolism was 5.5 events per 100 person-years for those receiving combination therapy and 3.1 events per 100 person-years for those receiving chemotherapy alone (ratio = 1.8, 95% CI = 0.94 to 3.33; p = .076). Development of an arterial thromboembolic event was associated with a prior arterial thromboembolic event (p<0.001) or age of 65 years or older (p = 0.01).

Proteinuria has occurred in all bevacizumab clinical trials. Bevacizumab therapy has been associated with the development of proteinuria in up to 36% of patients with colorectal cancer (Avastin PI), where Grade 3–4 proteinuria (>3.5 g protein per 24 h urine or nephrotic syndrome) was observed in 6.5% of patients. A meta-analysis of randomized controlled trials with patients receiving bevacizumab indicated a relative risk of 1.4 for proteinuria with bevacizumab at a low dose (2.5 to 7.5 g/kg) and 1.6 at a high dose (10 to 15 mg/kg) suggesting a possible dose-dependency to bevacizumab-associated proteinuria (Izzedine H., 2010).

Table 2 (adapted from Izzedine, 2010) summarizes the incidence of proteinuria in several randomized Phase 2-3 trials.

Table 2 – Incidence of proteinuria in bevacizumab Phase 2-3 controlled randomized trials

Disease	Author	Treatment	n	Proteinuria (%)	
				Grades 1-4	Grades 3-4
Metastatic CRC	Hurwitz, 2004	IFL	397	21.7	0.8
		IFL + bevacizumab 5 mg/kg	393	26.5	0.8
	Hurwitz, 2005	5-FU/LV + placebo	98	25.1	0
		5-FU/LV + bevacizumab 5 mg/kg	109	34.9	1.8
Metastatic RCC	Giantonio, 2007	FOLFOX4	285	NA	0
		FOLFOX4 + bevacizumab 10 mg/kg	287	NA	0.7
		Placebo	40	15	0
	Yang, 2003	Placebo + bevacizumab 3 mg/kg	37	15	2
		Placebo + bevacizumab 10 mg/kg	39	25	3
	Rini, 2008	IFN- α	349	NA	0

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Disease	Author	Treatment	n	Proteinuria (%)	
				Grades 1–4	Grades 3–4
NSCLC	Sandler, 2006	IFN- α + bevacizumab 10 mg/kg	366	NA	15
		Carboplatin/Paclitaxel	444	NA	0
		Carboplatin/Paclitaxel + bevacizumab 15 mg/kg	434	NA	3.1

The risk of bleeding and hemorrhage is increased in patients treated with VEGF and VEGFR targeting agents. The most common types of bleeding described are mild spontaneous mucocutaneous bleeding and serious tumor-related bleeding. In all trials of bevacizumab, mucocutaneous hemorrhage has been observed in 20–40% of patients, with mild epistaxis being the most common presentation.

Lung carcinomas (especially squamous cell) and gastrointestinal tract tumors are associated with the highest risk and greatest severity of bleeding following VEGF inhibition. Severe or fatal hemorrhage events described in the Avastin PI include hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding. Across indications, the incidence of \geq Grade 3 hemorrhagic events among patients receiving bevacizumab ranged from 1.2% to 4.6%. In a Phase 2 randomized study comparing carboplatin/paclitaxel vs. bevacizumab and carboplatin/paclitaxel in previously untreated NSCLC (Johnson D., 2004), six out of 13 patients with squamous cell histology (31%) experienced a major life-threatening bleeding event described as hemoptysis or hematemesis, and four of these events were fatal. All six patients had centrally-located tumors close to major blood vessels. Five patients had cavitation or necrosis of tumors, either at baseline or developing during bevacizumab therapy. Because squamous cell tumors are more frequently centrally located and have a greater tendency to cavitate as compared to adenocarcinoma, it is not clear whether histology alone is the central risk factor for bleeding, or simply a surrogate for other risk factors.

E4599 was the trial leading to the approval of bevacizumab in NSCLC. E4599 (Sandler, 2006) was a randomized controlled trial that excluded patients with squamous histology. Grade 3–5 pulmonary hemorrhage events observed were 2.3% (10 of 427 patients) in the bevacizumab and chemotherapy arm compared with 0.5% (2 of 441) of those treated with chemotherapy only. Five of the hemoptysis events in the bevacizumab-containing arm were fatal.

The incidence of gastrointestinal perforation in the setting of CRC is 1.96 per 1000 procedures for colonoscopy and 0.88 for sigmoidoscopy. Perforation from either procedure occurs more frequently in older patients and in patients with co-morbidities (Wasif Said, 2007). Hypoxia, inflammation, impaired wound healing, diarrhea, and other effects that result from VEGF blockage increase the risk of bowel perforation and fistula. Aside from ovarian carcinoma, these complications are not as commonly observed in other tumor types.

In patients with metastatic colorectal cancer treated with bevacizumab, the rate of bowel perforation or gastro intestinal fistula was approximately 2.4% across clinical studies, compared with <1% in the comparator arms. In a recent meta-analysis (Hapani, 2009) of the risk of

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gastrointestinal perforation in patients treated with bevacizumab that included 12,294 patients with a variety of solid tumors from 17 randomized controlled trials, the incidence was 0.9% (95% CI 0.7–1.2) among patients receiving bevacizumab, with a mortality of 21.7% (11.5–37.0). Patients treated with bevacizumab had a significantly increased risk of gastrointestinal perforation compared with patients treated with control medication, with a relative risk of 2.14 (95% CI 1.19–3.85; $p=0.011$). Risk varied with bevacizumab dose and tumor type. Relative risks for patients receiving bevacizumab at 5 and 2.5 mg/kg per week were 2.67 (95% CI 1.14–6.26) and 1.61 (0.76–3.38), respectively. Higher risks were observed in patients with colorectal carcinoma (relative risk 3.10, 95% CI 1.26–7.63).

Wound healing is a complex process involving angiogenesis and closely regulated interactions between endothelial cells, platelets, and the coagulation cascade. VEGF inhibition can impair wound healing at a surgical site through the dehiscence of a previously healed wound, or delay or cause failure of wound healing in patients who underwent surgery following treatment with an anti-VEGF agent. Although most clinical trials with antiangiogenesis therapies required at least 28 days from any major surgery before starting treatment, the incidence of wound healing complications in the bevacizumab trials described in the Avastin label in subjects with colorectal cancer during the course of treatment was 15%, compared to 4% in patients who did not receive bevacizumab.

In a retrospective analysis of randomized trials in patients with metastatic CRC, for a subset of patients who had surgeries 28–60 days before initiating bevacizumab, Scappaticci et al. (Scappaticci, 2005) described a lower incidence of wound complications (1.3%). A Phase 3 adjuvant trial (NSABP-C08) in patients with CRC who received bevacizumab and chemotherapy at least 28 days after colectomy confirmed that although the rate of serious wound complications was low (1.7%), the rate was higher than that in the chemotherapy-alone control arm (0.3%) (Chen H, 2009). Current guidelines are largely empiric and recommend that bevacizumab be withheld for 4 weeks before elective surgery.

Cardiomyopathy and congestive heart failure have been reported following the administration of bevacizumab, mainly in the metastatic breast cancer setting and associated with anthracycline and taxane exposure. However, few trials have included prospective cardiac monitoring, and therefore, the extent of asymptomatic ventricular dysfunction cannot be fully assessed (Chen H, 2009).

On August 3, 2012, ziv-aflibercept was approved for the treatment –in combination with FOLFIRI- of patients with metastatic colorectal cancer who had progressed after an oxaliplatin-containing regimen. During the ziv-aflibercept review, data from 258 patients (data publicly available on http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125418Orig1s000MedR.pdf) enrolled in monotherapy studies TED6115/6, ARD6122/3, ARD6772, EFC6125 were analyzed. The most frequently reported (HLT) AE was asthenic conditions (asthenia and fatigue) in 46% of patients (12% Grades 3-4), followed by hypertension in 32% of patients (15% Grades 3-4). Nausea and vomiting were also frequent (29% and 28% respectively). AEs related to class-

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effect such as dysphonia, epistaxis, and proteinuria were observed in 26%, 10%, and 12% of patients, respectively. The incidence and pattern of AEs observed in the single-arm studies for those patients who received aflibercept at 4 mg/kg/dose was consistent with the toxicity observed in the aflibercept arm of the pivotal study, VELOUR. Some toxicities, particularly myelotoxicity, that were most likely related to the concomitant use of chemotherapy in the randomized trials, were not frequently reported in the single-agent studies.

The ziv-aflibercept (Zaltrap®) USPI contains box warnings for hemorrhage, gastrointestinal perforation, and compromised wound healing. In addition, in the Warning and Precautions section the label summarizes the risks of fistula formation, hypertension, RPLS, arterial thrombotic events, proteinuria, neutropenia and neutropenic complications, diarrhea, and dehydration.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 11856 for the development of ramucirumab was filed on July 29 2004. The original IND was filed by ImClone, which is now a fully-owned Eli Lilly subsidiary. The BLA was filed by Eli Lilly. Both names are interchangeably used in this particular application.

On May 28, 2008 FDA and ImClone held a Type B pre-Phase 3 meeting to discuss the development plan for ramucirumab in gastric cancer and reach agreement on the design for CP12-0715 (REGARD). FDA agreed with ImClone in most aspects of the proposal, with the exception of the following:

- 1) Stratification factors for randomization and analysis: ImClone proposed using weight loss and geographic region as stratification factors, and FDA recommended the addition of tumor localization (gastric vs. GEJ). FDA agreed to review the results of the REAL-2 study supporting ImClone's position that tumor location did not have an impact on prognosis.
- 2) Statistical design: REGARD was originally powered at 90% with an alpha=0.05 with 651 subjects in a 2:1 ratio of ramucirumab/best supportive care vs. placebo/best supportive care. Because this study was intended to serve as a single pivotal study for licensure, FDA stated that it should be based on a higher significance level and the results should be internally consistent across relevant subgroups. Alternatively, a second study in gastric cancer could generate supportive evidence to confirm the effect of ramucirumab on overall survival.

ImClone's position was that a similar study design with an alpha=0.01 would require approximately 1000 subjects, a difficult study to conduct considering that, in their estimation, only 15% of patients with gastric cancer are eligible for second line therapy, the largest randomized study published at that time in this setting had 64 patients, and no studies up to that time had demonstrated overall survival advantage.

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Reviewer's comment: on May 27 2010, ImClone and FDA held a meeting to discuss study CP12-0922, "A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel With or Without Ramucirumab in Patients with Metastatic Gastric Adenocarcinoma."

The REGARD protocol was submitted on June 10 2009. Amendments to the REGARD study were submitted on September 19, 2009 (v 4.0), April 6, 2010 (v 5.0), May 11, 2010 (v 5.1), December 21, 2010 (v 6.0), and December 1, 2011 (v 7.0). A summary of these changes and complete protocol descriptions can be found in Table 4 and Section 5.3.

On September 23, 2010, FDA issued a letter requesting that ImClone delete a change in version 5.1 that would have allowed subjects who were to start a new anticancer treatment to be assessed for PFS (to censor them for PFS evaluation). *Reviewer's comment: this change was included in protocol version 6, submitted 12/21/2010.* In addition, a general comment regarding premedication for infusion reactions applicable to all ramucirumab protocols was reiterated. Because premedication was recommended but not required, FDA requested ImClone adopt uniform rules regarding infusion reaction prophylaxis so that an adequate dosing and administration section of the label can be written.

On November 15, 2011, a Type C CMC meeting was held to discuss post-pivotal trial process changes and comparability plans. Drug substance Process A material was used in Phase 1 clinical studies, Process B material was used in Phase 2 clinical studies, and Process C material was being used in Phase 2 and Phase 3 clinical studies. Process C was to be manufactured at the commercial scale and at the proposed commercial facility. There were some changes in Process C from the process used in Phase 3 clinical trials and intended for marketing, designed to improve process control and consistency and product quality. These changes were proposed to be implemented subsequent to the validation of the commercial process. Generally speaking, FDA agreed that the plans for manufacturing were adequate and technical aspects were discussed.

On January 1, 2012, a Type C clinical pharmacology meeting was held to discuss population PK analyses for BLAs for the treatment of gastric cancer [REDACTED] carcinoma. Although (b) (4) FDA agreed to the general population PK analysis plans, FDA did not agree and strongly discouraged ImClone regarding a plan for an early database snapshot (with 75% of the OS events from the REGARD study) for the PK analysis, as unblinding of the data could jeopardize the integrity of the trial and potentially introduce bias. ImClone summarized the rationale for their proposal and the steps to be taken to control data integrity. FDA had no recommendations for additional measures to be taken and that ImClone will need to provide evidence in the BLA that the integrity of the trial had not been compromised by this analysis. ImClone would need to provide a summary of the steps taken to ensure integrity including evidence that the analysis plans for primary and key secondary endpoints had been finalized prior to the conduct of the population PK analysis.

On February 16 2012, FDA granted an orphan drug designation for ramucirumab for the treatment of patients with gastric cancer.

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On November 14 2012, FDA granted a Fast Track designation for the development of ramucirumab for the treatment of patients with gastric cancer.

On January 17, 2013, FDA and ImClone held a pre-BLA meeting to discuss the high-level results of the REGARD study, the proposed data package for the REGARD study to support filing of a complete application under the PDUFA V program, the overall content and format of the proposed BLA, the proposed submission plans to enable a rolling submission of the BLA under the Fast Track program, Lilly's request for priority review, proposed amendments including the 120 day safety update, and proposed expanded access program for ramucirumab for patients with advanced gastric cancer.

During the meeting, FDA expressed concern regarding the ability of the REGARD study as a single study to provide substantial evidence of effectiveness given the modest effect on overall survival demonstrated in the ramucirumab arm and the different magnitude of effect observed in some subgroups. Given that this is a new molecular entity, and given the effects observed in the REGARD study, FDA anticipates that this application will be discussed at an ODAC meeting in order to determine whether the Agency should wait for the results of the RAINBOW study prior to determining whether ramucirumab should be approved for the treatment of patients with gastric cancer. ImClone believed that the results of REGARD were robust and clinically meaningful and would support a finding of substantial evidence of effectiveness. ImClone stated that they would share with FDA the results of RAINBOW once they became available. FDA encouraged ImClone to submit the results of the RAINBOW trial in the BLA, but agreed that the results of the RAINBOW trial will not be required for filing. FDA requested that ImClone submit top-line results including datasets verifying the primary analysis, if these data become available during review of the BLA.

FDA and ImClone discussed and agreed on the contents of the clinical summaries and general contents of a BLA, including data from the ramucirumab safety database regarding infrequent adverse events observed in studies that such as RPLS, perforation, fistula, thrombotic microangiopathy, and Grade 4-5 hemorrhage.

FDA requested additional information regarding infusion reactions and premedication, as approximately 20% of subjects did not receive infusion reaction prophylaxis and the rate of these events in this subpopulation was not submitted in the meeting package.

FDA recommended that ImClone's evaluation of the impact of anti-product antibodies on PK include all antibodies, not just neutralizing antibodies. ImClone agreed to provide this evaluation.

The timelines for a rolling submission were discussed, and because ImClone needed to address some of FDA requests it was agreed that a new timeline would be submitted. FDA did not object to ImClone's proposal to initiate an expanded access program.

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On January 23, 2013, ImClone and FDA held a pre-BLA CMC meeting to seek concurrence from the Agency on the structure and content of the Quality Module (Modules 2.3 and 3) of the BLA, and regarding the proposed timing of pre-approval inspections. FDA stated Lilly needs to provide details of the manufacturing process [REDACTED] ^{(b) (4)} in the BLA, and other technical aspects of the submission were discussed.

On March 15 2013 FDA granted ImClone the proposed proprietary name, Cyramza.

On March 26 2013 agreed and accepted ImClone's proposed plan and timeline for the rolling submission.

2.6 Other Relevant Background Information

2.6.1 Gastric and GEJ adenocarcinoma

Epidemiology

More than 90% of stomach cancers are adenocarcinomas. Squamous cell carcinoma and adenocarcinoma account for more than 90% of esophageal cancers; however, the incidence of squamous cell esophageal carcinoma has been steadily declining, while the incidence of adenocarcinoma rose by 350 percent from 1974 to 1994, when adenocarcinoma surpassed the incidence of squamous cell esophageal carcinoma as the dominant histology (Devessa S., 1998). At the same time, the incidence of distal gastric cancer declined, while the incidence of proximal gastric cancer and distal esophageal adenocarcinoma increased. The shift in localization and the probable common etiology of distal esophageal and gastric carcinoma led to a common approach for the treatment of gastric and gastroesophageal junction (GEJ) carcinomas (Wijnhoven B., 1999), and most clinical studies conducted since the mid 1990s include patients with gastric and GEJ tumors. This review will use the term “gastric carcinoma” as a broad term that includes gastric adenocarcinoma and GEJ adenocarcinoma.

About one million new cases of stomach cancer were estimated to have occurred in 2008, making it the fourth most common malignancy in the world, behind cancers of the lung, breast, and colorectum. The incidence of gastric cancer varies with different geographic regions; more than 70% of cases occur in developing countries, and half the world total occurs in Eastern Asia. Age-standardized incidence rates are about twice as high in men as in women, ranging from 3.9 in Northern Africa to 42.4 in Eastern Asia for men, and from 2.2 in Southern Africa to 18.3 in Eastern Asia for women.

Stomach cancer is the second leading cause of cancer death in both sexes worldwide (736,000 deaths, 9.7% of the total). The highest mortality rates are estimated in Eastern Asia (28.1 per 100,000 in men, 13.0 per 100,000 in women), the lowest in Northern America (2.8 and 1.5 respectively). High mortality rates are also present in both sexes in Central and Eastern Europe, and in Central and South America (<http://globocan.iarc.fr/factsheet.asp>).

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Although the incidence of gastric cancer has been declining in Western countries, it is still a major health problem and a leading cause of cancer mortality. In the U.S., from 2005-2009, the median age at diagnosis for cancer of the stomach was 70 years of age (81% of patients were 55 years or older and over 60% were 65 years or older). The age-adjusted incidence rate was 7.6 per 100,000 men and women per year. The age-adjusted death rate was 3.6 per 100,000 men and women per year, and the median age at death for cancer of the stomach was 73 years of age (<http://seer.cancer.gov/statfacts/html/stomach.html#incidence-mortality>). It is estimated that 21,600 new cases of gastric cancer were diagnosed in 2012, and 10,990 patients died from gastric cancer in the same time period (Siegel R., 2013). In addition, in the U.S., the incidence and mortality rates of stomach cancer vary by race/ethnicity and sex. Incidence rates are much lower among Whites than other U.S. racial/ethnic groups. Mortality rates are highest in Asians/Pacific Islanders and African Americans, followed by American Indians/Alaska Natives, Hispanics, and Whites. Men have higher stomach cancer incidence and mortality rates than women (<http://www.cancer.gov/researchandfunding/snapshots/pdf/Stomach-Snapshot.pdf>).

Risk factors for stomach cancer include *Helicobacter pylori* (H. pylori) infection, certain medical and genetic conditions, smoking, family history of stomach cancer, a high-salt diet, and a diet low in fruits and vegetables. There is no standard or routine screening test for stomach cancer. Standard treatments for stomach cancer include surgery, chemotherapy, radiation therapy, and chemoradiation.

Treatment

Surgery

Surgery is the only potentially curative treatment for localized gastric cancer. However, almost 60% of patients who undergo a complete resection will relapse and die due to their disease; consequently, the overall 5-year survival rate of patients with resectable gastric cancer ranges from 10% to 30% (De Vita F., 2007).

Radiotherapy

In the setting of metastatic gastric cancer, radiation therapy is usually reserved for symptom control, especially pain or uncontrolled bleeding. Chemoradiotherapy is also administered to patients in the adjuvant setting (generally for patients with gastric cancer) or neoadjuvant setting (generally for patients with GEJ tumors being treated under esophageal cancer protocols).

First-line chemotherapy and targeted agents

In Western countries, 80–90% of patients are diagnosed at an advanced stage when the tumor is inoperable or develop recurrence within 5 years after surgery. The 5-year survival for advanced/metastatic gastric cancer is less than 10% and, despite the recent development of new chemotherapy regimens and the introduction of biologic therapy, median overall survival for patients with metastatic disease remains less than 1 year.

The appropriate management of patients with locoregional advanced non-resectable, recurrent, or metastatic gastric adenocarcinoma is variable. Treatment decisions in advanced gastric cancer have to consider more than just the potential benefit of chemotherapy, as patients with advanced

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gastric cancer may frequently have nutritional deficiencies be frail, or present with symptoms derived from high tumor burden. Because the main aims of treatment are to prolong survival and reduce the burden of symptoms, clinicians must balance treatment benefits while trying to minimize toxicities.

A Cocharane Collaboration meta analysis (updated by Wagner A. et al, 2010) assessed the efficacy of chemotherapy versus best supportive care, combination versus single agent chemotherapy, and different combination chemotherapy regimens in advanced gastric cancer. The meta analysis analyzed data from 35 trials, with a total of 5726 patients. In the meta analysis, the comparison of chemotherapy versus best supportive care (BSC) consistently demonstrated a significant benefit in overall survival in favor of the group receiving chemotherapy (HR 0.37; 95% CI 0.24 to 0.55, 184 participants). The comparison of combination versus single-agent chemotherapy provided evidence for a modest survival benefit in favor of combination chemotherapy (HR 0.82; 95% CI 0.74 to 0.90, 1914 participants), with increased toxicity in the combination chemotherapy arms.

When comparing 5-FU/cisplatin-containing combination therapy regimens with or without anthracyclines (HR 0.77; 95% CI 0.62 to 0.95, 501 participants) and 5-FU/anthracycline-containing combinations with or without cisplatin (HR 0.82; 95% CI 0.73 to 0.92, 1147 participants), there was a significant survival benefit for regimens including 5-FU, anthracyclines and cisplatin. Both the comparison of irinotecan versus non-irinotecan (HR 0.86; 95% CI 0.73 to 1.02, 639 participants) and docetaxel versus non-docetaxel containing regimens (HR 0.93; 95% CI 0.75 to 1.15, 805 participants) showed non-significant overall survival effects in favor of the irinotecan and docetaxel-containing regimens. The authors concluded that chemotherapy significantly improves survival in comparison to best supportive care. In addition, combination chemotherapy improves survival compared to single-agent 5-FU. The authors stated that all patients should be tested for their HER-2 status and trastuzumab should be added to a standard fluoropyrimidine/cisplatin regimen in patients with HER-2 positive tumors.

In the U.S., docetaxel was approved for the first-line treatment of gastric cancer in March 2006 based on the results of a multicenter, open-label, randomized trial that enrolled a total of 445 patients, treated with docetaxel 75 mg/m² on Day 1 in combination with cisplatin (C) 75 mg/m² on Day 1 and fluorouracil (F) (750 mg/m² per day for 5 days) or cisplatin (100 mg/m² on Day 1) and fluorouracil (1000 mg/m² per day for 5 days) every 3 weeks for the TCF arm and 4 weeks for the CF arm. Time to progression (TTP) was the primary endpoint. The hazard ratio for TTP was 1.47 (CF/TCF, 95% CI: 1.19;1.83) with a significantly longer TTP (p=0.0004) in the TCF arm. Approximately 75% of patients had died at the time of this analysis. Median OS was significantly longer supporting approval (9.2 vs. 8.6 p=0.0201) in the TCF arm with a HR of 1.29 (95% CI: 1.04–1.61).

In Europe and in the U.S., fluoropyrimidine and platinum-based combinations with or without the addition of a third drug, typically docetaxel (D) or epirubicin (E), are the most widely used chemotherapy combinations for first-line advanced gastric cancer. In the U.S. docetaxel is the preferred agent for use in combination with cisplatin (C) (i.e., DCF), based on the V325 trial in

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which improved survival was observed with DCF compared with CF (HR: 0.77; p = 0.02) (Van Cutsem E., 2006). The DCF regimen was, however, associated with severe toxicities, particularly myelosuppression with a 29% incidence of febrile neutropenia, and DCF triplet chemotherapy is thus typically considered only in carefully selected patients with good PS. Other treatment approaches have included the use of newer fluoropyrimidines and platinum agents. Two trials have evaluated the non-inferiority of capecitabine (X) to infusional 5-fluorouracil (F), and oxaliplatin (O) to cisplatin, in the combination regimens CX, OX, ECX, EOX and EOF (Kang Y., 2009; Koizumi W., 2008; Cunningham D., 2008).

HER-2 overexpression is observed approximately in 15-22% of patients with gastric cancer. FDA approved trastuzumab for the treatment of HER-2 positive gastric cancer based on the results of the ToGA study, a randomized trial that demonstrated a significantly improved median OS with trastuzumab in combination with chemotherapy (CX or CF) compared with chemotherapy alone (13.8 vs 11.1 months; HR: 0.74; p = 0.0046), and improved median PFS (6.7 vs. 5.5 months; HR: 0.71; p = 0.0002) (Bang Y, 2010). Time to progression (TTP), overall RR (ORR) and duration of response were also significantly improved with the addition of trastuzumab (Bang Y., 2010).

The role of antiangiogenic agents was explored in a small Phase 2 single-arm study with the combination of irinotecan, cisplatin, and bevacizumab, where 47 patients with previously untreated metastatic gastric and/or GEJ showed a median time to progression of 8.3 months and a median OS of 12.3 months (Shah M., 2006). Based on pre-clinical evidence and the results of this small Phase 2 study, a multinational, randomized, placebo-controlled trial to evaluate the efficacy of adding bevacizumab to capecitabine-cisplatin in the first-line setting of advanced gastric cancer (AVAGAST, Ohtsu 2011) was conducted. In the AVAGAST study, patients received bevacizumab 7.5 mg/kg or placebo in combination with cisplatin 80 mg/m² on Day 1 plus capecitabine 1000 mg/m² twice daily for 14 days every 3 weeks. Cisplatin was administered for 6 cycles and capecitabine and bevacizumab were administered until disease progression or unacceptable toxicity; 5FU was allowed if patients who were not able to tolerate oral medications. A total of 774 patients were enrolled (387 per arm). Median OS was 12.1 months in the bevacizumab plus arm and 10.1 months in the control group (HR 0.87, 95% CI 0.73;1.03, p=0.1002). The addition of bevacizumab to cisplatin/capecitabine increased the toxicity of the chemotherapy regimen, particularly hypertension, venous thromboembolism, perforations, diarrhea, and hand-foot syndrome.

Second-line treatment

Almost all patients with advanced gastric cancer will develop progressive disease after first-line therapy. Relatively few patients in Western countries (approximately 20% to 50% of patients receiving first-line treatment) receive second-line treatment (Chau I, 2004). NCCN guidelines list, in addition to chemotherapy, best supportive care and participation in clinical trials as appropriate options. A number of agents have demonstrated activity in the second-line setting in small Phase 2 trials, with modest benefit; however, no single regimen has shown superior activity. Commonly used second-line treatment approaches include re-challenge with cisplatin and fluorouracil (if progression occurs more than 3–6 months after first-line therapy), taxane

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monotherapy, irinotecan monotherapy or FOLFIRI or FOLFOX (Wesolowski R., 2009). In more recent Phase 3 trials, the percentage of patients receiving second-line therapy has ranged from 14% to as high as 42–45% (Price T., 2012).

The following table (modified from Price T., 2012) summarizes the results of some of these Phase 2 studies.

Table 3 - Phase 2 trials of second-line chemotherapy in advanced/metastatic gastric cancer

Treatment	Patients (n)	ORR	mTTP/PFS (months)	mOS (months)
Docetaxel 75 mg/m ² every 3 weeks	49	16	2.5	8.3
FOLFIRI every 2 weeks	38	29	3.7	6.4
Irinotecan 125 mg/m ² weekly x 3 weeks every 4 weeks	37	20	2.6	5.2
Irinotecan 160 mg/m ² plus docetaxel 65 mg/m ² every 3 weeks	49	20	2.7	8.9
Paclitaxel 80 mg/m ² weekly x 3 weeks every 4 weeks	38	24	2.1	5

Interpretation of these data is limited by the small sample size and/or the fact that different treatments and dosing schedules were used and the studies were conducted in single centers or countries.

The AIO trial, which closed prematurely owing to poor accrual, was the first Phase 3 study to investigate second-line chemotherapy in advanced gastric carcinoma. This was an open-label, randomized trial for patients with gastric or EGJ carcinoma who had received one line of prior therapy and experienced progression during or within 6 months of first-line therapy. Patients were randomized to receive irinotecan 250-350 mg/m² every two weeks plus best supportive care versus best supportive care alone. The primary endpoint was OS in the ITT, with an estimated OS in the best supportive care arm of 2.5 months. The study enrolled 40 patients (21 into the irinotecan arm and 19 in the best supportive care arm). Median OS was 4 months in the irinotecan arm and 2.4 months in the best supportive care arm (HR 0.48, 95% CI 0.25; 0.92, nominal p=0.012).

To study the benefits of second-line chemotherapy in gastric cancer, a multicenter, open-label, randomized Korean trial (Kang JH., 2012) enrolled 202 patients with advanced gastric cancer who were previously treated with one or two chemotherapeutic regimens with platinum and fluoropyrimidines (prior exposure to taxanes and irinotecan was not allowed). Patients were randomized to receive (2:1) chemotherapy with docetaxel 60 mg/m² every 3 weeks or irinotecan 150 mg/m² every 3 weeks (physician's choice) or best supportive care. With a median follow-up of 20 months, 91% of patients had died. Median OS increased from 3.8 months in the best supportive care arm to 5.3 months in the chemotherapy arm (HR 0.65, 95% CI 0.48;0.89, p=0.007). For exploratory purposes, the authors compared OS between docetaxel (median, 5.2

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months, 95% CI 3.8;6.6) and irinotecan (median, 6.5 months; 95% CI 4.5;8.5) and found no significant difference (two-sided p= 0.116).

COUGAR-02 (Ford H., 2013) was a multicenter, open-label, randomized Phase 3 trial for patients with locally advanced or metastatic esophageal or gastric adenocarcinoma who had progressed within 6 months of fluoropyrimidine/platinum chemotherapy. Patients were randomized to receive either docetaxel 75 mg/m² every 3 weeks for up to 6 cycles or active symptom control (which may have included radiotherapy). The primary endpoint was OS. A total of 168 patients were randomized (84 patients per arm). Only 23% of patients in the docetaxel arm were able to complete treatment, as 40% of them had disease progression during treatment: 15% died during treatment, and 31% experienced dose-limiting toxicities; in the best supportive care arm, 36% of patients completed treatment (38% patients died within 2 months of enrollment). Docetaxel improved survival over supportive care alone (5.2 months vs. 3.6 months, HR 0.67, 95% CI 0.49;0.92, p=0.01), but with significant toxicities (21% Grade 4 events).

The investigators of the AOI, Kang, and COUGAR-02 studies concluded that second-line chemotherapy should be offered to patients with advanced/metastatic gastric carcinoma.

Ultimately, there is no uniform clinical standard of care for patients with previously treated metastatic gastric cancer, and no treatment has been specifically approved by FDA for patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma following progression on initial chemotherapy.

2.6.2 VEGF/VEGFR inhibition

Angiogenesis is a multistep process, regulated by a complex balance of positive and negative regulatory factors. The two most potent regulatory molecules stimulating the formation of new blood vessels are VEGF and bFGF (beta fibroblast growth factor). The mammalian VEGF family consists of five glycoproteins: VEGFA, VEGFB, VEGFC, VEGFD (or FIGF) and placental growth factor (PIGF). The VEGF ligands bind to and activate three receptor tyrosine kinases: VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3 (Flt-4). In response to ligand binding, the VEGFR tyrosine kinase activates a network of downstream signaling pathways, including phospholipase C, PI3K, GAP, the Ras GTPase-activating protein and MAPK (Rodhart J., 2008). The activation of the VEGF pathway results in numerous changes within the tumor vasculature, including endothelial cell proliferation, migration, invasion, survival, vascular permeability, and vasodilation.

The proliferative and mitogenic activities of VEGF, as well as vascular permeability, appear primarily mediated by VEGFR-2. VEGFR-1 is expressed on endothelial cells and monocytes and mediates cell motility (Giles F. 2001). Transcription of the VEGF gene is regulated by hypoxia. Cellular and circulating levels of VEGF are increased in many malignancies, hematologic and non-hematologic, and are adversely associated with prognosis (Ellis L., 2008).

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2.6.2 VEGF/VEGFR in gastric/GEJ adenocarcinoma

VEGF may be overexpressed in gastric cancer and upregulation of VEGF family members has been associated with more aggressive clinical disease (Tanigawa N, 1997; Feng C. 2002). VEGF-A, VEGF-C, and VEGF-D upregulation in resected gastric cancer have been correlated with more frequent tumor recurrence and shorter survival (Karayiannakis A, 2002; Jüttner S. 2006).

As described above, AVAGAST (Ohtsu, 2011) was a multinational, randomized, double-blind, Phase 3 study designed to compare the efficacy of bevacizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for patients with advanced gastric cancer. Although bevacizumab was associated with a longer progression-free survival (nominal effect on point estimate) versus placebo (median, 6.7 v 5.3 months; hazard ratio [HR], 0.80) and higher overall response rate (46.0% v 37.4%), the difference in overall survival, the primary study end point, did not reach statistical significance (12.1 v 10.1 months; HR, 0.87; p=0.1002). AVAGAST contained a mandatory biomarker program in which blood samples and tissue were gathered to examine the hypotheses that plasma and tumor tissue markers involved in the VEGF pathway may have predictive value for the efficacy of bevacizumab in gastric cancer. The markers evaluated were circulating VEGF-A and tumor expression of VEGF-A, VEGFR-1 and VEGFR-2, and neuropilin-1.

The results of this biomarker analysis were recently published (Van Cutsem E., 2012). Baseline plasma samples were available from 712 patients (92%) and tumor samples from 727 (94%). All tumor biomarkers, except for VEGFR-1 (81%) and neuropilin-1 (88%), were analyzed in at least 90% of the overall study population. Patient characteristics of the biomarker populations were similar to those of the overall population, and there were no noteworthy differences between treatment groups in the baseline levels of each of the biomarkers. The authors concluded that plasma VEGF-A and tumor neuropilin-1 showed *potential prognostic* effects. For plasma VEGF-A, patients in the placebo group with high baseline plasma VEGF-A levels had a shorter median overall survival (8.3 months) than patients with low levels (12.9 months); for tumor neuropilin-1, patients in the placebo group with low expression levels had a shorter overall survival (9.8 months) than those with high expression levels (11.1 months).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of adequate quality for the clinical review.

The applicant did a thorough job requesting information from investigators, and the CRFs and narratives were complete and provided the information needed to supplement the databases..

This reviewer could not identify any issue that questions the integrity of the submission.

3.2 Compliance with Good Clinical Practices

All study reports contained in the BLA included a statement that the trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

On the basis of number of patients treated at the study sites and efficacy results, FDA identified three sites for inspections: site #410 (MD Anderson Cancer Center, Texas, USA), #852 (Hospital da Cancer de Barretos, Sao Paulo, Brazil), and #234 (Gangnam Severance Hospital, Seoul, North Korea).

3.3 Financial Disclosures

Financial disclosures were provided from investigators, sub-investigators, and Independent Data Monitoring Committee (IDMC) members for one study, CP12-0715 (I4T-IE-JBVD or REGARD), 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 Adenocarcinoma (GEJ) Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy.

Elli Lilly submitted Forms 3454, 3455, and a list of the investigators who did not respond to their requests regarding the submission of disclosable arrangements. A total of 589 investigators and sub-investigators in 29 countries reported no disclosable interests. There were two subinvestigators, who did not provide the information as required, despite multiple attempts from the Applicant to obtain the documents before the individuals left the institutions where they received training. Principal investigators at each site were contacted and they did not have a conflict of interest. The New Zealand site enrolled 2 patients, 6 patients were enrolled at the Spanish site.

There were two investigators who received honoraria from the Applicant: One investigator from [REDACTED] (b) (6), received 34,100.00 USD. One investigator from [REDACTED] (b) (6) received 27,725 USD. A total of 43 patients from 16 sites were enrolled in the U.S. [REDACTED] (b) (6) site; in this site, the HR was 1.54, favoring the placebo arm (decreases the chance of bias). Only [REDACTED] (b) (6) was enrolled at the [REDACTED] (b) (6) site.

Eli Lilly stated that they did not enter into any financial compensation with the investigators that reported no disclosable interests or the two investigators who did not submit the requested information.

In conclusion, there were no financial conflicts of interest that may have compromised the integrity of the results of the pivotal study REGARD.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

At the time of the completion of this review, the CMC review was still ongoing. For further details, please refer to final reviews to be completed by Drs. Dougherty and Kennett. The following summary reflects the Applicant's data.

Ramucirumab is composed of 4 polypeptide chains: 2 identical heavy (γ) chains, each consisting of 446 amino acids and 2 identical light (κ) chains, each consisting of 214 amino acids. The estimated molecular weight for the entire antibody is 146.8 kDa.

(b) (4) . (b) (4) Li Lilly stated that validation of the manufacturing process used to produce commercial material was successfully completed, and an analytical comparability assessment confirmed that the drug substance manufactured using the commercial process (b) (4)

Drug product for Phase 3 clinical studies was supplied as a sterile injectable liquid in single use vials containing 500 mg/50 mL, and stored at 2 – 8 °C. Two sites manufactured product for Phase 3 clinical studies:

(b) (4) An additional manufacturer of the ramucirumab drug product, Eli Lilly and Company (Lilly), Indianapolis, IN is proposed to manufacture commercial supply.

In an unrelated inspection, Lilly was advised that a Warning Letter was issued to (b) (4) on (b) (4). Lilly stated that they are aware of the Warning Letter and will submit a revised BLA, withdrawing the (b) (4) site and listing the Lilly Indianapolis IN Technology Center as the sole drug product manufacturing site for ramucirumab. Lilly stated that if approved, they will be able to supply the market with ramucirumab from the Indianapolis site.

FDA agreed (communicated to Lilly on November 27, 2013) that a submission of a revised Section 3.2.P.3.1, Manufacturers would not constitute a major amendment.

4.2 Clinical Microbiology

(b) (4)

(b) (4) The drug

product is available in two presentations, 500 mg/50 mL and 100 mg/10 mL.

The drug substance is manufactured at ImClone Systems LLC. The site was inspected from November 4-13, 2013 and the inspection was classified as NAI (no action indicated). The proposed shelf-life for drug substance is (b) (4)

The drug substance review from Drs Hughes and Kalavati dated January 10, 2013, recommended approval of ramucirumab from a CMC microbiology product quality perspective. The review of the microbial controls in drug product manufacture and sterility assurance of drug product is still pending, but no serious issues have been discussed at internal meetings.

4.3 Preclinical Pharmacology/Toxicology

For a complete review, please refer to Dr. Khasar's and Dr. Helms's review.

Following ICH S6 and ICH S9, genotoxicity and carcinogenicity studies were performed with ramucirumab. Reproductive and developmental toxicity testing of ramucirumab was not conducted (see discussion in Sections 7.6.1 and 7.6.2).

The key findings of the nonclinical safety/toxicology studies of ramucirumab were as follows:

- Ramucirumab was well tolerated in the 5-week repeat-dose toxicity study at dose levels from 4 to 40 mg/kg for 4 doses. The NOAEL (no-observed-adverse-effect level) in this study was 40 mg/kg, the highest dose administered.
- No treatment-related adverse effects were observed after 11 weekly administrations of ramucirumab at dose levels of 5, 16, and 50 mg/kg to female cynomolgus monkeys in the 39-week study. A NOAEL (no-observed effect level) for ramucirumab was not established after once weekly intravenous administration for 39 weeks in cynomolgus monkeys.
- Pathological changes in the bone growth plate (thickening, osteochondropathy of the epiphyseal growth plate) occurred after 39 once weekly administrations of ramucirumab to monkeys at doses of 5 mg/kg and higher.
- Pathological changes indicative of renal toxicity (increased kidney weight, glomerulonephritis with secondary changes in the renal tubules, collecting ducts and interstitium) were evident after 39 weekly doses of 16 and 50 mg/kg of ramucirumab.

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- Clinical pathology indicators of renal toxicity (increased BUN and creatinine, decreased serum albumin, and urinary protein loss) were manifested at 16 and 50 mg/kg after 26 weeks.
- Ramucirumab did not impair wound healing in a linear incision model in monkeys at doses up to 50 mg/kg.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Ramucirumab is a monoclonal antibody that specifically binds VEGF Receptor 2 (VEGFR-2), preventing the interaction with activating ligands and intracellular downstream signaling. VEGFR-2 is expressed predominantly in the endothelial and hematopoietic cells and overexpressed in the vasculature of human cancers.

The nonclinical pharmacology characterization of ramucirumab included *in vitro* studies of the binding and functional inhibition of VEGFR-2 by ramucirumab. Ramucirumab binding to VEGFR-2 inhibits cellular responses that result from VEGFR-2 activation by VEGF-A and VEGF-C, including proliferation of human endothelial cells, and VEGF-induced phosphorylation of VEGFR-2 in human umbilical vein endothelial cells (and also in engineered to express human VEGFR-2 animal models).

4.4.2 Pharmacodynamics

The pharmacodynamics of ramucirumab has been evaluated in *in-vitro* and *in-vivo* models. Ramucirumab does not cross-react with the murine homolog of human VEGFR-2 and *in-vivo* evaluations were conducted using a surrogate of ramucirumab (DC101, which is a rat anti-mouse VEGFR-2-specific monoclonal antibody).

The key findings from nonclinical pharmacology studies of ramucirumab are as follows:

- Ramucirumab binds with high affinity to human VEGFR-2 and is a potent inhibitor of soluble VEGF Receptor 2 binding to VEGF-A, blocking VEGF-A stimulated activation. VEGF-C and VEGF-D interactions with VEGFR-2 are also blocked.
- Ramucirumab is highly specific for VEGFR-2 and does not cross-react with VEGFR-1 and VEGFR-3.
- Ramucirumab inhibits sprouting and proliferation of endothelial cells following stimulation with VEGF-C.

Data from Phase 1 and 2 studies (data submitted for studies JVBO, JVBP, JVHQ, and JVBR) in humans showed that across all dose groups tested, increases in serum VEGF relative to baseline

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occurred following ramucirumab infusion, suggesting that ramucirumab is binding to VEGFR-2 and preventing receptor binding of circulating VEGF. In contrast to VEGF concentrations, sVEGFR-1 and sVEGFR-2 concentrations generally decreased immediately after ramucirumab infusion and then recovered to near pretreatment levels during the treatment cycle.

4.4.3 Pharmacokinetics

For a complete review, please refer to Dr. Zhang and Dr. Hong review. Data from multiple Phase 1, 2 (Studies JVBM, JVBN, JVBI, JVBW, etc) and the REGARD data have been submitted to the BLA.

The REGARD study and Study JVBW (a Phase 1b, single-arm, open-label, multicenter, study in combination with paclitaxel in Japanese subjects with advanced gastric cancer) provided the primary PK data this application.

The geometric mean half-life ($t_{1/2}$) of ramucirumab in Study JVBW was approximately 8 days (range: 6 to 9) following IV infusion of a single dose of 8 mg/kg ramucirumab. Following an 8 mg/kg every-2-week ramucirumab dose regimen, trough concentrations exceeded the target trough concentration associated with antitumor activity in preclinical models (18 μ g/mL) in the majority of patients. In REGARD, trough samples collected prior to infusion at Cycles 4 and 7 showed the geometric mean trough concentrations (C_{min}) were 49.5 μ g/mL (percent coefficient of variation [CV%] = 80.6; range: 6.3 to 228 μ g/mL) and 74.4 μ g/mL (CV% = 58.3; range: 13.8 to 234 μ g/mL), respectively. Eli Lilly concluded that based upon multiple linear regression analysis of these C_{min} data in REGARD suggested that age, gender, body weight, hepatic status, and renal function did not appear to influence ramucirumab PK to an extent that would warrant any dose adjustment.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

One study was used to support efficacy (JVBD, REGARD). Refer to Section 7 below regarding studies used to support safety.

5.2 Review Strategy

The efficacy analysis was centered on the evaluation of one trial, JBVD or “REGARD”, 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

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Adenocarcinoma (GEJ) Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy.

The safety analysis was based on data from REGARD, and an integrated database with 334 patients treated with ramucirumab in several Phase 1 and 2 monotherapy studies (Table 24). This pooled population was heterogeneous and uncontrolled, and therefore data from this population was used in this review as supportive data, in particular data regarding VEGF/R inhibition-related toxicity.

5.3 Discussion Study CP12-0715 (REGARD)

One study supported this application, **IMCL CP12-0715 (I4T-IE-JBVD or REGARD), 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 Adenocarcinoma (GEJ) Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy.** The following summarizes the protocol latest version (amendment 6.0 [version 7.0], that was dated 31 Oct 2011 and submitted to the IND on December 21 2011). Changes in the protocol between versions are summarized in Table 4.

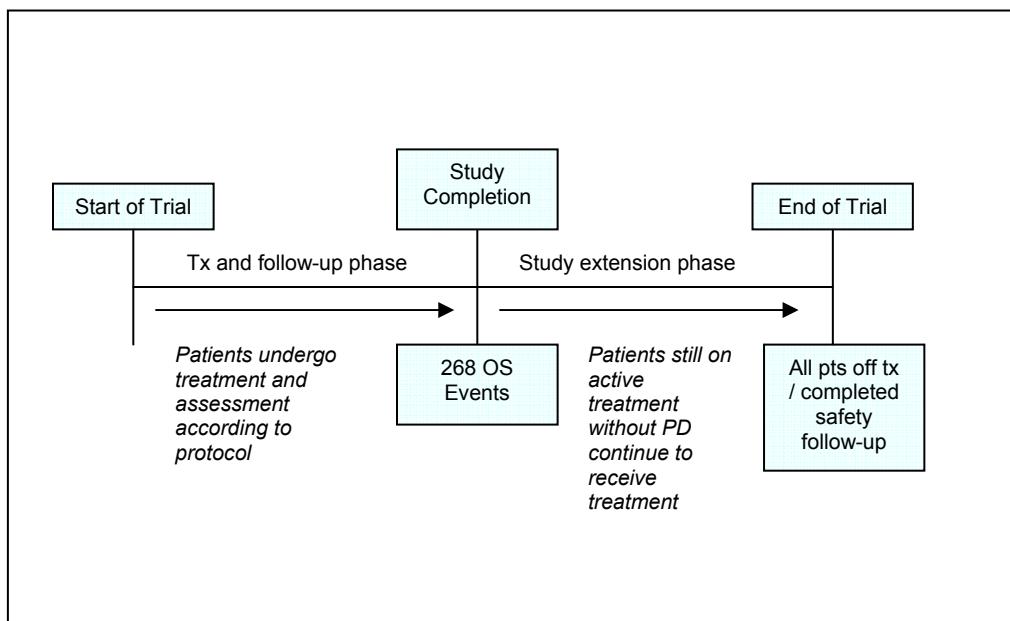
At the time the study was designed and initiated, there was no evidence that any therapy was superior to other agents/regimens and no agent had been demonstrated to improve survival over best supportive care (BSC). Analyses of efficacy data from studies of second-line therapy for gastric cancer had been limited by the small numbers of patients, use of varied first-line regimens, and heterogeneous patient populations. Given the lack of a regimen specifically approved in this setting and the lack of an established standard of care, the Applicant considered BSC as an appropriate control.

Study design

REGARD is a placebo-controlled, double-blinded, multicenter Phase 3 study of subjects with metastatic gastric cancer (including adenocarcinoma of the gastroesophageal junction) and radiographic evidence of disease progression on prior standard first-line chemotherapeutic regimens. Patients were randomized on a 2:1 basis to receive BSC plus ramucirumab administered every 2 weeks or BSC plus placebo administered every 2 weeks, respectively. Radiographic assessment of disease status was performed every 6 weeks. Subjects were treated until there was evidence of progressive disease, unacceptable toxicity, withdrawal of consent, or until other withdrawal criteria were met.

After 268 deaths were to be observed for analysis of the primary endpoint, the study would be completed. At this time, patients who were on study drug were unblinded; those receiving active study drug and experiencing ongoing clinical benefit (i.e., no disease progression) could continue to receive study therapy in the extension phase. Figure 1 summarizes the study design.

Figure 1 - REGARD: Study diagram (modified from the submission)



Objectives:

Primary objective: To evaluate the overall survival of patients with metastatic gastric cancer (including adenocarcinoma of the GEJ) following disease progression on first-line platinum- or fluoropyrimidine-containing combination chemotherapy who undergo treatment with ramucirumab plus BSC versus placebo plus BSC.

Secondary objectives:

- To evaluate progression free survival (PFS), including 12-week PFS rate, associated with ramucirumab versus placebo
- To evaluate the objective response rate (ORR)
- To evaluate the duration of response
- To evaluate the quality of life (QoL)
- To evaluate the safety profile of ramucirumab
- To examine the pharmacodynamic profile of ramucirumab
- To assess the immunogenicity of ramucirumab.

Study population (modified for brevity)

Inclusion criteria

1. Histologically- or cytologically-confirmed gastric carcinoma, including gastric adenocarcinoma or GEJ adenocarcinoma (patients with adenocarcinoma of the distal esophagus were eligible if the primary tumor involves the GEJ).
2. Metastatic disease or locally recurrent, unresectable disease.
 - Patients with non-regional lymph node metastases were eligible; lymph node metastases must be measurable as defined by RECIST 1.0.

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- For patients who received prior radiation therapy, measurable or evaluable lesions must be outside the radiation field, or (for lesions within the radiation field) there must be documented progression following radiation therapy.
- 3. Measurable disease and/or evaluable disease, defined as at least one unidimensionally-measurable target lesion (≥ 20 mm with conventional techniques or ≥ 10 mm by spiral CT), as defined by RECIST 1.0. Examples of evaluable, non-measurable disease included gastric, peritoneal, or mesenteric thickening in areas of known disease, or peritoneal nodules that were too small to be considered measurable by RECIST.
- 4. 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.
- 5. Disease not amenable to potentially curative resection.
- 6. ≥ 18 years of age.
- 7. Life expectancy of ≥ 12 weeks.
- 8. Resolution to Grade ≤ 1 (or to Grade ≤ 2 in the case of neuropathy) of all clinically significant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy.
- 9. ECOG PS 0-1.
- 10. Adequate hepatic function: total bilirubin ≤ 1.5 mg/dL and ALT/AST $\leq 3.0 \times$ ULN (or $5.0 \times$ ULN in the setting of liver metastases).
- 11. Adequate renal function: serum creatinine $\leq 1.5 \times$ ULN, or creatinine clearance (measured via 24-hour urine collection) ≥ 40 mL/minute.
- 12. Urinary protein $\leq 1+$ on dipstick or routine urinalysis; if urine dipstick or routine analysis was $\geq 2+$, a 24-hour urine collection for protein must demonstrate < 1000 mg of protein in 24 hours to allow participation in the study.
- 13. Adequate hematologic function: ANC $\geq 1000/\mu\text{L}$, hemoglobin $\geq 9 \text{ g/dL}$, and platelets $\geq 100,000/\mu\text{L}$.
- 14. INR ≤ 1.5 and a PTT ≤ 5 seconds above the ULN (unless receiving anticoagulation therapy). The protocol required that patients on full-dose anticoagulation receive a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If receiving warfarin, the patient must have had an INR ≤ 3.0 and no active bleeding within 14 days prior to the first dose of study therapy or a pathological condition with a high risk of bleeding (e.g., tumor involving major vessels or known varices). Patients on anticoagulation therapy with unresected primary tumors or local tumor recurrence following resection were not eligible.
- 15. If prior anthracycline therapy as part of first-line regimen, the patient must be able to engage in ordinary physical activity without significant fatigue or dyspnea (NYHA Class I function).
- 16. Patients, if sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods).
- 17. Female patients of childbearing potential must have tested negative for pregnancy within 7 days prior to randomization.
- 18. Provided informed written consent.

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Exclusion criteria

1. Documented and/or symptomatic brain or leptomeningeal metastases.
2. Grade 3-4 gastrointestinal bleeding within 3 months prior to randomization.
3. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to randomization.
4. Ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, uncontrolled thrombotic or hemorrhagic disorder, or any other serious uncontrolled medical disorders in the opinion of the investigator.
5. Ongoing or active psychiatric illness or social situation that would limit compliance with study requirements.
6. Uncontrolled or poorly-controlled hypertension despite standard medical management.
7. Serious or non-healing wound, ulcer, or bone fracture within 28 days prior to randomization.
8. Chemotherapy, radiotherapy, immunotherapy, or targeted therapy for gastric cancer within 2 weeks prior to randomization.
9. Any investigational therapy within 30 days prior to randomization.
10. Major surgery within 28 days prior to randomization, or subcutaneous venous access device placement within 7 days prior to randomization.
11. Prior therapy with an agent that directly inhibits VEGF or VEGFR-2 activity (including bevacizumab), or any antiangiogenic agent.
12. Chronic anti-platelet therapy, including aspirin, NSAIDs, dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.
13. Elective or planned major surgery to be performed during the course of the clinical trial.
14. Known allergy to any of the treatment components.
15. Pregnant or lactating.
16. HIV positive.
17. Known alcohol or drug dependency.
18. Concurrent active malignancy other than adequately-treated non-melanomatous skin cancer, other noninvasive carcinoma, or in situ neoplasm. A patient with previous history of malignancy is eligible, provided that he/she has been free of disease for > 3 years.

Study treatment

Centers enrolled/registered patients into the study using either an electronic data capture (EDC) system or by accessing a call-in Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) that randomly assigned patients on a 2:1 basis to receive either ramucirumab or placebo, respectively. Upon completion of randomization, the first dose of ramucirumab or placebo was administered within 7 days.

The ramucirumab dose was selected based on the results of a Phase 1 study (JVBM) that evaluated weekly doses of ramucirumab ranging from 2 to 16 mg/kg. The MTD for weekly

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dosing was identified as 13 mg/kg (DLTs in the 16-mg/kg weekly dose cohort included Grade 3 deep vein thrombosis and Grade 3 hypertension). Activity was observed across a range of doses. Pharmacokinetic results from this study suggested that ramucirumab exhibited nonlinear pharmacokinetic (PK) characteristics between 2 and 8 mg/kg; PK profiles appeared to be linear at and above 8 mg/kg, suggesting saturation of the VEGFR-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, JVBN. Two dose regimens, 8 mg/kg every 2 weeks and 10 mg/kg every 3 weeks, were selected for subsequent studies. These doses and schedules were selected because they were associated with PK profiles suggesting target receptor saturation. The Applicant stated that preliminary efficacy was observed in Phase 1 studies at and below these doses and schedules.

Patients in the ramucirumab group received ramucirumab I.V. infusion every 2 weeks at a dose of 8 mg/kg and BSC as determined appropriate by the investigator(s). Patients in the placebo group received an equivalent volume of placebo by I.V. infusion every 2 weeks, and BSC as determined appropriate by the investigator(s). The infusion of ramucirumab/placebo was delivered over 60 minutes (infusion rate should not exceeding 25 mg/minute).

All patients continued to receive treatment until there was evidence of progressive disease, unacceptable toxicity, or withdrawal of consent, or until other withdrawal criteria were met.

Premedication was recommended, but only required in the setting of prior Grade 1-2 infusion reaction. Standard guidelines to manage infusion reactions were provided in the protocol. Subjects with a Grade 3-4 infusion reaction to ramucirumab/placebo received no further ramucirumab/placebo.

Dose modifications

Dose modifications were permitted for ramucirumab/placebo in the setting of non-life-threatening, reversible Grade 3-4 clinical adverse events (i.e., fatigue, anorexia, fever) that resolved to Grade ≤ 1 within one treatment cycle (approximately 2 weeks). Once ramucirumab/placebo was re-administered, if there was a second occurrence of the event, ramucirumab/placebo was dose reduced to 6 mg/kg. A second dose reduction to 5 mg/kg every other week was permitted for this level of event (Grade 3-4). Subsequent dose increases were not permitted.

Asymptomatic Grade 3-4 laboratory abnormalities did not require dose interruptions, modifications, or discontinuation of ramucirumab/placebo unless determined to be clinically significant by the investigator.

For Grade 1-2 asymptomatic hypertension, instructions were to continue ramucirumab/placebo; for symptomatic Grade 1-2 hypertension ramucirumab/placebo was to be held until resolution after initiation of antihypertensive therapy. For Grade 3 hypertension not associated with symptoms, ramucirumab/placebo was to be continued with more intensive anti-hypertensive therapy. If systolic BP remained ≥ 160 mmHg or diastolic BP ≥ 100 mmHg > 2 weeks after

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initiation of additional anti-hypertensive therapy, then ramucirumab/placebo was held while continuing appropriate anti-hypertensive therapy. If the Grade 3 hypertension was associated with symptoms, ramucirumab/placebo was held until symptoms resolved with anti-hypertensive therapy. If ramucirumab/placebo was held more than once for hypertension, then ramucirumab/placebo was dose reduced up to two times. Patients with Grade 4 hypertension or patients whose hypertension was poorly controlled (> 160 mmHg systolic or > 100 mmHg diastolic for > 4 weeks) despite appropriate oral medication (> 2 oral agents at maximum tolerated dose) were discontinued from receiving investigational ramucirumab/placebo.

Patients who developed Grade 3-4 venous thrombotic events or pulmonary embolism were allowed to continue study therapy if the event was not considered to be life-threatening in the opinion of the investigator, the patient was asymptomatic, and/or the event could be adequately treated with low molecular weight heparin-based therapy. Study treatment was discontinued for Grade 3-4 arterial thromboembolic events, or any PE/DVT occurring or intensifying during anticoagulant therapy.

Ramucirumab/placebo therapy was discontinued in the event of any Grade 3-4 bleeding and/or gastrointestinal perforation.

If, while on therapy, a patient developed proteinuria $\geq 2+$ per a dipstick or routine urinalysis, ramucirumab/placebo therapy was continued as scheduled, and a 24-hour urine collected prior to the subsequent scheduled treatment cycle. If the protein level was $< 2\text{g}/24$ hours, the patient continued on study therapy at the same dose without interruption. If the protein level was 2 to 3 $\text{g}/24$ hours, study therapy for the subsequent cycle was held for up to 2 weeks and a 24-hour urine collection repeated. Treatment was resumed at a reduced dose level (6 mg/kg every other week) once the protein level returned to $< 2\text{g}/24$ hours. A second dose reduction (to 5 mg/kg every other week) was permitted if the protein level $> 2\text{g}/24$ hours recurred. The patient was discontinued from the study if the protein level was $> 3\text{g}/24$ hours, if there was a third occurrence of proteinuria $> 2 \text{ g}/24$ hours, or if the protein level did not return to $< 2\text{g}/24$ hours within 2 weeks.

Concomitant therapy

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment was offered to all patients during this trial.

Additional concurrent anticancer treatment was not permitted.

Chronic antiplatelet therapy, including NSAIDs (e.g., ibuprofen, naproxen, and others), dipyridamole or clopidogrel was not permitted. Aspirin was permitted at doses ≤ 325 mg once daily. At study entry, patients on full-dose anticoagulation must have been on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If on warfarin, an INR ≤ 3 with no active bleeding or pathological condition present that carried a high risk of bleeding (eg, tumor involving major vessels or known varices) was allowed.

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It was recommended that if major surgery was required, the surgery either should have been performed more than 28 days prior to randomization or postponed until at least 28 days after study completion, when possible, and that subcutaneous venous access devices be placed at least 7 days prior to randomization if their use was likely to be warranted.

Treatment withdrawal

The investigator could withdraw a patient from ramucirumab/placebo for any of the following reasons:

- The Sponsor or investigator terminated the study.
- Unacceptable adverse event/toxicity.
- Grade 3-4 infusion reaction.
- Grade 3-4 arterial thrombotic event.
- Grade 3-4 venous thrombotic event that considered life-threatening in the opinion of the investigator, or that could not be adequately treated with low molecular weight heparin-based therapy.
- PE/DVT occurring or intensifying during anticoagulant therapy.
- Grade 3-4 bleeding or hemorrhagic event.
- Any therapy-related event deemed life-threatening.
- Any event that would require study therapy to be modified by more than two dose reductions or that necessitated two or more consecutive missed doses of ramucirumab/placebo.
- Radiographic determination of progressive disease.
- Protocol noncompliance.
- Intercurrent illness or change in the patient's condition that rendered the patient unsuitable for further treatment in the opinion of the investigator.
- Withdrawal of consent.
- A decline in ECOG PS of ≥ 2 points (i.e., from 0 to 2, or 1 to 3) during the course of therapy on study, even in the absence of radiographic evidence of disease progression.
- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.

Efficacy assessments

The complete schedule of efficacy assessments can be found in Table 68. Patients were evaluated for response according to RECIST Version 1.0 guidelines every 6 weeks. In addition to a baseline scan, confirmatory scans were obtained no fewer than 4 weeks following initial documentation of objective response. The protocol recommended that the same method of assessment be used to characterize each identified and reported lesion at baseline and at reassessment.

Safety assessments

Toxicity was assessed using the NCICTCAE 4.02 dictionary. The protocol used standard (CRF 312.32) definitions of adverse events (AEs) and serious adverse events (SAEs). All identified adverse events were to be recorded and described in the eCRF. All laboratory test values were recorded on the appropriate laboratory test results pages of the eCRF, with instructions to capture

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as an AE any laboratory test result that met the criteria for an SAE, any laboratory abnormality that required the patient to have study therapy discontinued, modified, or interrupted, and any laboratory abnormality that required the patient to receive specific corrective therapy.

Adverse events of interest to ImClone included infusion reactions, hypertension, arterial or venous thrombotic events, hemorrhagic events, and proteinuria.

All scheduled monitoring procedures are summarized in Table 68.

Statistical methods

Randomization was stratified by weight loss ($\geq 10\%$ over the prior 3 months versus $< 10\%$), geographic region (North America, Europe, Australia, and New Zealand versus South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia versus Asia), and location of the primary tumor [gastric (including tumors of the gastric cardia that extend into the GEJ) versus GEJ (including tumors of the distal esophagus that extend into the GEJ, and tumors involving the GEJ when precise identification of the organ of origin is not possible)].

The primary statistical analysis included all enrolled, randomized patients following the ITT principle, including eligible and ineligible patients. For secondary analyses, the per protocol population (PPP), defined as patients who were randomized and treated, patients who did not have a major protocol violation, such as noncompliance with the inclusion or exclusion criteria, or other major protocol noncompliance during the study was used

Safety analyses were performed on all patients who received the investigational product. Adverse events that were unrelated to treatment and occurred more than 30 days after the administration of the last dose of treatment were not reported or analyzed. Safety evaluation was performed based on the actual regimen (ramucirumab or placebo) that a patient received.

The protocol stated the sample size was 348 patients with 268 events required for the final analysis. The sample size assumed OS to be exponentially distributed, with median OS of 5 months in the control arm (placebo + BSC) and an increase of at least 45% in the ramucirumab plus BSC arm (median 7.25 months, HR = 0.69).

The sample size was determined using a group sequential analysis methodology based on the following assumptions:

- Overall one-sided type I error rate is 0.025 (or two-sided at 0.05) and study power of 80%;
- Median OS of 5 months in the placebo plus BSC control arm;
- It is of clinical interest to show a 45% (2.25-month) improvement in median OS in the ramucirumab arm (i.e., 7.25 months, or HR = 0.69);
- Randomization ratio of 2:1 (ramucirumab plus BSC: placebo plus BSC);
- One interim futility analysis at 35% of total number of OS events, with a non-binding futility boundary to be determined using beta-spending function Gamma (-1);
- 30-month accrual period with assumed accrual rate; and
- Drop-out rate of 10%.

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An interim futility analysis was planned at approximately Month 25, with approximately 229 patients enrolled. During the interim analysis, the beta spent was about β (0.35) = 4.9%, and the futility boundary was approximately HR = 0.992 (e.g., median OS of approximately 5.04 months for the ramucirumab arm vs. 5 months for the control arm). The overall type I error rate was not be adjusted for futility analysis.

The primary analysis is the comparison of the OS observed with ramucirumab versus placebo for the ITT population using a log-rank test stratified by randomization strata, with an additional analysis using an unstratified log-rank test. The estimation of survival curves for the two treatment groups was generated using the Kaplan-Meier method, and a stratified Cox regression model to compare the treatments was to be used to generate the hazard ratio. In the event of a large percentage of discordance between the randomization strata based on the IVRS/IWRS and the eCRF, a sensitivity analysis was planned. Additional unstratified Cox regression models were performed to explore the effects of prognostic variables, such as the stratification variables, and intrinsic/extrinsic factors on treatment response.

Secondary efficacy endpoints included progression-free survival, 12-week PFS rate, objective response rate, and duration of response. The analysis of the secondary endpoints was adjusted by the stratification factors and performed in a hierachal way. PFS was defined as the time from the date of randomization until the date of objectively determined progressive disease (PD) or death due to any cause, whichever occurred first. However, for PD or deaths without progression occurring after two or more missed tumor assessments, PFS was censored at the time of the last tumor assessment in the primary analysis. A sensitivity analysis using PD and death as events, regardless of the number of missed visits was planned. Patients alive and without disease progression were censored at the time of the last objective tumor assessment. Patients who did not progress and were subsequently lost to follow-up (or who initiated new anticancer therapy) had their data censored on the day of their last objective tumor assessment as will patients who begin new anticancer therapy. The analyses of PFS followed the same methods as the OS analyses (Kaplan-Meier method, using the log-rank test, stratified by randomization factors, etc.).

The 12-week PFS rate was defined as the probability of being alive and progression-free 12 weeks after randomization. The 12-week PFS rate in each treatment group was estimated using the Kaplan-Meier method with 95% confidence intervals.

The ORR was equal to the proportion of patients achieving a best overall response of partial or complete response (PR + CR). Patients who did not have a tumor response assessment for any reason were considered non-responders and included in the denominator when calculating the response rate. The ORR in each treatment group was compared using the Cochran-Mantel-Haenszel test adjusting for the stratification variables.

The REGARD protocol was modified several times. Table 4 summarizes the main changes to the protocol.

Table 4 - REGARD: Summary of main changes to protocol

Protocol version	Main changes to protocol
Original (3/5/2008)	
Version 2.0 (7/22/2008)	<p>Revised the planned number of study centers from 200 to approximately 250.</p> <p>Criterion #13 was amended to require hemoglobin ≥ 9 g/dL (prior version: 8 g/dL).</p> <p>Addition of location of primary tumor (gastric vs. GEJ) to the list of stratification factors.</p> <p>Addition of a section specifying that premedication was not required prior to administration of ramucirumab or placebo but may be used at the investigator's discretion in the setting of a prior infusion reaction.</p> <p>The sample size of 651 patients was changed to 615 patients.</p>
Version 3.0 (11/4/2008)	<p>The secondary endpoint of "16-week PFS" was changed to "12-week PFS."</p> <p>Inclusion criterion #3 was amended to allow for the inclusion of patients with non-measurable, evaluable disease.</p> <p>Radiological assessment of tumor response was changed to every three treatment cycles (i.e., every 6 weeks). In prior versions radiological assessments were scheduled every four cycles (i.e., every 8 weeks).</p> <p>The IDMC convened for this study was to meet to conduct a review of safety data when 50 and 150 patients received at least three cycles of study drug (instead of two).</p> <p>Addition of a provision censoring tumor progression data on the date of last objective tumor assessment for patients who began a new anticancer therapy.</p> <p>No patient was enrolled under the original protocol through amendment 3.0 (inclusive).</p>
Version 3.1 (12/23/2008)	Administrative changes
Version 4.0 (7/1/2009)	<p>Adverse event reporting changed to NCICTCAE Version 4.0.</p> <p>The planned geographic region strata were amended throughout so patients would be stratified according to geographic region as follows: North America, Europe, Australia, and New Zealand vs. South and Central America, India, Egypt, South Africa, Jordan, Lebanon, and Saudi Arabia vs. Asia.</p>
Version 5.0 (2/8/2010)	Adverse event reporting changed to NCICTCAE Version 4.02.
Version 5.1 (4/20/2010)	<p>Addition of language clarifying that the analysis of the secondary endpoints would be adjusted by the stratification factors. Secondary endpoints would be analyzed at the same time as OS and at the same level of significance. Since these analyses were to be performed in a hierarchy, no multiplicity adjustments were deemed by the sponsor as necessary, as secondary variables could not be claimed as evidence if the primary endpoint was not significant.</p>
Version 6.0 (11/23/2010)	<p>The planned sample size for this study was reduced to 315 patients from 615 patients, and all statistical assumptions for accrual period, follow-up period, and drop-out rate, and the parameters to be used for interim analyses of futility and for the final primary analysis of efficacy were adjusted. In addition, due to the reduction in the size of the study, the previously planned interim analysis for unequivocal efficacy (to have been conducted when 344 OS events were observed) was deleted, as well as the third planned interim analysis for futility (at 75% of the total expected events).</p> <p>The minimum duration of survival follow-up after discontinuation of study therapy (and after the required number of OS events have been reported) was reduced from 18 months to one year.</p>

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Version 7.0 (10/31/2011)	<p>Increase the sample size of this study to 348 patients from 315 patients (protocol Version 6.0). In addition, the planned number of futility analyses was reduced from two (at 25% and 50% of the expected number of overall survival events) to one (at 35% of the expected number of events), and the futility analysis changed from binding to non-binding.</p> <p>At the time of this amendment, 280 patients had been enrolled in the study.</p>
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6 Review of Efficacy

Efficacy Summary

The efficacy of ramucirumab in the treatment of locally advanced or metastatic gastric or gastroesophageal junction (GEJ) carcinoma that has progressed after one line of treatment with a platinum- and fluoropyrimidine- based therapy (for advanced/metastatic disease or in the adjuvant setting if progressed during treatment or within 4 months after treatment) was demonstrated in one well conducted clinical trial, IMCL CP12-0715 (I4T-IE-JBVD or REGARD), 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 Adenocarcinoma (GEJ) Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy. This improvement in overall survival was further confirmed by the high-level results of a second trial in the same setting, study I4E-IE-JVBE (CP12-0922; RAINBOW, entitled A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase 3 Study of Weekly Paclitaxel with or without Ramucirumab in Patients with Metastatic Gastric Adenocarcinoma, Refractory to or Progressive After First-Line Therapy with Platinum and Fluoropyrimidine).

The primary objective of Study I4T-IE-JBVD was to demonstrate an improvement in overall survival (OS). The secondary objectives were to compare PFS, response rate (both as per RECIST 1.1 criteria) between the two treatment arms, to evaluate the safety profile in the two treatment arms, to assess immunogenicity of IV ramucirumab, and to assess pharmacokinetics of IV ramucirumab.

Treatment consisted of either ramucirumab or placebo at 8 mg/kg on Day 1 every 2 weeks in combination with best supportive care (which excluded chemotherapy, immunotherapy, and other investigational drugs).

Patients were randomized (using either an electronic data capture system or by accessing a call-in Interactive Voice Response System [IVRS] or Interactive Web Response System [IWRS]) on a 2:1 basis to receive either ramucirumab or placebo, respectively. Randomization was stratified by weight loss ($\geq 10\%$ over the prior 3 months versus $< 10\%$), geographic region (North America, Europe, Australia, and New Zealand versus South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia versus Asia), and location of the primary tumor [gastric (including tumors of the gastric cardia that extend into the GEJ) versus GEJ (including

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tumors of the distal esophagus that extend into the GEJ, and tumors involving the GEJ when precise identification of the organ of origin is not possible)].

Patients received treatment until disease progression, unacceptable toxicity, or patient's refusal. Following documentation of progressive disease, patients were followed for survival status until death or withdrawal of patient consent or until the cutoff date for the final analysis.

Response and disease status were assessed every 6 weeks during study treatment, and at the end of study treatment.

The first patient was enrolled on October 6, 2009 and the last patient was enrolled on January 10, 2012. A total of 355 patients were randomized, 238 patients randomized to the ramucirumab arm and 117 patients to the placebo arm. Two patients in each treatment arm were not treated. At the time of data cut-off, 14 patients (5.8%) in the ramucirumab arm and 1 patient (0.8%) in the placebo arm were still receiving study treatment.

Patient demographic characteristics were balanced between the two treatment arms. Median age at randomization was 60 years in the ramucirumab arm and 61 years in the placebo arm; there was a slight imbalance in the proportion of patients 65 years of age or older (34% in the ramucirumab arm and 39% in the placebo arm). Most patients were men (71% and 68% in the ramucirumab and placebo arms, respectively) and White (76% and 78% in the ramucirumab and placebo arms, respectively). Initial disease characteristics were generally similar and balanced between treatment arms. All patients had a diagnosis of adenocarcinoma.

The most frequent primary site was the stomach (75% in the ramucirumab arm and 74% in the placebo arm). All patients received prior anti-cancer treatment. The majority of patients enrolled in the study received prior platinum/fluoropyrimidine combination therapy (84% and 75% in the ramucirumab and placebo arms, respectively). Study arms were balanced regarding response to prior therapy and duration of response.

At the time of the data cut-off, 94% patients in the ramucirumab arm and 97% patients in the placebo arm had discontinued treatment. The main reason for treatment discontinuation was disease progression [126 patients (53%) in the ramucirumab arm and 73 patients (62%) in the placebo arm]. The analysis of the physician stated reason for treatment discontinuation showed that 11% patients in the ramucirumab arm and 6% of patients in the placebo arm discontinued treatment because of an adverse event. The analysis of the safety database showed a similar result, with 14% discontinuations in the ramucirumab arm and 7% discontinuations in the placebo arm due to adverse events.

The analysis of OS was performed on the ITT population, 238 patients in the ramucirumab arm and 117 patients in the placebo arm. At the time of the data cut-off for the final analysis (July 25, 2012), the median follow-up time (i.e., time from randomization to the time of death or censoring) was 4.9 months in the ramucirumab arm and 3.7 months in the placebo arm. The survival analysis was based on a total of 278 deaths: 179 events (75%) reported in the

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ramucirumab arm and 99 events (85%) reported in the placebo arm. Survival estimates using the Kaplan Meier method were compared using a log-rank test (Cox method) stratified by factors specified at the time of randomization. The addition of ramucirumab to standard of care resulted in a survival benefit, with a statistically significant log rank test with a p-value of 0.0473 and an estimated hazard ratio of 0.776 (95% CI: 0.603 to 0.998). The use of ramucirumab in addition to standard of care resulted in a risk of death reduction of 22% when compared to placebo and standard of care. Median overall survival (95% CI) in the ramucirumab arm was 5.2 months (4.4 to 5.7), compared to 3.8 months (2.8 to 4.7) in the placebo arm. FDA statistical review (see Dr. Hui statistical review) agrees with most of the results that were submitted in the Application by Eli Lilly.

Although the study was not powered to demonstrate a statistical difference in survival among patient subgroups, two subgroups showed a difference in magnitude of effect that prompted further investigation. Women in the REGARD study did not appear to benefit from treatment (HR 1.431, 95% CI 0.448; 4.539). Some demographic characteristics of women were not well balanced between arms: median age of women receiving ramucirumab was 60 years (the same as men receiving ramucirumab), but median age in women receiving placebo was 54 years of age. Women in the ramucirumab arm had a higher incidence of gastric tumors when compared with women in the placebo arm (93% vs. 82%), and had higher incidence of diffuse histology (with a worse prognosis) when compared with women in the placebo arm (49% vs. 34%). The only relevant toxicities that occurred at a higher incidence rate in women receiving ramucirumab were Grade 3-5 hypertension and anemia. Pharmacokinetic analyses found that the minimum targeted serum concentration was exceeded by a greater degree in women than in men (even when adjusted by body weight). There were no toxic deaths or other safety factors that could explain this difference in overall survival. The applicant also pointed out that the survival of women in the ramucirumab arm was similar to their male counterparts, but survival of women in the placebo arm appeared longer. Differences in baseline characteristics such as age and histology may have influenced the treatment effect observed in the REGARD trial.

REGARD was stratified by geographic location. The Asian stratum enrolled only 18 patients (5%), and therefore the analysis of this subgroup was not interpretable. However, when looking at the North America region (North America, Europe, Australia, and New Zealand), which enrolled 69% of patients, the magnitude of the effect achieved with the addition of ramucirumab to the standard of care (HR 0.896, 95% CI 0.667; 1.205) was of a lesser magnitude than the benefit observed in the South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia region (24% patients, HR 0.464, 95% CI 0.265; 0.813). Caution must be used in the interpretation of this analysis. The most likely explanation for the subgroup effects related to chance effects observed in non-random populations (i.e., the subgroup populations analyzed).

Treatment with ramucirumab reduced the risk of disease progression or death by 52% (HR = 0.483; 95% CI: 0.376, 0.620; p<0.0001). Median time to disease progression in the ramucirumab arm was 2.1 (95% CI 1.5; 2.7) months and 1.3 (95% CI 1.3; 1.4) months. Type I error for evaluation of PFS as a secondary endpoint was controlled using gate keeping

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methodology. Because the curves appeared to separate around the median (likely based on the timing of tumor assessments), the HR may be the better estimate for the treatment effect on PFS.

The protocol was overall well conducted, and protocol violations were minimal and did not impact the integrity of the data.

Although statistically significant, FDA had the following concerns regarding the study results: modest magnitude of effect, borderline significance and whether the results would be reproducible for this NME, and the potential for a detrimental treatment effect in women. Eli Lilly addressed these concerns by submitting the high level results of a second study, RAINBOW, a Phase 3 randomized study comparing ramucirumab/paclitaxel vs. placebo/paclitaxel for the second-line treatment of gastric/GEJ adenocarcinoma. A total of 665 patients (330 patients in the ramucirumab/paclitaxel arm and 335 patients in the placebo/paclitaxel arm) were enrolled in the RAINBOW study. Generally speaking, patients in the RAINBOW study were similar to patients in the REGARD study, with the exception of race and histology, as there were more Asian patients in the RAINBOW study (Asian patients constituted 16% of patients in REGARD).

The primary endpoint for the RAINBOW study was OS. Ramucirumab in combination with paclitaxel reduced the risk of death in this population by 19% (stratified log rank test HR = 0.807; 95% CI 0.678, 0.962; p=0.0169), prolonging median survival time (9.63 months [95% CI: 8.48, 10.81] in the ramucirumab arm vs. 7.36 months [95% CI: 6.31, 8.38] in the placebo arm, a 2.27 months difference). One hundred and ninety three women (101 and 92 in the ramucirumab/paclitaxel and placebo/paclitaxel arms respectively) enrolled in this study, and they appeared to benefit from ramucirumab treatment at least as much as in the general study population with a (lower point estimate of the) median HR of 0.672 (0.483; 0.935, nominal p= 0.01740). In addition, in the RAINBOW study, there was a (nominally) statistically significant improvement in OS in Region 1, which included the US and Europe (HR=0.726, 95% CI 0.580; 0.909 and a p=0.0050). These data support the hypothesis that the subgroup analysis results in the REGARD study are likely related to the small sample and random effects.

In conclusion, data from the REGARD study (supported by the high-level results of the RAINBOW study) support the conclusion that the addition of ramucirumab to the second line treatment of gastric/GEJ carcinoma results in clinical benefit.

6.1 Indication

Eli Lilly proposed the following indication for this submission: Ramucirumab is indicated for the treatment of advanced gastric cancer or gastro-esophageal junction adenocarcinoma, as a single-agent after prior chemotherapy.

The recommended ramucirumab dose is 8 mg/kg every two weeks.

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6.1.1 Methods

The efficacy analysis was focused on the results of one trial, IMCL CP12-0715 (I4T-IE-JBVD or REGARD), 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 Adenocarcinoma (GEJ) Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy.

The efficacy analysis is also supported by the submission of the high-level results of a second study in the second line treatment of gastric or GEJ carcinoma, study I4E-IE-JVBE (CP12-0922; RAINBOW, entitled A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase 3 Study of Weekly Paclitaxel with or without Ramucirumab in Patients with Metastatic Gastric Adenocarcinoma, Refractory to or Progressive After First-Line Therapy with Platinum and Fluoropyrimidine). The review of this second trial results can be found in Section 6.1.10. Additional trials evaluated for safety analyses were reviewed in the Safety Section.

6.1.2 Demographics

The first patient was enrolled on October 6, 2009 and the last patient was enrolled on January 10, 2012. The study data cut-off date was July 25, 2012; 290 patients had died at the time of data cut-off.

A total of 459 patients were screened for this study, and 104 patients were considered screening failures and consequently were not randomized. The majority of screening failures (70%) were related to patients not being eligible for the trial for having one or more of the exclusion criteria.

Three hundred and fifty five patients from 119 sites in 29 countries were randomized in the REGARD study; 238 (67%) patients in the ramucirumab/BSC care arm and 117 (33%) patients in the placebo/BSC arm. Patients were enrolled from Argentina (6), Australia (12), Bosnia & Herzegovina (4), Brazil (38), Canada (10), Chile (2), Colombia (3), Czechoslovakia (37), Egypt (1), Spain (16), Great Britain (17), Guatemala (8), Croatia (7), Indonesia (3), India (24), Italy (34), Korea (17), Lebanon (1), Malta (5), New Zealand (2), Philippines (2), Poland (13), Romania (17), Russia (22), Thailand (1), Turkey (6), Taiwan (3), U.S. (43), and South Africa (1). Geographic region was a stratification factor: 165 (69%) and 80 (68%) patients in the ramucirumab/BSC and placebo/BSC arms respectively were enrolled in Region 1 (North America, Europe, Australia, and New Zealand), 55 (23%) and 9 (25%) patients in the ramucirumab/BSC and placebo/BSC arms respectively were enrolled in Region 2 (South and Central America, India, South Africa, Jordan, Egypt, Saudi Arabia, and Lebanon), and 18 (7%) and 8 (7%) patients in the ramucirumab/BSC and placebo/BSC arms respectively were enrolled in Region 3 (Asia).

Patient demographic characteristics were balanced between the two treatment arms (Table 5). Median age at randomization was 60 years old in the ramucirumab arm and 61 years old in the placebo arm; there was a slight imbalance in the proportion of patients 65 years of age or older

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(34% in the ramucirumab arm and 39% in the placebo arm). Most patients were men (71% and 68% in the ramucirumab and placebo arms respectively) and White (76% and 78% in the ramucirumab and placebo arms respectively).

Table 5 - REGARD: Patients demographics (ITT population)

	Ramucirumab/BSC N=238 (%)	Placebo/BSC N=117 (%)
Age		
Median age (range)	60 (31-86)	61 (24-88)
Mean age (\pm SD)	59.9 \pm 10.8	60.5 \pm 12.3
Age \geq 65	82 (34)	46 (39)
Age \geq 75	21 (9)	13 (11)
Gender		
Male	169 (71)	79 (68)
Female	69 (29)	38 (32)
Race		
White	181 (76)	91 (78)
Black	4 (2)	2 (2)
Asian	39 (16)	17 (15)
Other	14 (6)	7 (6)

Patient demographic characteristics are balanced between arms. However, when analyzed by gender, there were some imbalances in demographic characteristics. Median age of women receiving ramucirumab was 60 years, the same as men receiving ramucirumab; however, the median age of women receiving ramucirumab was 6 years older than women who received placebo. Women in the ramucirumab arm had a higher incidence of gastric tumors when compared with women in the placebo arm (93% vs. 82%), and had higher incidence of diffuse histology when compared with women in the placebo arm (49% vs. 34%).

Table 6 summarizes baseline disease characteristics.

Table 6 - REGARD: Disease characteristics at study entry

	Ramucirumab/BSC N=238 (%)	Placebo/BSC N=117 (%)
ECOG PS		
0	67 (28)	31 (26)
1	171 (72)	85 (73)
2	0	1 (1)
Weight loss \geq 10%	41 (17)	20 (17)
Location of tumor		
Gastric	178 (75)	87 (74)
GEJ	60 (25)	30 (26)
Histology		
Intestinal	52 (22)	35 (30)
Diffuse	96 (40)	44 (38)
Other/not available	90 (38)	38 (32)

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Measurable disease	218 (92)	106 (91)
Metastases		
≥ 3 sites	75 (33)	46 (39)
Peritoneal	64 (27)	45 (38)
Liver	104 (44)	56 (48)

Patients in the placebo arm have a higher incidence of intestinal histology (histology with better outcome than diffuse histology) and peritoneal metastases.

The majority of patients enrolled in the study received prior platinum/fluoropyrimidine combination therapy (84% and 75% in the ramucirumab and placebo arms respectively), and 90% patients in each arm received fluoropyrimidine therapy in combination with other drugs. Study arms were balanced regarding response to prior therapy and duration of response; the majority of patients relapsed/progressed within 6 months of starting the prior chemotherapy treatment (65% and 71% in the ramucirumab and placebo arms respectively). Table 7 summarizes the prior treatments received and responses.

Table 7 - REGARD: Prior treatment

	Ramucirumab/BSC N=238 (%)	Placebo/BSC N=117 (%)
Prior treatment		
First-line chemotherapy	238 (100)	117 (100)
Adjuvant therapy only	199 (84)	103 (88)
Neoadjuvant therapy only	37 (16)	14 (2)
	2 (1)	0
Chemotherapy		
Fluoropyrimidines	229 (96)	112 (96)
- Fluoropyrimidine in combination	213 (90)	105 (90)
Platinum alone	9 (4)	5 (4)
Best response to prior Tx		
PR	15 (8)	7 (6)
PD	158 (79)	78 (76)
SD	25 (13)	16 (13)
PFS ≤ 6 months	154 (65)	83 (71)

Arms were well balanced regarding baseline co-morbid conditions, with 63% of patients in both arms suffering from gastrointestinal conditions and 49% patients in the ramucirumab and 47% patients in the placebo arm suffering from cardiovascular conditions.

Table 8 summarizes the differences between randomization stratification factors between the interactive voice recognition system (IVRS) used for stratification and the data in the CRFs. There were no discrepancies in the region stratification stratum.

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Table 8 - REGARD: IVRS-CRF randomization factors comparison

IVRS	CRF			
	Ramucirumab/BSC N=238 (%)	Placebo/BSC N=117 (%)	Ramucirumab/BSC N=238 (%)	Placebo/BSC N=117 (%)
Weight loss prior 3 months				
≥ 10%	41 (17)	20 (17)	37 (16)	17 (15)
<10%	192 (83)	97 (83)	201 (85)	100 (86)
Location of primary tumor				
Gastric	178 (75)	87 (74)	179 (75)	85 (73)
GEJ	60 (25)	30 (26)	59 (25)	32 (27)

Discrepancies between the stratification factor that was entered by the site into the IVRS system for use in the randomization, and the data that were entered into the eCRF were noted in 8% of patients, but in each individual cell differences were ≤ 2%. It is unlikely that these differences had an impact on the study result, but a sensitivity analysis in the primary endpoint was conducted to further explore the impact.

6.1.3 Subject Disposition

The study data cut-off date was July 25, 2012: of the 355 patients enrolled 50 (21%) patients in the ramucirumab arm and 15 (13%) patients in the placebo arm were alive. Two patients per arm never received treatment (one patient died subsequently to randomization, and the other three patients developed performance status decline, symptomatic brain metastases and laboratory abnormalities before receiving study drugs). A total of 236 patients in the ramucirumab arm and 115 patients in the placebo arm received study treatment; 15 patients (4%) patients were still receiving treatment (14 patients in the ramucirumab arm and 1 patient in the placebo arm).

Reasons for treatment discontinuation are summarized in Table 9.

Table 9 - REGARD: Treatment discontinuations

	Ramucirumab/BSC N=238 (%)	Placebo/BSC N=117 (%)
Progressive disease	126 (53)	73 (62)
Symptomatic deterioration	41 (17)	16 (14)
Death	20 (8)	13 (11)
Withdrawal of consent	8 (3)	2 (2)
Adverse event	25 (11)	7 (6)
Other reasons	3 (1)	3 (3)*

* Patient 6050004 never received treatment.

Reasons listed as treatment discontinuations in the “other” category are ineligibility for the study, progressive disease, physician’s decision secondary to underlying illness, withdrawal of consent, brain metastases, and death.

Eight patients in the ramucirumab arm withdrew from the study after withdrawal of consent; further analysis of the CRFs showed that 3 patients had disease progression (subject ID# 202-0008, 534-0004, and 565-0002), one patient had global health deterioration (ECOG PS score went from 0 to 2, subject ID#801-0002), one patient withdrew consent after experiencing rising levels of creatinine and delay in chemotherapy treatment (subject ID#202-0007), and there was no other reason for withdrawal in three patients (subject ID#205-0002, 229-0003, and 563-0009).

Two patients in the placebo arm withdrew their consent (subject ID#177-0001 and 590-0006); both patients had clinical progression of disease.

Adverse events resulting in treatment discontinuations are analyzed in Section 7.3.3.

6.1.4 Protocol violations

There were few major protocol violations. These violations were reported by the applicant in 13 (5%) patients in the ramucirumab and 9 (8%) patients in the placebo arm. The applicant divided the major protocol violations in three categories: patients randomized in violation of one or more entry criteria, patients receiving the wrong treatment, and violations concerning protocol compliance (Table 10).

Table 10 - REGARD: Summary of major protocol violations

	Ramucirumab/BSC N=238 (%)	Placebo/BSC N=117 (%)
Pts w/ protocol violations	13 (5)	9 (8)
Received wrong treatment	1 (<1)	1 (<1)
Compliance with protocol procedures	3 (1)	0
Violation of entry criteria	10 (4)	8 (7)

FDA analyses of the raw (listings) dataset (IE.xpt), demographics analysis dataset (ADLS.xpt), vital signs analysis dataset (ADVS.xpt), and laboratory assessments dataset (ADLB.xpt) showed *potential* discordance with based on eligibility pertaining to hypertension.

Table 11 - REGARD: FDA analysis of entry criteria violations

	Ramucirumab/BSC N=238	Placebo/BSC N=117
Exclusion criteria		
#04: Active infection, symptomatic CHF, unstable angina pectoris, symptomatic/poorly controlled cardiac arrhythmia, uncontrolled thrombotic/hemorrhagic disorder, or other serious/uncontrolled disorder	0	1
#06: Blood pressure above the following values: Systolic BP above 140 mm Hg* Diastolic BP above 90 mm Hg	35 (15) 27 (11)	19 (16) 9 (8)
#07: serious or non-healing wound, ulcer, or bone fracture	1	0

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#08: chemotherapy, radiotherapy, immunotherapy, or targeted therapy for gastric cancer, within 2 weeks prior to randomization.	1	0
#12: Chronic antiplatelet therapy	0	1
#18: Concurrent malignancy	0	1
Inclusion criteria		
#4: Disease progression during/within 4 mo after last dose of 1st-line treatment for metastatic disease (or within 6 m after last dose of adjuvant treatment)	3 (1)	3 (3)
#9: ECOG 0-1.	1	0
#12: Proteinuria criterion	0	1
#13: Hematological criterion**	0	2
#14: INR <=1.5 & PTT <=5 sec above ULN	0	1
#17: Negative serum pregnancy test within 7 days prior to randomization.	0	1

* Including 5 patients (ID#3310002, 4100006, 606005, 6340002, 6350003) in the ramucirumab and 2 patients (ID# 4170001 and 6370004) in the placebo arm with systolic baseline blood pressure above 160 mm Hg. One patient (ID# 5300002) in the placebo arm had a baseline diastolic pressure of 105 mm Hg.

** Patients 1200001 and 8520007 were enrolled with Grade 3 anemia.

In the Applicant's analysis, the more frequent protocol violation was the inclusion of subjects with relapse/progression of disease after prior treatment outside of the 4-6 month window (adjuvant and neoadjuvant therapy respectively). In FDA analysis, the most common *potential* violations were the inclusion of subjects with blood pressure parameters above the ones established in the eligibility criteria. Note however, that this (FDA) analysis of blood pressure would represent the strictest interpretation of the eligibility criteria for blood pressure. The eligibility criteria excluded patients with uncontrolled hypertension, but did not define uncontrolled hypertension (presumably this was left to clinical judgment). This reviewer would agree; however, that a patient with a transient systolic blood pressure greater 140 mmHg would not be considered as having uncontrolled blood pressure and thus, many of these patients were appropriately eligible for the trial. The impact of this FDA analysis would be related to safety concerns regarding the inclusion of these subjects, but not the efficacy results of the study. Protocol violations were balanced between arms.

Two patients (one per arm) received the wrong treatment (in one occasion each, patients 5260004 and 6600004). Three patients in the ramucirumab arm reported as having compliance with the protocol issues had their baseline scans performed more than 17 days prior to randomization.

6.1.4 Analysis of Primary Endpoint

Overall survival in the ITT

The primary endpoint of the REGARD study was overall survival, measured as the time from study enrollment to the date of death. The analysis of OS was performed on the ITT population, 238 patients in the ramucirumab arm and 117 patients in the placebo. Cutoff date was July 25, 2012. FDA review (see Dr. Zhang and Dr. He's statistical review) confirmed most of the results

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presented by Eli Lilly, and there were no significant differences between Eli Lilly's and FDA review.

Patients were not unblinded to assigned treatment after treatment discontinuation. Systemic anticancer therapy (with well balanced types of treatment between arms) was received by 30% of patients in the ramucirumab arm and 38% patients in the placebo arm.

At the time of the data cut-off for the final analysis, the median follow-up time was 4.9 months in the ramucirumab arm and 3.7 months in the placebo arm. The analysis was based on a total of 278 deaths: 179 events (75%) reported in the ramucirumab arm and 99 events (85%) reported in the placebo arm. Fifty one patients (21%) in the ramucirumab arm and 21 patients (18%) in the placebo arm were alive at the cutoff date. Information on survival was available for all but 12 (3.3%) patients: 4 patients were lost to follow up and 5 patients withdrew consent (3.7% total) in the ramucirumab arm and 2 patients were lost to follow up and one patient withdrew consent (2.5% total) in the placebo arm.

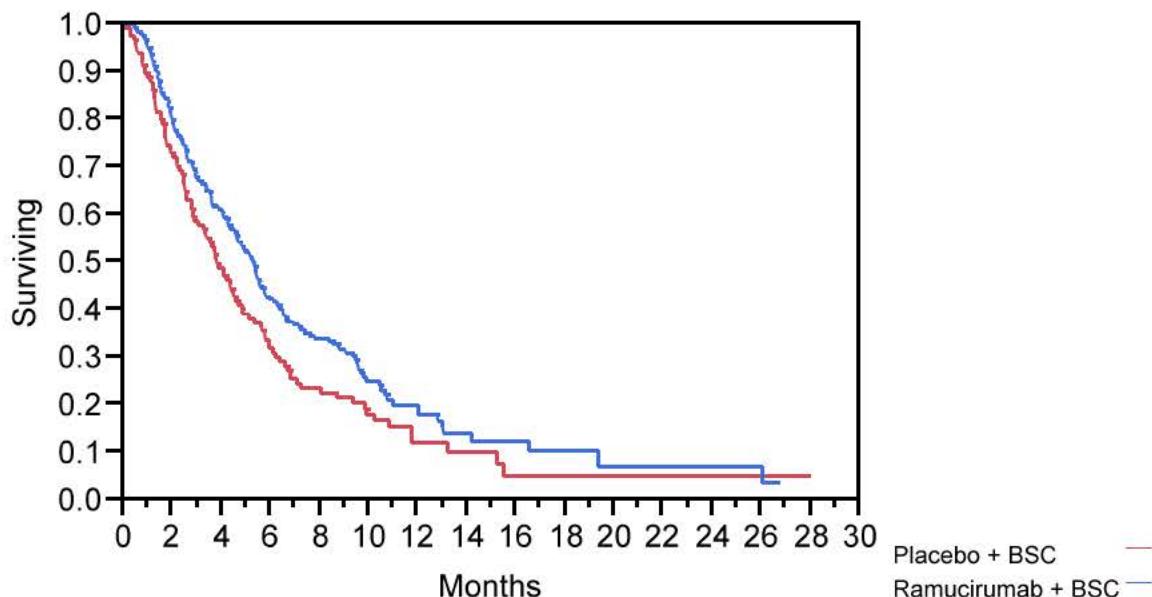
Survival estimates using the Kaplan Meier method were compared using a log-rank test (Cox method) stratified by factors specified at the time of randomization (weight loss over the prior 3 months [$<10\%$ vs. $\geq 10\%$]; location of primary tumor [gastric vs. GEJ], and geographical region [North America, Europe, Australia, and New Zealand vs. South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia vs. Asia]). The addition of ramucirumab to standard of care resulted in a survival benefit, with a statistically significant log rank test with a p-value of 0.0473 and an estimated hazard ratio of 0.776 (95% CI: 0.603 to 0.998). The use of ramucirumab in addition to standard of care resulted in a risk of death reduction of 22% when compared to placebo and standard of care. Median overall survival (95% CI) in the ramucirumab arm was 5.2 months (4.4 to 5.7), compared to 3.8 months (2.8 to 4.7) in the placebo arm. Table 12 summarizes the primary endpoint analysis results.

Table 12 - REGARD: Overall survival analysis (ITT)

	Ramucirumab (n=238)	Placebo (n=117)
Deaths	179 (75%)	99 (85%)
Median OS (95% CI), months	5.2 (4.4; 5.7)	3.8 (2.8; 4.7)
Stratified log rank test p value	0.0473	
Stratified HR (95%CI)	0.776 (0.603; 0.998)	
Unstratified log rank test p value	0.0347	
Unstratified HR (95%CI)	0.767 (0.60; 0.981)	

There was a median of 13 patients per stratum (12 strata total). An unstratified analysis was conducted to assess the impact of the stratification on the analysis (and to support the robustness of the data), which showed (Table 12) a HR (95% CI) of 0.767 (0.60; 0.981) and a p value of 0.0347. Figure 2 shows the unstratified Kaplan Meier plot for the ITT population.

Figure 2 - REGARD: Unstratified overall survival Kaplan Meier curve



To further explore the impact of the discrepancies between the stratification factors that were entered by sites into the IVRS system for use in the randomization, and the data that were entered into the eCRF, Eli Lilly conducted a pre-specified sensitivity analysis. The stratified log-rank test using the stratification factors based on the data as recorded on the CRF was (nominally) statistically significant ($p=0.0419$), with a corresponding HR of 0.769 (95% CI: 0.597, 0.992) from a stratified Cox proportional hazards model.

In the per-protocol population, the stratified analysis showed a HR 0.755 (95% CI 0.584; 0.977) and a p value 0.0320.

Subgroup analyses

Figure 3 (copied from Dr. Zhang's review) shows a Forrest plot for subgroup analysis of overall survival based on the ITT population.

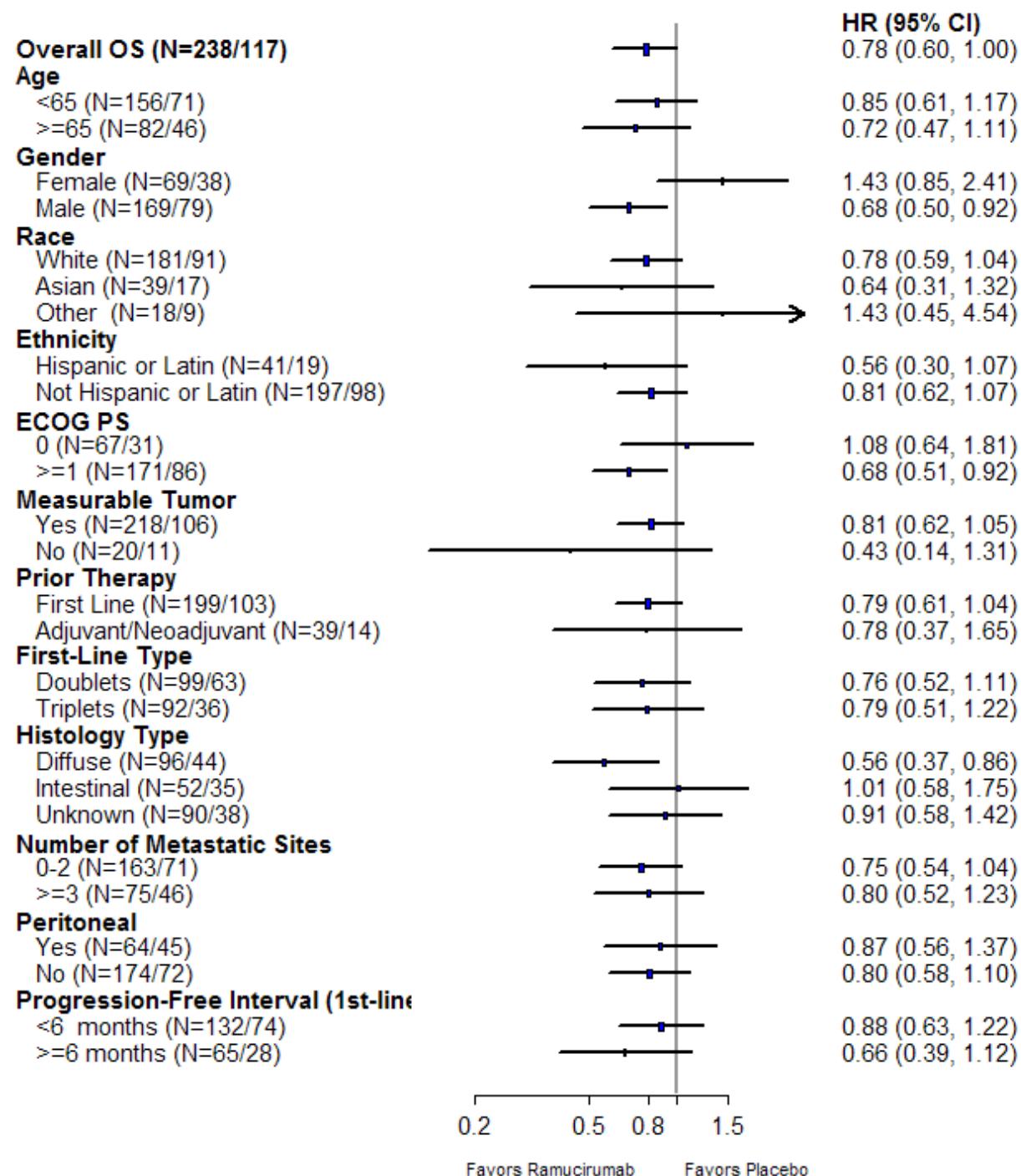
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Figure 3 - REGARD: Forrest plot for subgroup analysis of overall survival (ITT population)



The study lacked power to show statistically significant results in these subgroups (small number of patients, with subsequent wide confidence intervals); however, in this exploratory analysis,

women who received ramucirumab had a HR greater than 1.0 favoring the placebo arm (HR 1.431, 95% CI 0.448; 4.539). Figure 4 and Figure 5 show the unstratified Kaplan Meier curves by gender.

Figure 4 - REGARD: Overall survival Kaplan Meier curve women

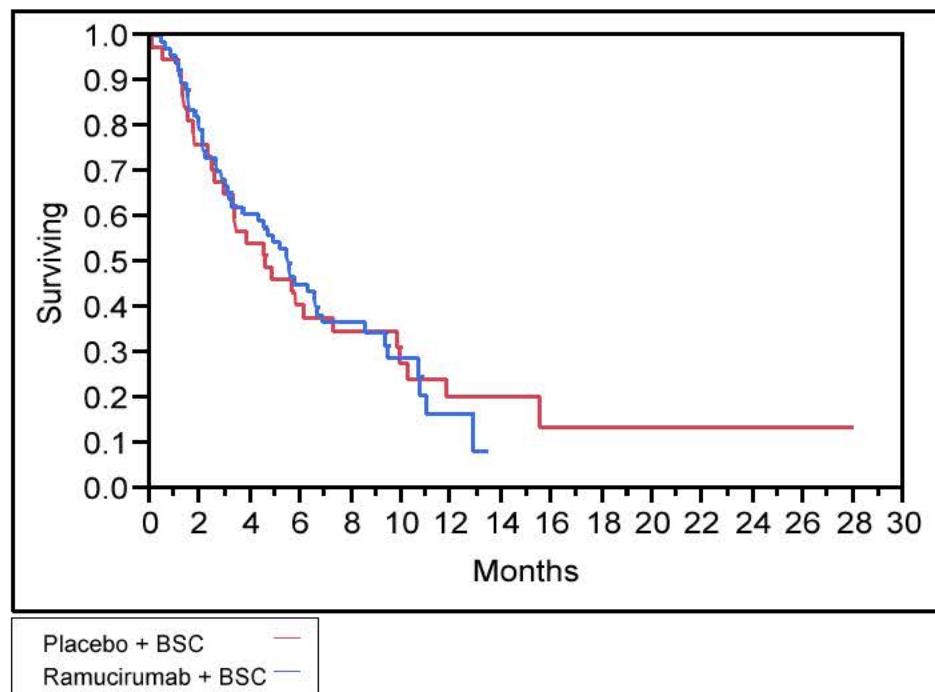
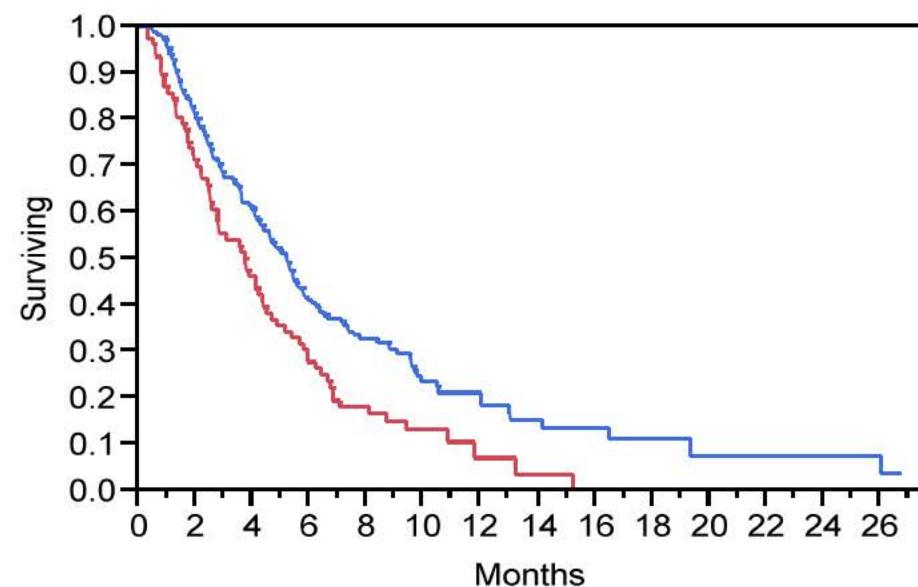


Figure 5 - REGARD: Overall survival Kaplan Meier curve men



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Placebo + BSC	—
Ramucirumab + BSC	—

To further explore this difference in outcomes, demographic characteristics (Table 13) by gender were explored.

Table 13 - REGARD: Demographic and baseline characteristics by gender

	Ramucirumab/BSC; n (%) N=236		Placebo/BSC; n (%) N= 115	
	Males (n=169)	Females (n=67)	Males (n=77)	Females (n=38)
Age (median)	60	60	62	54
Race				
White	131 (78)	49 (73)	63 (82)	26 (68)
Asian	27 (16)	11 (16)	11 (14)	6 (16)
Other	11 (7)	6 (9)	3 (3)	6 (16)
Geographic region				
1*	122 (72)	42 (63)	53 (69)	25 (66)
2**	35 (20)	19 (28)	18 (23)	11 (29)
3***	12 (7)	6 (9)	6 (8)	2 (5)
Weight loss				
< 10%	141 (83)	58 (87)	66 (86)	33 (87)
≥ 10%	28 (17)	9 (13)	11 (14)	5 (13)
Tumor location				
Gastric	115 (68)	62 (93)	53 (69)	31(82)
GEJ	54 (32)	5 (7)	24 (31)	7 (18)
Histology subtype				
Intestinal	41 (24)	11 (16)	27 (35)	8 (21)
Diffuse	61 (36)	33 (49)	30 (39)	13 (34)
Other	67 (39)	23 (34)	20 (26)	17 (45)
Histology grade				
Well differentiated	78 (46)	15 (22)	50 (65)	4 (11)
Poorly, undifferentiated or unknown	91 (54)	52 (78)	27 (35)	34 (89)
Peritoneal metastases	38 (22)	25 (37)	28 (36)	17 (45)
First line				
PFS < 6 months	113 (68)	40 (61)	54 (70)	27 (71)
≥ 6 months	54 (32)	26 (39)	23 (30)	11 (29)
ECOG PS				
0	116 (69)	14 (21)	22 (28)	8 (21)
1	53 (31)	53 (79)	54 (70)	30 (79)
2	0	0	2 (1)	0
Hypoalbuminemia (below median)	79 (48)	36 (56)	31 (41)	19 (50)

1*: North America, Europe, Australia, and New Zealand

2**: South and Central America, India, South Africa, Jordan, Egypt, Saudi Arabia, Lebanon

3***: Asia

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Median age of women receiving ramucirumab was 60 years old, the same as men receiving ramucirumab. However, women were (median) 6 years younger in the placebo group compared to women who received ramucirumab. Women in the ramucirumab arm had a higher incidence of gastric tumors when compared with women in the placebo arm (93% vs. 82%), and had higher incidence of diffuse histology (with a worse prognosis) when compared with women in the placebo arm (49% vs. 34%). As reviewed in Section 7.5.3, although toxicities differed in some preferred terms by gender, the only (severe) ones with notable differences were Grade 3-5 hypertension and anemia. Pharmacokinetic analyses found that the minimum targeted serum concentration was exceeded by a greater degree in women than in men (even when adjusted by body weight). There were no deaths related to these terms or other safety factors that may contribute to explain this difference in overall survival.

Women's survival in the ramucirumab arm was similar to their male counterparts, but survival of women in the placebo arm appeared longer. Differences in baseline characteristics such as age and histology may have influenced the treatment effect observed in the REGARD trial.

On October 30, 2013 (BLA 125477/08), Eli Lilly submitted the high level results of the RAINBOW study (complete protocol description and FDA analysis of the results can be found in Section 6.1.10), a Phase 3 randomized study comparing ramucirumab/paclitaxel vs. placebo/paclitaxel for the second-line treatment of gastric/GEJ adenocarcinoma. A total of 665 patients (330 patients in the ramucirumab/paclitaxel arm and 335 patients in the placebo/paclitaxel arm) were enrolled in the RAINBOW study. Generally speaking, patients in the RAINBOW study were similar to patients in the REGARD study, with the exception of race and histology, as there were twice as many Asian patients in the RAINBOW study (Asian patients constituted 16% of patients in REGARD).

The primary endpoint for the RAINBOW study was OS. Ramucirumab in combination with paclitaxel reduced the risk of death in this population by 19% (stratified log rank test HR = 0.807; 95% CI 0.678, 0.962; p=0.0169), prolonging median survival time (9.63 months [95% CI: 8.48, 10.81] in the ramucirumab arm vs. 7.36 months [95% CI: 6.31, 8.38] in the placebo arm, a 2.27 months difference). One hundred and ninety three women (101 and 92 in the ramucirumab/paclitaxel and placebo/paclitaxel arms respectively) were enrolled in this study, and they appeared to benefit from ramucirumab treatment at least as much as in the general study population with a median HR of 0.672 (0.483; 0.935, nominal p= 0.01740). These data support the hypothesis that the subgroup analysis results in the REGARD study were likely related to the small sample and random effects.

Although the Forrest plot shows a negative result for patients with race "other", this was a very small subgroup (27 patients, 7.6%) and the results were not informative.

In the AVAGAST study (Ohtsu A. 2011), 774 patients with advanced gastric cancer were enrolled and randomized to receive first-line treatment with bevacizumab or placebo in combination with capecitabine and cisplatin. Although the median overall survival was 12.1 months in the bevacizumab arm vs. 10.1 months in the placebo arm, the study failed to meet its

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primary endpoint. However, an exploratory subgroup analysis suggested that there were regional differences in the efficacy of antiangiogenic therapy. Patients enrolled in the North American and Latin American regions appeared to have longer survival with the addition of bevacizumab (median 11.5 vs. 6.8 months for placebo chemotherapy, HR 0.63 95% CI 0.43; 0.94), whereas patients enrolled in the Asian region (90% Japan and Korea) appeared to have no benefit (HR 0.97 95% CI 0.75; 1.25), and European patients had intermediate results (HR 0.85 95% CI 0.63; 1.14). Similar differences in median OS were observed in the placebo arm. The authors hypothesized that difference in presentation and management of gastric cancer (more aggressive surgical and chemotherapy approaches in Asian countries, imbalances in histologic types, etc) may have been responsible for the difference observed in the efficacy of bevacizumab, but the study design could not answer these questions.

REGARD was stratified for geographic location. The Asian stratum enrolled only 18 patients (5%), and therefore the analysis of this subgroup was not interpretable. However, when looking at the North America region (North America, Europe, Australia, and New Zealand), which enrolled 69% of patients, the magnitude of the effect achieved with the addition of ramucirumab to the standard of care (HR 0.896, 95% CI 0.667; 1.205) is of a lesser degree than the benefit observed in the South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia region (24% patients, HR 0.464, 95% CI 0.265; 0.813). Figure 6 and Figure 7 show the Kaplan Meier curve for OS by region. Figure 8 shows (copied from Dr. Zhang's review) the Kaplan meier estimate in the U.S. and Canada subpopulation.

Comment: These disparate subgroup analyses across trials and drugs demonstrate why caution must be used in their interpretation (any why in general, they should be viewed as hypothesis generating). The most likely explanation for the subgroup effects relate to chance effects observed in non-random populations (i.e., the subgroup populations analyzed).

Figure 6 - REGARD: Overall survival Kaplan Meier curve in the South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia region

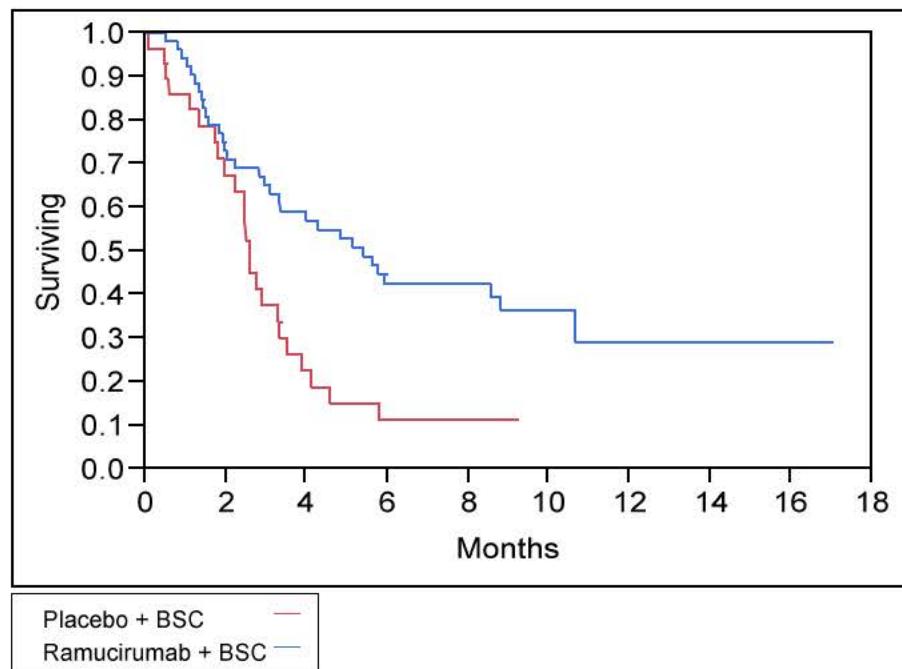


Figure 7 - REGARD: Overall survival Kaplan Meier curve in the North America, Europe, Australia, and New Zealand region

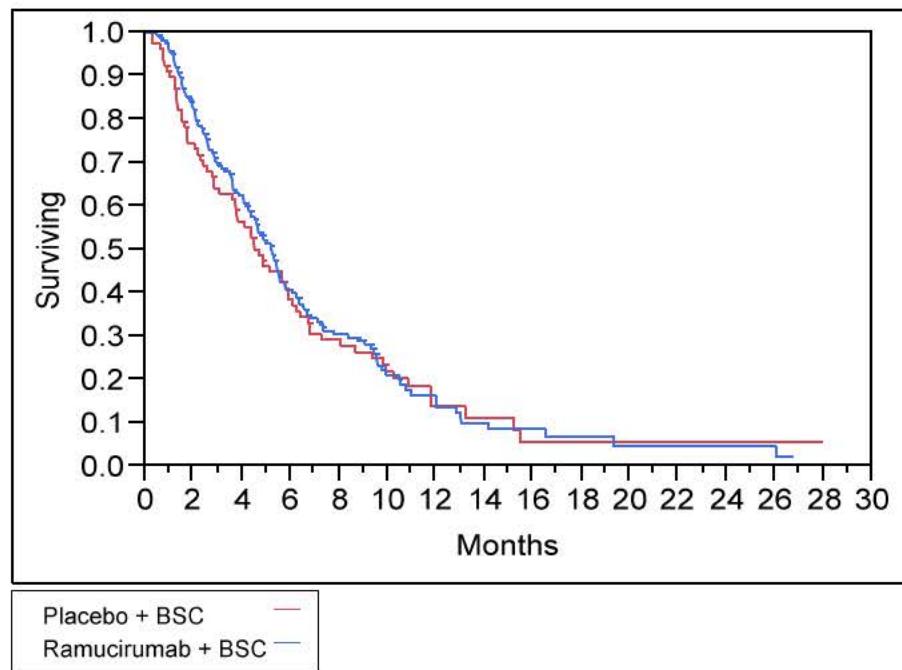
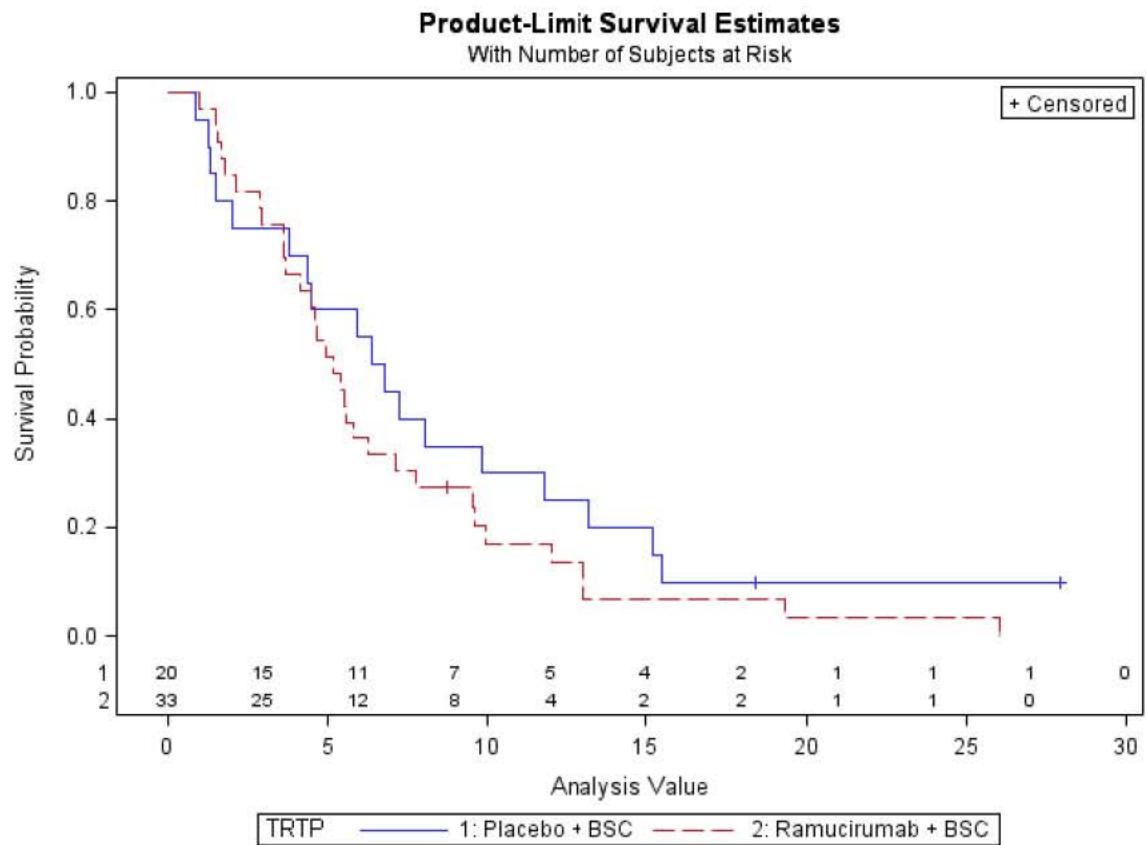


Figure 8 - REGARD: Overall Survival Kaplan Meier curve in Canada and the U.S.



The Applicant did not provide a hypothesis for the difference in outcome; to further explore the results, demographic and baseline characteristics analysis was performed (Table 14).

Table 14 - REGARD: Demographic and baseline characteristics by geographic region

	Ramucirumab/BSC		Placebo/BSC	
	NA (N= 164)	LA (n=54)	NA (N=78)	LA (N=29)
Age (median)	61	54	64	53
Gender				
Males	122 (74)	35 (65)	53 (68)	18 (62)
Females	42 (26)	19 (35)	25 (32)	11 (38)
Race				
White	156 (95)	24 (44)	74 (95)	15 (52)
Asian	3 (2)	17 (31)	1 (1)	8 (28)
Other	5 (3)	13 (24)	3 (4)	6 (21)
Weight loss				
< 10%	136 (83)	44 (81)	65 (83)	24 (83)
≥ 10%	28 (17)	10 (19)	13 (17)	5 (18)
Tumor location				

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Gastric	114 (70)	45 (83)	54 (69)	24 (83)
GEJ	50 (30)	9 (17)	24 (31)	5 (17)
Histology subtype				
Intestinal	38 (23)	14 (26)	22 (28)	11 (38)
Diffuse	68 (41)	13 (24)	32 (41)	8 (28)
Other	58 (35)	27 (50)	24 (31)	10 (35)

NA: North America, Europe, Australia, and New Zealand

LA: South and Central America, India, South Africa, Jordan, Egypt, Saudi Arabia, Lebanon

As expected, there were racial differences in the populations. Patients in the NA region were mostly White (95% in both arms), whereas the racial composition in the LA was varied, with Whites representing 44% and 52% in the ramucirumab and placebo arms, respectively. Patients in the LA region were younger (median 54 and 53 years of age in the ramucirumab and placebo arms respectively vs. 61 and 64 years of age in the ramucirumab and placebo arms respectively in the NA region), and there were more women in both arms. Tumors with diffuse histology were more frequently observed in the NA region (41% in both arms vs. 24% in the ramucirumab arm and 28% in the placebo arm, of the LA region). GEJ cancers were also more frequently observed in the NA arm.

In the RAINBOW study, there was a (nominally) statistically significant improvement in OS in Region 1, which included the US and Europe (HR=0.726, 95% CI 0.580; 0.909 and a nominal p=0.0050).

6.1.5 Analysis of Secondary Endpoints(s)

Progression free survival (PFS)

Disease response/progression imaging assessments (CT scans or MRI of all known disease) were to be obtained every 6 weeks (± 3 days) until documented progression for patients who discontinued study therapy for any reason other than PD.

Patients who had neither radiographic progression nor death were censored at the day of their last adequate radiographic tumor assessment or date of randomization if no adequate tumor assessment was available. If death or PD occurred after 2 or more missing/incomplete (or not evaluable) radiographic visits, censoring occurred at the date of the last adequate radiographic visit prior to the missed visits. If a new therapeutic anticancer treatment was administered prior to documented progression or death, the patient was censored at the date of last adequate tumor assessment prior to the new anticancer therapy. Patients who withdrew from the study due to symptomatic deterioration without radiographic evidence of PD were censored at the day of their last adequate radiographic tumor assessment for the primary analysis of PFS (a sensitivity analysis was conducted censoring patients when symptomatic deterioration was reported).

Treatment with ramucirumab reduced the risk of disease progression or death by 52% (HR = 0.483; 95% CI: 0.376, 0.620; p<0.0001). Median time to disease progression in the ramucirumab arm was 2.1 (95% CI 1.5; 2.7) months and 1.3 (95% CI 1.3; 1.4) months. Type I error for evaluation of PFS as a secondary endpoint was controlled using gate keeping

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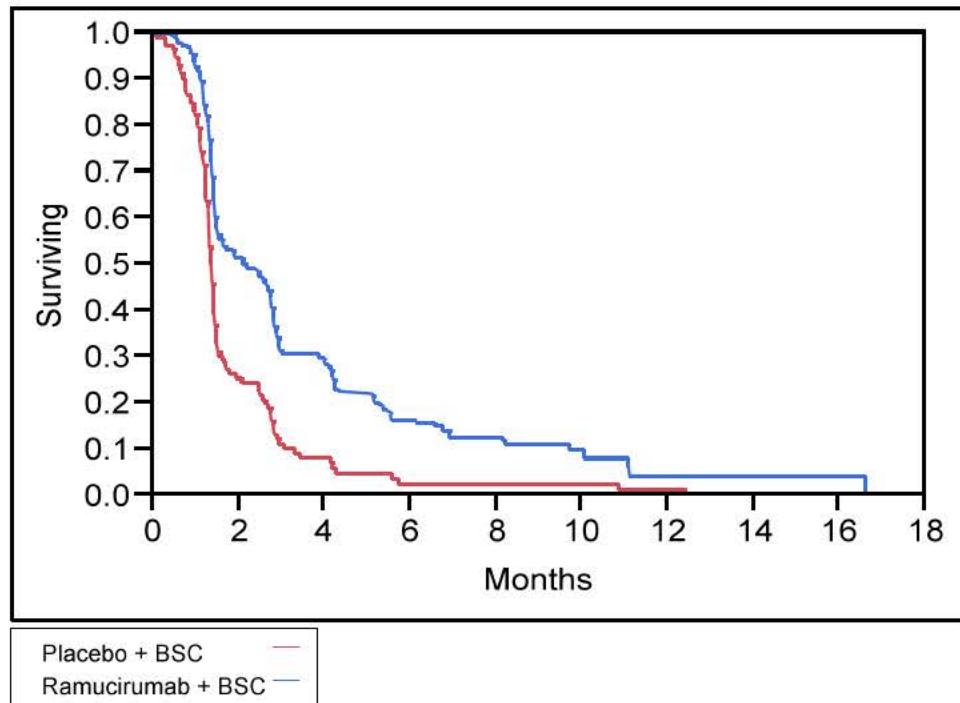
methodology. Because the curves appear to separate around the median (likely based on the timing of tumor assessments), the HR may be the better estimate for the treatment effect on PFS.

Table 15 - REGARD: PFS analysis (ITT population)

	Ramucirumab (n=238)	Placebo (n=117)
# Events	199 (84%)	108 (92%)
# Censored	39 (16%)	9 (8%)
Median OS (95% CI), months	2.1 (1.5; 2.7)	1.3 (1.3; 1.4)
Stratified log rank test p value	<0.0001	
Stratified HR (95%CI)	0.483 (0.376; 0.620)	
Unstratified log rank test p value	<0.0001	
Unstratified HR (95%CI)	0.506 (0.398; 0.644)	

Figure 9 shows the (unstratified) Kaplan Meier PFS curve.

Figure 9 - REGARD: PFS Kaplan Meier curve (ITT population)



Eli Lilly conducted additional sensitivity PFS analyses to evaluate the robustness of the PFS results. All these analyses were similar to the main analysis and resulted in statistically positive results; however, as concluded above, these results lack clinical significance as 0.8 months difference in mPFS cannot be considered clinical benefit.

6.1.6 Other Endpoints

Response rate and duration of response were secondary endpoints. Lilly stated in the report of the REGARD study that there was only one patient (ramucirumab arm) that experienced a complete response (CR). Partial responses were observed in 7 patients in the ramucirumab arm and 3 patients in the placebo arm (3.4% overall response rate in the ramucirumab arm and 2.6% in the placebo arm). Because the number of patients with CR/PR response was small, the duration of response was not analyzed as per the statistical plan and will not be discussed in this review.

6.1.7 Subpopulations

Reviewed in Section 6.1.4 above.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Because only one dose was assessed in the REGARD trial, this section is not relevant to the application.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Analyses: Supportive Studies

During the review cycle of this BLA, on October 10, 2013, FDA and Eli Lilly held a teleconference where the high level results of clinical study I4E-IE-JVBE (CP12-0922; RAINBOW, entitled A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase 3 Study of Weekly Paclitaxel with or without Ramucirumab in Patients with Metastatic Gastric Adenocarcinoma, Refractory to or Progressive After First-Line Therapy with Platinum and Fluoropyrimidine) were discussed. In addition, in the Filing Letter issued on October 22 2013, FDA requested the following items from Lilly:

- a. Copies of the pre-Phase 3 meeting minutes for the RAINBOW study.
- b. Copies of the protocol, all amendments, and the statistical analysis plan.
- c. Brief report describing the major efficacy findings of the primary and secondary endpoints and the overall survival estimates in relevant subgroups.
- d. Datasets to reproduce efficacy findings for overall survival in the ITT population and in relevant subgroups.
- e. Safety information only if the information would strengthen the WARNINGS and PRECAUTIONS section of the label (i.e., indicate increased severity of a specific adverse

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reaction or include a new adverse reaction and/or that would change the risk/benefit assessment of ramucirumab.

The requested information was submitted on October 30, 2013.

The following protocol synopsis summarizes the RAINBOW protocol version 3.0 (dated October 8 2012).

Protocol synopsis

RAINBOW was a multinational, randomized, double-blind, placebo-controlled Phase 3 study that enrolled patients with histologically or cytologically confirmed metastatic gastric or GEJ cancer. Patients were randomized (1:1) to receive paclitaxel 80 mg/m² plus ramucirumab 8 mg/kg (Arm A) or paclitaxel plus placebo 8 mg/kg (Arm B). Paclitaxel was administered on Days 1, 8, and 15, in combination with either ramucirumab or placebo given on Days 1 and 15 (28-days cycles).

Disease status was assessed every 6 weeks (\pm 3 days) following the first dose of study therapy for the first 6 months following the first dose, and every 9 weeks (\pm 3 days) thereafter, until radiographic documentation of progressive disease. Patients in both arms received all treatments until there was radiographic or symptomatic progression of disease, toxicity requiring cessation, protocol non-compliance, or withdrawal of consent.

The primary objective was to evaluate the overall survival of metastatic gastric or GEJ adenocarcinoma patients after failure of any platinum and fluoropyrimidine doublet with or without an anthracycline (epirubicin or doxorubicin) who undergo treatment with paclitaxel plus ramucirumab compared to patients treated with paclitaxel plus placebo.

The secondary objectives of this study were PFS, TTP, best ORR, ORR, safety, assessments of PROs, immunogenicity, pharmacokinetic profile, and pharmacodynamic profile.

The study was planned to enroll 663 patients (age \geq 18 years) with histologically or cytologically confirmed, metastatic or unresectable gastric or GEJ adenocarcinoma who received at least one cycle of first-line therapy with any platinum/fluoropyrimidine doublet with or without an anthracycline (epirubicin or doxorubicin), and who have discontinued first-line therapy prior to study entry for treatment-refractory or PD. Documented objective radiographic or clinical disease progression (e.g., any new or worsening malignant effusion documented by ultrasound examination) which may have been confirmed by pathologic criteria (histology and/or cytology) if appropriate, during first-line therapy, or within 4 months after the last dose of first-line therapy with any platinum/fluoropyrimidine doublet with or without an anthracycline (epirubicin or doxorubicin) for unresectable or metastatic disease was required. Patients who received any other chemotherapy (e.g., taxanes) were excluded. Laboratory, organ function, prior and concomitant medical history eligibility criteria were the same as the REGARD study.

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Randomization stratification factors were disease measurability (measurable vs. non-measurable disease), geographic region (Europe/Israel/North America/Australia vs. Asia [including East Asia – Japan, South Korea, China, Hong Kong, Taiwan – and South East Asia Malaysia, Thailand, Singapore] vs. Rest of the World [including South America]), and time to progression on first-line therapy (< 6 months vs. ≥ 6 months).

The study was designed with a 90% power to detect a hazard ratio of 0.75 (median OS in the paclitaxel plus ramucirumab arm of 9.33 months vs. 7 months in the paclitaxel/placebo arm) with a one sided alpha of 0.025. One interim analysis for futility was planned once 25% of the planned number of events was observed. The final analysis of the primary endpoint (on the ITT population) was planned to be performed once 510 OS events (deaths) occurred. Secondary endpoints would be tested only if the study was positive.

Results

The following results summarize Eli Lilly's brief study report for RAINBOW. The only data that was re-analyzed by this reviewer was the survival data, as the survival dataset was included in the submission (following Eli Lilly and FDA's agreement on the October 10, 2013 teleconference). (b) (4)



Demographics

Between December 23, 2010 and September 23, 2012, 665 patients (330 patients in the ramucirumab/paclitaxel arm and 335 patients in the placebo/paclitaxel arm) were enrolled in 27 countries in the RAINBOW study. At the data cut-off date (July 12, 2013), 13 patients in the ramucirumab/paclitaxel arm (4%) and 7 patients in the placebo/paclitaxel arm (2%) were receiving treatment, and 77% patients in both arms were dead. Table 16 summarizes the patient disposition.

Table 16 - RAINBOW: Patients disposition (ITT)

	Ramucirumab/paclitaxel N=330; n (%)	Placebo/paclitaxel N=335; n (%)
Died	256 (77)	260 (77)
Alive	63 (19)	55 (16)
Lost to follow-up	3 (1)	9 (3)
Withdrew consent	8 (2)	11 (3)
Treated	326 (99)	330 (99)
On treatment	13 (4)	7 (2)
Off treatment	313 (95)	323 (97)
- Disease progression	236 (72)	255 (76)
- Adverse event	39 (12)	38 (11)
- Death	12 (4)	13 (4)
- Withdrawal of consent	23 (7)	13 (4)
- Other/Lost to follow-up	3 (1)	4 (1)

Table 17 summarizes the demographic and baseline characteristics, which were well balanced between arms with the exception of ECOG performance status. More patients with an overall better performance status (score 0) were enrolled in the placebo arm. Generally speaking, patients in the RAINBOW study were similar to patients in the REGARD study, with the exception of race and histology. Asian patients were enrolled twice as frequently in the RAINBOW study than in the REGARD study (Asian patients constituted 16% of patients in REGARD).

Table 17 - RAINBOW: Demographic and baseline characteristics (ITT)

	Ramucirumab/paclitaxel N=330; n (%)	Placebo/paclitaxel N=335; n (%)	
Gender			
Male	229 (69)	243 (73)	
Female	101 (31)	92 (27)	
Age	Median (range) ≥ 65 y.o.	61 (25-83) 126 (38)	61 (24-84) 123 (37)
Race	White Asian Other	208 (63) 110 (33) 12 (4)	199 (59) 121 (36) 15 (5)
ECOG PS	0 PS 1	117 (35) 213 (65)	144 (43) 191 (57)
Stratification factors			
Geographic region			
- Region 1 (US/Europe/Australia)	198 (60)	200 (60)	
- Region 2 (Rest of the world*)	23 (7)	21 (6)	
- Region 3 (Asia**)	109 (33)	114 (34)	
Measurable disease	267 (81)	273 (81)	
Non-measurable disease	63 (19)	62 (19)	
Time to PD on 1 st line therapy			
- < 6 months	250 (76)	256 (76)	
- ≥ 6 months	80 (24)	79 (24)	

*Argentina, Brazil, Chile, Mexico.

** Hong Kong, Japan, Korea, Singapore, Taiwan

Table 18 summarizes the pre-treatment disease characteristics. Disease characteristics were well balanced between arms.

Table 18 - RAINBOW: Disease characteristics

	Ramucirumab/paclitaxel N=330; n (%)	Placebo/paclitaxel N=335; n (%)
Tumor location		
Gastric	264 (80)	264 (79)
GEJ	66 (20)	71 (21)
Histology		
Intestinal	145 (44)	135 (40)
Diffuse	115 (35)	133 (40)
Mixed	21 (6)	14 (4)

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Unknown	49 (15)	53 (16)
Metastases	324 (98)	324 (97)
Peritoneal metastases	163 (49)	152 (45)
Weight loss		
< 10%	277 (84)	286 (85)
≥ 10%	53 (16)	47 (14)

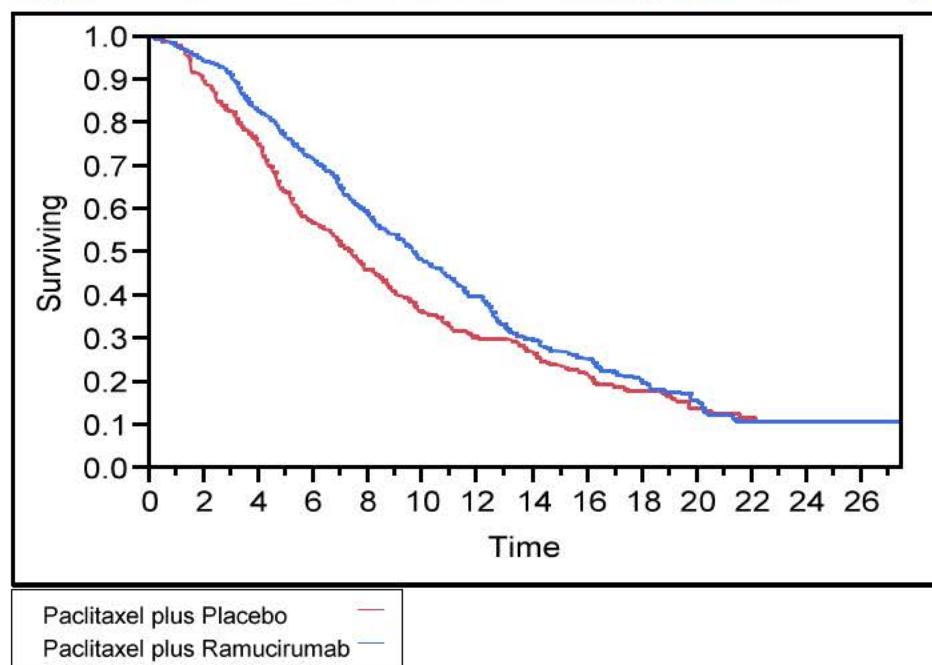
Patients in the REGARD study had a lower incidence of intestinal histology (22% in the ramucirumab arm and 30% in the placebo arm vs. 44% and 43% in the ramucirumab and placebo arms of the RAINBOW study respectively) and higher incidences of mixed/other/unknown histologies (38% in the ramucirumab arm and 32% in the placebo arm vs. 21% and 20% in the ramucirumab and placebo arms of the RAINBOW study respectively). The intestinal histology is associated with a better prognosis than the diffuse histology (both studies were similar in regards to diffuse histology tumors).

Efficacy

The primary endpoint for the RAINBOW study was OS. Ramucirumab in combination with paclitaxel reduced the risk of death in this population by 19% (stratified log rank test HR = 0.807; 95% CI 0.678, 0.962; p=0.0169), prolonging median survival time (9.63 months [95% CI: 8.48, 10.81] in the ramucirumab arm vs. 7.36 months [95% CI: 6.31, 8.38] in the placebo arm, a 2.27 months difference).

Figure 10 shows the Kaplan Meier (unstratified, FDA analysis) curve for survival.

Figure 10 - RAINBOW: Overall survival Kaplan Meier curve (ITT)



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The Kaplan Meier curve separates from the beginning, with larger differences in survival rates at earlier landmark points (6 months and 12 months). Because these are arbitrary time-points, this reviewer recommends against their use in product labeling. Table 19 summarizes the primary and secondary efficacy endpoint results.

Table 19 - RAINBOW: Study results summary

	Ramucirumab/paclitaxel N=330	Placebo/paclitaxel N=335
Survival		
Number of deaths – n (%)	256 (78)	260 (78)
Median survival – months (95% CI)	9.63 (8.48; 10.81)	7.36 (6.31; 8.38)
Stratified log-rank		0.0169
Stratified HR (95% CI)		0.807 (0.678; 0.962)
PFS		
Number of events – n (%)	279 (85)	296 (88)
Median PFS – months (95% CI)	4.40 (4.24; 5.32)	2.86 (2.79; 3.02)
Stratified log-rank		< 0.0001
Stratified HR (95% CI)		0.635 (0.536; 0.572)
Response rate		
CR – n (%)	2 (0.6)	1 (0.3)
PR – n (%)	90 (27)	53 (19)
SD – n (%)	172 (51)	159 (47)
PD – n (%)	43 (13)	83 (25)
Not evaluable/no evaluation – n (%)	23 (7)	39 (12)
Objective response rate (CR+PR)	92 (28)	54 (16)

These results support both the primary endpoint results and confirm the benefit of the addition of ramucirumab for the second-line treatment of patients with gastric/GEJ adenocarcinoma as shown in the REGARD study. To further explore some subsets of patients that appeared to not be benefiting from treatment with the same magnitude of effect in the REGARD study, FDA requested Eli Lilly to conduct subset analyses in the RAINBOW study by geographic region and gender.

In the RAINBOW study, there was a (nominal) statistically significant improvement in OS in Region 1, which included the US and Europe (HR=0.726, 95% CI 0.580; 0.909 and a nominal p=0.0050). An nominal improvement in OS was also observed in both male and female patients treated with ramucirumab plus paclitaxel (see Table 20).

Table 20 - RAINBOW: Overall survival by gender

	Ramucirumab/paclitaxel N=330	Placebo/paclitaxel N=335
Males	229	243
Events	174 (76%)	185 (76%)
Median OS (95% CI)	10.64 (9.03; 12.16)	7.82 (6.18; 9.40)
HR (95% CI) and p-value	0.814 (0.657; 1.009) – p=0.0604	
Females	101	92

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Events	82 (81%)	75 (82%)
Median OS (95% CI)	7.92 (6.93; 9.59)	6.83 (4.93; 7.52)
HR (95% CI) and p-value	0.672 (0.483; 0.935) – p= 0.0174	

These subgroup results, also exploratory, support the hypothesis that the negative findings in the REGARD study in these two subgroups was likely due to chance.

Safety

FDA requested Eli Lilly to submit safety information *only* if the information would strengthen the WARNINGS and PRECAUTIONS section of the label (i.e., indicate increased severity of a specific adverse reaction or include a new adverse reaction and/or that would change the risk/benefit assessment of ramucirumab). Table 21 shows an overview of the adverse events in the safety population.

Table 21 - RAINBOW: Summary of adverse events (safety population)

	Ramucirumab/paclitaxel N=327; n (%)	Placebo/paclitaxel N=329; n (%)
Any AE	324 (99)	322 (98)
Grade \geq 3	267 (82)	206 (63)
SAE	153 (47)	139 (42)
AE leading to discontinuation of any study drug	102 (31)	80 (24)
AE leading to discontinuation of ramucirumab/placebo	68 (21)	68 (21)
AE leading to discontinuation of paclitaxel	91 (28)	76 (23)
Fatal AE	39 (12)	51 (16)

Based on a preliminary review of data for RAINBOW (including treatment-emergent adverse event rates and severity, treatment-emergent serious adverse events, adverse events of special interest, and selected consolidated terms), Eli Lilly concluded that there were no new safety signals identified that would contribute to any proposed modifications to the WARNINGS and PRECAUTIONS section of the proposed label for ramucirumab as a single-agent in gastric cancer. However, there was an imbalance in the incidence of Grade 3 gastrointestinal hemorrhage in RAINBOW (see below Table 22) and therefore, Lilly proposed to specify gastrointestinal hemorrhage in [REDACTED] ^{(b)(4)} the WARNINGS and PRECAUTIONS section of the proposed label for ramucirumab as a single-agent in gastric cancer.

Table 22 - RAINBOW: Adverse events of special interest

	Ramucirumab/paclitaxel N=327; n (%)		Placebo/paclitaxel N=329; n (%)	
	All Grades	\geq Grade 3	All Grades	\geq Grade 3
Bleeding/hemorrhage	137 (42) 100 (31)	14 (4) 0	59 (18) 23 (7)	8 (2) 0

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- GI hemorrhages	33 (10)	12 (4)	20 (6)	5 (2)
Hypertension	82 (25)	48 (15)	19 (6)	9 (3)
Proteinuria	55 (17)	4 (1)	20 (6)	0
IRR	19 (6)	2 (1)	12 (4)	0
Venous thromboembolic event	13 (4)	8 (2)	18 (6)	11 (3)
Congestive heart failure	8 (2)	2 (1)	4 (1)	2 (1)
Arterial thromboembolic event	6 (2)	3 (1)	5 (2)	3 (1)
GI perforation	4 (1)	4 (1)	1 (<1)	0

The RAINBOW safety data showed a similar adverse event profile compared to the REGARD study, particularly the adverse events of special interest (pathway-related). No events of impaired wound healing, fistula, or RPLS were reported in RAINBOW. New toxicities, mainly hematologic, can be attributed to the concomitant use of paclitaxel. As with bevacizumab and ziv-aflibercept, the incidence of chemotherapy-related complications increases when ramucirumab is combined with paclitaxel. Table 23 summarizes the AEs \geq Grade 3 occurring in $\geq 2\%$ of patients in the ramucirumab plus paclitaxel arm and at higher rate than in the placebo plus paclitaxel arm.

Table 23 – RAINBOW: AEs \geq Grade 3 occurring with at least 2% increased incidence in the ramucirumab/placebo arm

	Ramucirumab/paclitaxel N=327; n (%)		Placebo/paclitaxel N=329; n (%)	
	All Grades	\geq Grade 3	All Grades	\geq Grade 3
Neutropenia	178 (54)	133 (41)	102 (31)	62 (19)
Leukopenia	111 (34)	57 (17)	69 (21)	22 (7)
Hypertension	78 (24)	46 (14)	16 (5)	8 (2)
Faighe	130 (40)	23 (7)	106 (32)	13 (4)
Abdominal pain	101 (31)	18 (6)	67 (20)	11 (3)
Asthenia	69 (21)	18 (6)	45 (14)	6 (2)
Diarrhea	106 (32)	12 (4)	76 (23)	5 (2)
Hyponatremia	19 (6)	11 (3)	9 (3)	4 (1)
Physical health deterioration	17 (5)	11 (3)	18 (6)	11 (3)
Febrile neutropenia	10 (3)	10 (3)	8 (2)	8 (2)
Peripheral neuropathy	47 (14)	10 (3)	30 (9)	7 (2)
Dehydration	15 (5)	9 (3)	13 (4)	8 (2)
Dyspnea	42 (13)	8 (2)	31 (9)	2 (1)

More patients in the placebo/paclitaxel arm experienced death within 30 days of last dose of treatment (16% vs. 11% in the ramucirumab/paclitaxel arm). Most of these deaths were attributed to disease progression (8% and 12% in the ramucirumab and placebo arms, respectively). It appeared that there were not significant differences in the incidence of treatment-related deaths (3% vs. 4% in the ramucirumab vs. placebo arms respectively).

In summary, the RAINBOW study supports the findings of the REGARD study that there is a statistically significant effect on overall survival, and the safety profile described is consistent with the REGARD study and what it is expected for a VEGF/R inhibitor.

7 Review of Safety

Safety Summary

The main safety analyses were performed on JVBD/REGARD, the pivotal study for the proposed indication (236 patients exposed to ramucirumab). Additionally, data from 334 patients treated with ramucirumab monotherapy from Phase 1 dose-escalation and Phase 2 studies were analyzed to evaluate the toxicity profile of ramucirumab.

Pivotal trial: JVBD - REGARD

JVBD was a multinational, double-blind, placebo controlled study of IV ramucirumab or placebo 8 mg/kg administered intravenously every 2 weeks. Eligible patients with gastric or gastroesophageal carcinoma should have progressed during or after discontinuation of a prior platinum or fluoropyrimidine chemotherapy regimen for metastatic disease or progressed within 6 months following adjuvant therapy with a fluoropyrimidine or platinum regimen. Patients received treatment until documentation of disease progression, intolerable toxicity, or death.

A total of 351 patients received either ramucirumab or placebo in the JVBD trial (constituting the safety analysis dataset). At the time of data cut-off, 96% of these patients discontinued ramucirumab or placebo. In the analysis of disposition using the disposition dataset [n = 355 as this dataset comprised all patients in the ITT population (reasons stated by the attending physician for treatment withdrawal)] the main reason for treatment discontinuation was disease progression, which occurred with greater frequency in the placebo arm (62%) than in the ramucirumab arm (53%). Adverse events leading to treatment discontinuation (including adverse events with an outcome of treatment discontinuation) occurred with higher frequency in the ramucirumab arm (14%) than in the placebo arm (7%). However, the analyses of narratives and CRFs did not always allow for a clear distinction of the causes of withdrawal, because in the advanced gastric/GEJ carcinoma setting, progression of disease and some adverse events could not be distinguished.

Patients in the placebo arm received a median of 3 infusions (6 weeks of placebo). Patients treated in the ramucirumab arm received a median of 4 infusions (8 weeks of treatment). Median relative dose intensity for both arms was greater than 99% (only 3 patients in the ramucirumab arm and 1 patient in the placebo arm required dose reduction) in both arms.

Ramucirumab/placebo dose modifications (dose delays 7 days or longer or dose modifications) were more frequent in the ramucirumab arm (5.1% and 1.3%, respectively) than in the placebo arm (1.7% and 0.9%, respectively). Doses were held more frequently in the ramucirumab arm (20% versus 10% in the placebo arm).

Almost all patients in both arms of the JVBD study experienced adverse events. Grade 3-4 AEs were more frequently observed in the ramucirumab arm (55%) than in the placebo arm (51%). The incidence of non-fatal serious adverse events (SAEs) was 38% in both arms.

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At the SOC (MedDRA System Organ Class) level, the most frequently affected systems ($\geq 25\%$ incidence) were gastrointestinal (ramucirumab arm 69%, placebo arm 64%), general disorders and administration site conditions (ramucirumab arm 54%, placebo arm 56%), metabolism and nutrition disorders (ramucirumab arm 38%, placebo arm 42%), investigations (ramucirumab arm 39%, placebo arm 18%), and respiratory, thoracic, and mediastinal disorders (ramucirumab arm 25%, placebo arm 27%).

At the preferred term level, the most frequently reported events (incidence $\geq 20\%$) were fatigue (ramucirumab arm 25%, placebo arm 24%), decreased appetite (ramucirumab arm 24%, placebo arm 23%), vomiting (ramucirumab arm 20%, placebo arm 25%), nausea (ramucirumab arm 19%, placebo arm 26%), abdominal pain (ramucirumab arm 19%, placebo arm 25%), and constipation (ramucirumab arm 15%, placebo arm 23%). With the exception of fatigue and decreased appetite (where the incidence rates were similar), in all these events the incidence in the placebo arm was at least 5% higher than in the ramucirumab arm.

Grade 3-4 events (preferred term analysis) were more frequently observed in the placebo arm (ramucirumab arm 51%, placebo arm 55%). Events occurring with $\geq 2\%$ difference in the ramucirumab arm were pain (2% vs. none in the ramucirumab and placebo arms, respectively), hyponatremia (3% versus 1% in the ramucirumab and placebo arms, respectively), abdominal pain (5% versus 3% in the ramucirumab and placebo arms, respectively), and hypertension (7% versus 3% in the ramucirumab and placebo arms, respectively). Events occurring with $\geq 2\%$ difference in the placebo arm were asthenia (2% versus 7% in the ramucirumab and placebo arms respectively), dysphagia (2% versus 4% in the ramucirumab and placebo arms, respectively), and anemia (6% versus 8% in the ramucirumab and placebo arms, respectively).

At the time of data cutoff, 17 patients in the placebo arm (15% of the placebo safety population) and 59 patients in the ramucirumab arm (25% of the ramucirumab safety population) were alive. Most patients (64% in the placebo arm and 63% in the ramucirumab arm) died because of progression of disease. There were 54 deaths that occurred secondary to an adverse event with a start date within 30 days of the last dose of study treatment. However, if the events of disease progression, gastric cancer, and neoplasm are removed from this population, there were 26 patients (11% patients in the ramucirumab arm) and 12 patients (10% patients in the placebo arm) who experienced an adverse event with a fatal outcome. Treatment related deaths were more frequent in the ramucirumab arm, and although only four events were attributed by the investigators as treatment-related, it is not possible to rule out the contribution of the treatment to other events such as hemorrhage, perforations, etc.

Regarding adverse events of special interest (VEGF/R inhibition-related and assessed by combining multiple preferred terms), these events were observed, as expected, more frequently in patients in the ramucirumab arm. The incidence of hypertension was 17% in the ramucirumab arm and 8% in the placebo arm (Grades 3 incidence rates were 8% and 3% in the ramucirumab and placebo arms, respectively). There were no Grade 4 hypertensive events.

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The incidence of proteinuria was similar (3.0% in the ramucirumab arm and 2.6% in the placebo arm), with a single Grade 3 event in the ramucirumab arm. However, in 18 (8%) patients in the ramucirumab arm and 4 (3%) patients in the placebo arm, the urine analysis for proteinuria was considered “positive” or “+++” (presumably dipstick).

No arterial thromboembolic events were observed in the placebo arm. There were 4 patients in the ramucirumab arm who experienced 6 arterial thromboembolic events. Although the role of ramucirumab could not be ruled out, there were co-morbid factors (prior history of hypertension, concomitant sepsis, etc.) that have contributed. Eight subjects (7%) in the placebo arm and 9 subjects (4%) in the ramucirumab arm experienced venous thromboembolic events.

Bleeding/hemorrhagic events were more frequent in the ramucirumab arm (13% per-patient incidence) than in the placebo arm (11%). There was one event of fatal gastric/gastrointestinal hemorrhage per arm. The majority of events were Grade 1-2; the incidence of Grade 1-2 bleeding/hemorrhagic events in the ramucirumab arm was 10% versus 9% in the placebo arm. In the JVBD study, as expected, subjects in the ramucirumab arm experienced more hemorrhagic events than patients in the placebo arm; however, the incidence of serious, life-threatening or fatal events of hemorrhages was not increased.

Three instances of gastrointestinal perforation were reported (2 in the ramucirumab arm and one in the placebo arm), all fatal.

Although a safety concern was reported related to the use of ramucirumab in hepatocellular carcinoma (see below, hepatic events appeared related to decompensation of cirrhosis), the incidence of Grade 3-4 hepatic events in REGARD (including laboratory findings) was 8% in the ramucirumab arm versus 7% in the placebo arm.

Subgroup analyses (age, gender, geographic region, and tumor location) did not show any significant differences in toxicity in these groups.

In summary, treatment with ramucirumab in the JVBD study resulted in the increased incidence of certain VEGF/R inhibition-related toxicities; however, most patients tolerated ramucirumab without requiring dose reductions.

Supportive data:

In addition to patients enrolled in the REGARD trial, Eli Lilly submitted safety data and a high level overview from 334 patients treated with ramucirumab as a single agent in Phase 1 and 2 clinical studies. These included 191 patients enrolled in four single-agent trials investigating ramucirumab as a single agent, 66 patients in a QT study, and 77 patients from 3 dose-escalation studies in patients with advanced solid tumors. Because this population was heterogeneous, marked differences in the toxicity profiles were observed when evaluated in different disease settings (i.e., patients with ovarian carcinoma experienced more AEs than other patients, patients with renal cell carcinoma experienced more renal and urinary complications, etc).

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In this pooled population, the overall incidence of bleeding/hemorrhagic events was 48%, and the incidence of \geq Grade 3 events was 4%. Thirty one (16%) patients experienced epistaxis and in all but one case, these were Grade 1-2 in severity.

The overall incidence of hypertension (PTs included: hypertension, hypertensive crisis, blood pressure diastolic increased, and blood pressure increased) in the pooled phase 2 (n=191) population was 29%, and 10% of the pooled population had an event of Grade 3-4 hypertension. There were two Grade 4 events, one in a patient with renal cell carcinoma and another in a patient with HCC. Although not observed in the monotherapy studies nor the pivotal study, there was an event of RPLS in the metastatic colorectal cancer study when ramucirumab was used in combination with FOLFIRI.

Twenty seven out of 191 patients across the single-agent phase 2 studies (14%) experienced events within the SMQ liver disorders. Eleven of these patients had HCC as the baseline diagnosis and this population (n=42 in clinical trial JVHQ) had the highest incidence of such events (and \geq Grade 3 events). In some cases, the events appeared disease-related (e.g., esophageal varices, and liver transplant); however, drug-related hepatic decompensation could not be ruled out (for example, worsening of ascites in 6 patients with HCC; encephalopathy in one patient with HCC; and hepatorenal syndrome in one patient with HCC). The HCC study was revised to restrict the eligibility criteria to patients with no ascites and no prior history of hepatic encephalopathy.

Proteinuria was observed in 15% of patients in the pooled phase 2 population (n=191), and 2% experienced Grade 3-4 proteinuria. There was one event of nephrotic syndrome in a patient with melanoma.

The following arterial thromboembolic events were observed in the pooled population: acute coronary syndrome, angina pectoris, cerebral ischemia, myocardial infarction (all these events were Grade 3-4), and Grade 2 femoral artery occlusion and coronary artery disease.

In summary, the supportive data from Phase 1-2 single-arm studies was generally consistent with the safety data from the pivotal study, JVBD. The safety database was adequate and allowed for the characterization of the toxicity profile of ramucirumab.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary study used to evaluate safety was Study JVBD (REGARD). All the safety review is based on the REGARD study, unless specified. The protocol was designed to record all adverse events regardless of severity. The safety database from JVBD included data from 351 patients. Ramucirumab was administered to 236 of these patients.

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In addition, data from 334 patients treated with ramucirumab monotherapy from Phase 1 dose-escalation and Phase 2 studies (summarized in Table 24) studies was analyzed and summarized to support the safety findings of JVBD. As requested, ImClone provided data for events of special interest in 218 patients exposed to ramucirumab in combination with other chemotherapy agents.

Table 24 - Single agent ramucirumab studies

Study	Indication	Ramucirumab	# pts
JBVO	Melanoma	10 mg/kg every 3 weeks	50
JVBP	RCC	8 mg/kg every 2 weeks	39
JBVQ	HCC	8 mg/kg every 2 weeks	42
JVBR	Ovarian CA	8 mg/kg every 2 weeks	60
JBVK	QTc study	10 mg/kg every 3 weeks	66
JVBM	Solid tumors	2-16 mg/kg weekly for 4 weeks	37
JVBN	Solid tumors	6-10 mg/kg every 2 weeks or 15-20 mg/kg every 3 weeks	25
JBVI	Solid tumors	6-8 mg/kg every 2 weeks or 10 mg/kg every 3 weeks	15

7.1.2 Categorization of Adverse Events

The severity of the events was documented using NCI-CTCAE version 4.02. The MedDRA 15 dictionary was used to code adverse event data. A total of 419 preferred terms (PT) in 24 SOCs described all adverse events.

Verbatim terms in the adverse event dataset were reviewed to determine whether MedDRA PTs were appropriately coded. A total of 1651 preferred terms out of 2903 did not match (identically) the verbatim term. In the majority of cases, the either the verbatim term was corrected because of misspellings or typos or the verbatim term reflected a commonly used term (i.e., hoarseness instead of dysphonia, oral thrush instead of oral candidiasis, etc) that appeared to be correctly coded to the MedDRA dictionary PT. There was only one event (patient #331-0002) where the verbatim term was “palmo plantar erythrodyplasia” and was coded to the PT “red blood cell abnormality”; the correct PT *likely* should have been “palmo-planter erythrodysesthesia”; however this ultimately appeared to be an error when writing the verbatim term.

Once the events experienced by patients who never received treatment were removed from the dataset, there were 873 adverse events in 103 patients in the placebo arm and 2019 events in 224 patients in the ramucirumab arm. These included treatment-emergent adverse events of all grades and non-treatment-emergent adverse events. ImClone defined the treatment-emergent adverse events as follows:

- AEs that occurred on the day of or after the first dose of any study therapy and up to 30 days after the last dose of any study therapy (or up to any time if the event was an SAE considered possibly, probably, or definitely related to study treatment by the investigator);

- AEs that occurred prior to the first dose and worsened while on therapy and up to 30 days after the last dose of study treatment (or up to any time if the event was an SAE considered possibly, probably, or definitely related to study treatment by the investigator);

An analysis of the non-treatment-emergent adverse events (119 events) determined that 33 of these events occurred 30 days or more following receipt of the last dose of study-related therapy and all remaining events occurred before study treatment Day 1; therefore, all the safety review will be centered on the 2773 treatment-emergent events (843 events in 101 patients in the placebo arm and 1930 events in 223 patients in the ramucirumab arm).

7.1.3 Pooling of Data Across Studies

As summarized above (Table 24), Eli Lilly pooled safety data and provided high level overview from 334 patients treated with ramucirumab as a single agent in Phase 1 and 2 clinical studies. This population was heterogeneous and uncontrolled, and therefore was considered during this review as supportive data (in particular data regarding VEGF/R inhibition-related toxicity).

Of these pooled 334 patients, the dataset included adverse events for 189 of 191 patients (99%) treated in studies JVBO (49/50 melanoma patients in the ramucirumab only arm), JVBP (39/39 renal cell carcinoma patients), JVHQ (42/42 hepatocellular carcinoma patients), and JVBR (59/60 ovarian cancer patients).

Mean age of this pooled population was 61 years (range 26-92) and median age was 61 years (95% CI 60.36; 61.16); 102 patients were men and 87 were women. Table 25 summarizes the AEs by SOC in the pooled population; however, when the data is analyzed by disease (as each study explored the use of ramucirumab in a different disease setting) there are marked differences in the safety profile that can be explained by the studied population (Table 26).

Table 25 - Ramucirumab AEs by SOC, pooled monotherapy population

SOC	Pooled population N=191	
	Grade 1-2; n (%)	Grade 3-5; n (%)
Gastrointestinal disorders	114 (60)	26 (14)
Vascular disorders	45 (24)	22 (12)
Nervous system disorders	101 (53)	20 (10)
General disorders and administration conditions	128 (67)	18 (9)
Respiratory, thoracic and mediastinal disorders	80 (42)	13 (7)
Metabolism and nutrition disorders	68 (36)	14 (7)
Infections and infestations	53 (28)	10 (5)
Blood and lymphatic system disorders	27 (14)	10 (5)
Musculoskeletal and connective tissue disorders	88 (46)	8 (4)
Investigations	53 (28)	8 (4)
Renal and urinary disorders	38 (20)	7 (4)
Hepatobiliary disorders	3 (2)	7 (4)
Injury and procedural complications	30 (16)	6 (3)
Neoplasms	14 (7)	5 (3)
Cardiac disorders	12 (6)	5 (3)
Surgical and medical procedures	2 (1)	3 (2)

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SOC	Pooled population N=191	
	Grade 1-2; n (%)	Grade 3-5; n (%)
Psychiatric disorders	44 (23)	1 (1)
Reproductive system disorders	12 (6)	1 (1)
Ear and labyrinth disorders	10 (5)	1 (1)
Immune system disorders	6 (3)	1 (1)
Skin and subcutaneous tissue disorders	74 (39)	0
Eye disorders	24 (13)	0
Endocrine disorders	5 (3)	0

Patients with HCC appear to have the highest incidence of gastrointestinal disorders, psychiatric disorders (hepatic encephalopathy and related signs and symptoms), and vascular disorders, and the lowest incidences of blood and lymphatic disorders, cardiac disorders, and infections.

Patients with refractory ovarian carcinoma appear to have, overall, a higher rate of complications than the other studied populations. As expected, the RCC population experienced higher rates of renal and urinary disorders, but also respiratory and skin disorders.

Table 26 – Ramucirumab AEs by monotherapy study (SOC)

SOC	BO; n (%) N=50	BP; n (%) N=39	BQ; n (%) N=42	BR; n (%) N=60
Blood and lymphatic system disorders	8 (16)	9 (23)	3 (7)	17 (28)
Cardiac disorders	5 (10)	5 (13)	1 (2)	6 (10)
Ear and labyrinth disorders	2 (4)	2 (5)	2 (5)	5 (8)
Endocrine disorders	0	1 (3)	1 (2)	3 (5)
Eye disorders	6 (6)	4 (10)	3 (7)	11 (18)
Gastrointestinal disorders	31 (62)	26 (67)	36 (86)	47 (78)
General disorders and administration site conditions	37 (74)	27 (69)	33 (79)	49 (82)
Hepatobiliary disorders	3 (6)	0	6 (14)	1 (2)
Immune system disorders	2 (4)	0	2 (5)	3 (5)
Infections and infestations	9 (18)	18 (46)	5 (12)	31 (52)
Injury and procedural complications	11 (22)	9 (23)	8 (19)	8 (13)
Investigations	11 (22)	14 (36)	11 (26)	25 (42)
Metabolism and nutrition disorders	20 (40)	17 (44)	17 (40)	28 (47)
Musculoskeletal and connective tissue disorders	24 (48)	22 (56)	15 (36)	35 (58)
Neoplasm	4 (8)	4 (10)	2 (5)	9 (15)
Nervous system disorders	25 (50)	23 (59)	25 (60)	48 (80)
Psychiatric disorders	11 (22)	7 (18)	18 (43)	9 (15)
Renal and urinary disorders	12 (24)	10 (26)	8 (19)	15 (25)
Reproductive system disorders	3 (6)	1 (3)	2 (5)	7 (12)
Respiratory, thoracic and mediastinal disorders	18 (36)	24 (62)	17 (40)	34 (57)
Skin and subcutaneous tissue disorders	18 (36)	18 (46)	12 (29)	26 (43)
Surgical and medical procedures	0	3 (8)	2 (5)	0
Vascular disorders	15 (30)	10 (26)	22 (52)	20 (33)

As summarized in Table 27, overall, it appears from this pooled analysis by PT that the incidence of the most common events observed in the REGARD study (Table 34) and those that are known

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to be related to VEGF/R inhibition is within the expected range (note that these safety analyses of the pooled monotherapy population, from the ISS, included all AEs in the database including a limited number of AEs that were considered by the sponsor as non-treatment emergent. As such, the percentiles differ slightly from Lilly's; however, these differences did not change any safety conclusions related to the use of ramucirumab).

Table 27- Ramucirumab AEs by PT (incidence ≥ 5%), pooled monotherapy population

PT	All grades N=191; n (%)	Grade 1-2 N=191; n (%)	Grade 3-5 N=191; n (%)
Fatigue	116 (61)	102 (53)	14 (7)
Headache	89 (47)	80 (42)	9 (5)
Nausea	66 (35)	63 (33)	3 (2)
Edema peripheral	55 (29)	54 (28)	1 (1)
Hypertension	52 (27)	34 (18)	18 (9)
Diarrhea	50 (26)	46 (24)	4 (2)
Vomiting	45 (24)	42 (22)	3 (2)
Decreased appetite	43 (23)	41 (21)	2 (2)
Constipation	39 (20)	38 (20)	1 (1)
Abdominal pain	34 (18)	29 (15)	5 (3)
Arthralgia	33 (17)	31 (16)	2 (1)
Back pain	32 (17)	27 (14)	5 (3)
Cough	31 (16)	30 (16)	1 (1)
Dyspnea	31 (16)	26 (14)	5 (3)
Epistaxis	31 (16)	30 (16)	1 (1)
Weight decreased	28 (15)	28 (15)	0
Proteinuria	24 (13)	21 (11)	3 (2)
Pyrexia	24 (13)	23 (12)	1 (1)
Chills	23 (12)	23 (12)	0
Insomnia	23 (12)	22 (12)	1 (1)
Pain in extremity	19 (10)	17 (9)	2 (1)
Anemia	17 (9)	13 (7)	4 (2)
Dizziness	18 (9)	18 (9)	0
Infusion related reaction	18 (9)	12 (6)	6 (3)
Thrombocytopenia	17 (9)	10 (5)	7 (4)
Urinary tract infection	17 (9)	16 (8)	1 (1)
Abdominal distention	16 (8)	16 (8)	0
Anxiety	16 (8)	16 (8)	0
Myalgia	16 (8)	16 (8)	0
Dehydration	14 (7)	13 (7)	1 (1)
Dry skin	13 (7)	13 (7)	0
Dyspepsia	14 (7)	14 (7)	0
Gingival bleeding	14 (7)	13 (7)	1 (1)
Hyperglycemia	13 (7)	11 (6)	2 (1)
Pruritus	14 (7)	14 (7)	0
Rash	14 (7)	14 (7)	0
Stomatitis	14 (7)	14 (7)	0
Abdominal discomfort	11 (6)	11 (6)	0

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PT	All grades N=191; n (%)	Grade 1-2 N=191; n (%)	Grade 3-5 N=191; n (%)
Abdominal upper pain	11 (6)	10 (5)	1 (1)
Dysphonia	11 (6)	11 (6)	0
Hypomagnesemia	12 (6)	12 (6)	0
Ascites	9 (5)	5 (3)	4 (2)
Creatinine increased	9 (5)	8 (4)	1 (1)
Depression	10 (5)	10 (5)	0
Dysgeusia	9 (5)	9 (5)	0
Flushing	9 (5)	8 (4)	1 (1)
Musculoskeletal pain	10 (5)	9 (5)	1 (1)
Neuropathy peripheral	9 (5)	8 (4)	1 (1)
Oropharyngeal pain	9 (5)	9 (5)	0
Rhinitis	9 (5)	9 (5)	0
Upper respiratory tract infection	10 (5)	10 (5)	0
Vision blurred	9 (5)	9 (5)	0

Table 28 summarizes the adverse events of special interest (AESIs) in the pooled monotherapy population.

Table 28 - Ramucirumab: AESIs in the pooled monotherapy population

PT	All grades N=191; n (%)	Grade 1-2 N=191; n (%)	Grade 3-5 N=191; n (%)
Bleeding / hemorrhage events	91 (48)	84 (44)	7 (4)
Hypertension	56 (29)	37 (19)	19 (10)
Liver injury / failure	41 (21)	24 (13)	17 (9)
Proteinuria	26 (14)	22 (12)	4 (2)
Infusion related reaction	23 (12)	16 (8)	7 (4)
Renal failure	15 (8)	10 (5)	5 (3)
Arterial thromboembolic events	8 (4)	2 (1)	6 (3)
Venous thrombotic events	3 (2)	1 (1)	2 (1)
Cardiac failure	1 (1)	1 (1)	0
Fistula	2 (1)	1 (1)	1 (1)

In this pooled population, the overall incidence of bleeding/hemorrhagic events was 48%, and the incidence of \geq Grade 3 events was 4%. Thirty one (16%) patients experienced epistaxis and in all but one case, these were Grade 1-2 events. Seven percent of these patients experienced gingival bleeding and in all but one case, these were Grade 1-2 events. There was a fatal event of gastrointestinal hemorrhage in a patient with hepatocellular carcinoma on Day 13 of study treatment. The incidence of hematuria was 4% and vaginal hemorrhage was 3%. With the exception of one event of Grade 3 rectal hemorrhage and one event of Grade 3 hematemesis, all other events were Grade 1-2 and with incidence rates of \leq 2%.

The overall incidence of hypertension (PTs included: hypertension, hypertensive crisis, blood pressure diastolic increased, and blood pressure increased) in the pooled population was 27%, and 9% of the pooled population had an event of Grade 3-4 hypertension. There were two Grade 4 events, one in a patient with renal cell carcinoma who experienced hypertensive crisis on Day

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442 of study, and another patient with HCC who experienced hypertension on Day 29 of the study. Renal cell carcinoma is a known risk factor for hypertension, particularly when exposed to VEGF/R inhibitors. There were no events with a fatal outcome or events of RPLS in the monotherapy studies.

Regarding infusion reactions and prophylactic premedication, FDA recommended to the Applicant on meetings held on March 16, May 27, August 5, 2010, and June 8 2011 that protocols contain uniform rules regarding premedication so that an adequate dosing and administration section of a label can be written. These changes were implemented in ongoing Phase 3 studies, but prophylactic medication was not mandatory in any Phase 1 or 2 monotherapy studies. The sponsor attempted to analyzed the infusion reaction events and their relationship with premedication, but in half of the events it was unknown if the patients received any premedication, so no conclusion can be inferred regarding IRR prophylaxis in the pooled monotherapy population. The incidence of infusion-related reactions (PTs included: drug hypersensitivity, hypersensitivity, and infusion-related reaction) in the pooled population was 9%. Two thirds of these events were Grade 1-2 events, and the total incidence of Grade 3-4 IRR was 4% (excluding a patient with an allergic reaction to lisinopril). In 3 patients the Grade 3-4 IRR resulted in the withdrawal of ramucirumab. There was no uniformity in the use of prophylaxis for IRRs, so no conclusions are possible as the real incidence of immune-related adverse events and the need for prophylaxis treatment.

The Applicant and FDA are following ramucirumab's potential for liver toxicity. Following an internal safety data committee's unblinded review of 28 cases from Study CP12-0919, JVBF (a multicenter, randomized, double-blind, Phase 3 study of ramucirumab vs. best supportive care as second-line treatment in patients with HCC following first-line treatment with sorafenib), an imbalance was found in events searched under the hepatic disorders SMQ. In the JVBF study, the estimated exposure to ramucirumab was 208 patients. These events occurred in 22 cases in 20 patients, (9.6%) in the investigational arm compared to 6 cases in 6 patients (2.9%) in the placebo arm.

As per FDA request, Eli submitted to the IND an aggregated safety report for liver toxicity in patient receiving ramucirumab for non-HCC cancers using the same search criteria described above. Following the unblinded review of 13 cases from non-HCC cancer studies (the estimated exposure to ramucirumab was 2004 patients and to placebo was 1502 patients), an imbalance in the number of serious adverse events for the ramucirumab treated groups (11 cases, 0.55%) compared with the placebo groups (2 cases, 0.13%) was found.

FDA review of the report cases concluded that overall, these events did not appear to show that ramucirumab can cause direct drug-induced liver injury, but rather can exacerbate sequelae of cirrhosis (i.e., induce encephalopathy, increase ascites, or possibly cause hepatorenal syndrome). It is unclear if this is related to fluid shifts or some other mechanism.

The IDMC recommended that patients with cirrhosis at a level of Child-Pugh Class B (or worse) or cirrhosis with a history of hepatic encephalopathy or clinically meaningful ascites resulting

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from cirrhosis should not be further enrolled on Study JVBF. The IDMC also recommended discontinuing study drug (ramucirumab or placebo) for patients with new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis. Regarding non-HCC patients, all were confounded by the use of simultaneous known hepatotoxic drugs or liver metastatic disease. Follow-up aggregated reports (last report submitted and reviewed 7/10/2013) continued to show an imbalance of the same magnitude in the HCC study, while the differences in the non-HCC studies were of a lesser magnitude.

In the pooled monotherapy population, 27 patients (14%, Table 29) experienced events within the SMQ liver disorders. Eleven (41%) patients had HCC as the baseline diagnosis. In some cases, the events were clearly disease-related (i.e., ascites in 6 patients, esophageal varices, and liver transplant). ALT and AST were simultaneously increased in 6 patients and 1 patient each had increased ALT or AST; 3 patients had isolated hyperbilirubinemia or jaundice, and there were events of different combinations of transaminases, bilirubin, hyperammonemia, liver failure, signs/symptoms of hepatic encephalopathy, and hepatorenal syndrome. Four events in this SOC had a fatal outcome: 3 patients died of liver failure (2 patients with melanoma and one patient with HCC) and one patient with a diagnosis of HCC died due to hepatic encephalopathy. In three patients, the event was considered as not related, and in one subject with melanoma the investigator considered the event of liver failure as possibly related.

Table 29 - Ramucirumab liver injury in pooled monotherapy studies

PT	Study JVBQ (HCC, n=42) N (%)	Studies JBVO, JVBP, JVBR (Non-HCC n=149). N (%)
ALT increased	0	6 (4)
Ammonia increased	1 (2)	0
Ascites	6 (14)	0
AST increased	0	7 (5)
Asterixis	1 (2)	0
Hepatic encephalopathy	1 (2)	0
Hepatic failure	1 (2)	2 (1)
Hepatic pain	1 (2)	0
Hepatorenal syndrome	1 (2)	0
Hyperammonemia	1 (2)	0
Hyperbilirubinemia	2 (5)	1 (1)
Jaundice	0	2 (1)
Liver disorder	0	1 (1)
Liver function test abnormal	0	2 (1)
Liver transplant	1 (2)	0
Transaminases increased	0	3 (2)
Esophageal varices	1 (2)	0

Proteinuria was observed in 14% patients in the pooled population, and 2% experienced Grade 3-4 proteinuria. There was one event of nephrotic syndrome in a patient with melanoma, and the remaining Grade 3 events occurred in a patient with melanoma and two patients with renal cell carcinoma. Proteinuria was observed in 18% patients with ovarian cancer, 18% patients with RCC, 12% patients with melanoma, and 5% patients with HCC.

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Renal toxicity (PTs renal failure, acute renal failure, renal insufficiency, and creatinine increase) was observed in 11 patients (6%). All these patients were heavily pretreated and had predisposing conditions. In 6 patients, the only event was creatinine increase, but two patients had acute renal failure and 3 patients had events of renal failure/insufficiency. Although the event did not resolve in 6 patients, ramucirumab was withdrawn as a consequence of the renal event in only two patients.

The following arterial thromboembolic events were observed in the pooled population: acute coronary syndrome, angina pectoris, cerebral ischemia, myocardial infarction (all these events were Grade 3-4), and Grade 2 femoral artery occlusion and coronary artery disease.

In summary, the incidence and pattern of AEs observed in the single-arm studies for those patients who received ramucirumab monotherapy was generally consistent with the toxicity observed in the ramucirumab arm of the pivotal study, REGARD.

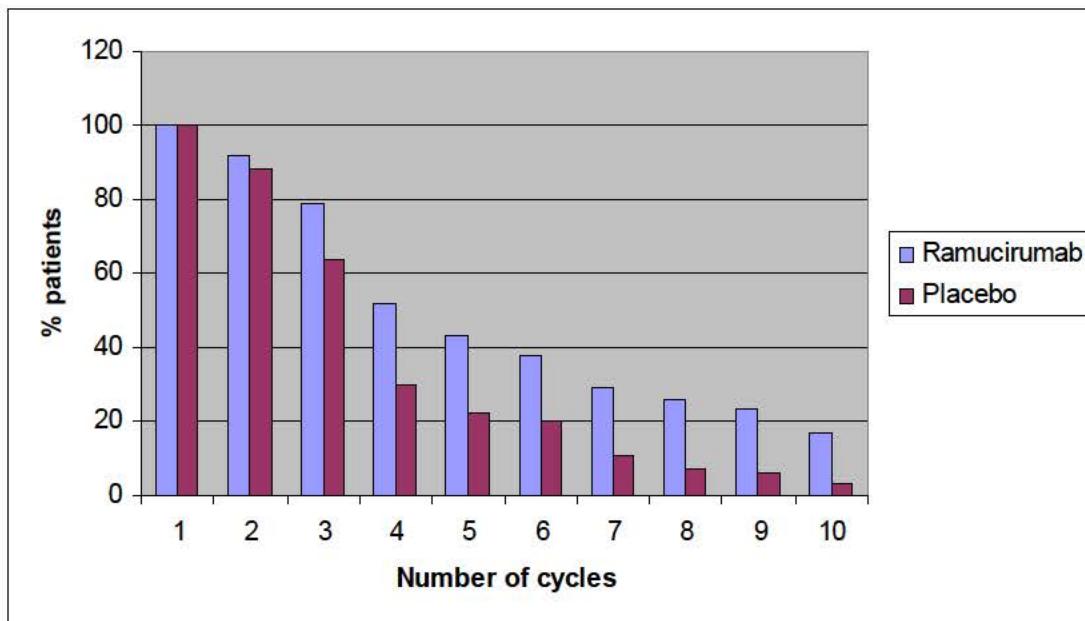
7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Of 355 randomized patients, 351 received at least 1 dose of study therapy (236 patients in the ramucirumab arm and 115 patients in the placebo arm). Reasons for not receiving treatment after randomization included death before the first dose, performance status decline, brain metastases, and laboratory abnormalities.

The median duration of therapy was 8 weeks for the ramucirumab arm (with a median of 4 cycles received) and 6 weeks for the placebo arm (with a median of 3 cycles received). However, the difference in the proportion of patients dropping off treatment after the second cycle was more pronounced in the placebo arm.

Figure 11 - REGARD: Exposure as a proportion patient/cycle



The median relative dose intensity was 99.6% for the ramucirumab arm, with 91.5% of patients receiving doses \geq 90% of the 8 mg/kg protocol-stipulated dose level. Only 3 patients in the ramucirumab arm and 1 patient in the placebo arm required dose reductions because of an AE. No patient in either arm underwent more than one dose reduction.

Dose delays of 7 days or longer were observed more frequently (5% vs. 2%) in the ramucirumab arm than in the placebo arm (Table 30). Ramucirumab doses were omitted in 20% patients versus 10% patients in the placebo arm. Infusion rate modifications (6% vs. 2% ramucirumab and placebo arms, respectively), or infusion interruption (1% vs. none, ramucirumab and placebo arms respectively), were also more frequent in the ramucirumab arm.

Table 30 - REGARD: Exposure summary

	Ramucirumab/BSC N=236	Placebo/BSC N=115
Median duration of treatment in weeks (range)	8.0 (2-72)	6.0 (2-60)
Median total number of cycles	4 (1-34)	3 (1-30)
Median dose intensity (mg/kg/week)	3.98 (2.4-4.6)	4 (2.6-4.4)
Median relative dose intensity (%)	99.6	100
Dose delay		
4-6 days delay	9 (3.8%)	5 (4.3%)
\geq 7 days delay	12 (5.1%)	2 (1.7%)
Dose reduction	3 (1.3%)	1 (0.9%)
Dose held	48 (20.3%)	12 (10.4%)

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In the Applicant's analysis, half of the instances of dose delay were for administrative reasons, including holidays, technical problems at the site, or personal reasons. There was not a single category of toxicity that predominantly drove the adverse event-related delays.

However, in the analysis of the safety dataset, 37 patients (16%) in the ramucirumab arm and 8 patients (7%) in the placebo arm had the dose delayed/modified because an adverse event. The majority of patients in the ramucirumab arm had a delayed dose because of a gastrointestinal disorder (10 pts: PTs were abdominal pain in 4 patients, dysphagia in 2 patients, vomiting in 2 patients, and intestinal obstruction and diarrhea in one patient each), a general disorder (8 patients: PTs were asthenia in 5 patients, fatigue in one patient , and pain in 2 patients), or an investigation abnormality (8 patients: PTs were neutropenia in 2 patients, and weight loss, alkaline phosphatase increase, transaminase increase, hemoglobin decrease, creatinine and uric acid increase, and blood pressure increase in one patient each). In the placebo arm, gastrointestinal disorders [3 patients with vomiting (2) or dysphagia (1)], a general disorder (3 patients, one each with fever, asthenia, and weakness), or an infection (2 patients) were the causes of the delay in dosing.

In summary, patients in the treatment arm were treated longer, although the median difference was only one cycle (consistent with the efficacy study results).

7.2.2 Explorations for Dose Response

Weekly doses of ramucirumab ranging from 2 to 16 mg/kg were evaluated in Study JVBM, a dose-escalation Phase 1 study. The MTD for weekly dosing was identified as 13 mg/kg. Two dose-limiting toxicities were observed in patients receiving the 16-mg/kg weekly dose, Grade 3 deep vein thrombosis and Grade 3 hypertension. The Applicant stated that preliminary efficacy was observed across all doses. Apparent nonlinear PK profiles were observed between 2 and 8 mg/kg; PK profiles appeared to be linear for doses at and above 8 mg/kg, 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, JVBN. 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 Phase 2-3 doses and schedules were selected because they were associated with PK profiles suggesting target receptor saturation; preliminary efficacy was observed at and below these doses and schedules in Phase 1 studies. A dose of 8 mg/kg every 2 weeks was selected for use in the REGARD study. As the REGARD study administered only one dose of ramucirumab (8 m/kg every 2 weeks), no dose-response assessments were conducted.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Routine clinical testing and monitoring were analyzed, and the results of these analyses are described in the Laboratory and Safety Sections of this review (Sections 7.3 and 7.4).

7.2.5 Metabolic, Clearance, and Interaction Workup

Ramucirumab and placebo were administered with best supportive care (i.e., treatments aimed at ameliorating symptoms, improve function, or treat complications from the disease and/or treatment). No formal analysis of interaction was conducted for this monoclonal antibody.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

A summary of the toxicities caused by other VEGFR inhibitors can be found in Section 2.4. The safety profile of anti-VEGFR agents is characterized by the occurrence of hypertension, proteinuria, arterial and venous thromboembolic events, hemorrhagic events (e.g., epistaxis, gastrointestinal bleeding, and hemoptysis), compromised wound healing, and less frequently, events such as reversible posterior leukoencephalopathy syndrome, gastrointestinal perforation and fistula, and cardiac dysfunction.

A review of the VEGF/R inhibition-dependent toxicities found with the use of ramucirumab is described in Section 7.3.5, Submission specific safety concerns.

7.3 Major Safety Results

The safety database of the REGARD study contains 2,773 treatment-emergent events (843 events in 101 patients in the placebo arm and 1,930 events in 223 patients in the ramucirumab arm).

Almost all patients in both arms experienced adverse events, but a higher proportion of patients (94%) experienced AEs in the ramucirumab arm than in the placebo arm (88%). Grade 3-4 AEs occurred more frequently in the placebo arm (55%) than in the ramucirumab arm (51%). Grade 1-2 AEs occurred more frequently in the ramucirumab arm (88%) than in the placebo arm (77%). There was a 2% difference in the incidence of fatal adverse events favoring the ramucirumab arm (15% versus 17% in the placebo arm). Table 31 summarizes the major safety results in the REGARD trial, including all outcomes and for the duration of the study since patient enrollment until 30 days after the last dose of study drug.

Table 31 - REGARD: Major safety results summary

	Ramucirumab/BSC (n;%) N=236	Placebo/BSC (n;%) N=115
Subjects who experienced an AE	223 (94)	101 (88)

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	Ramucirumab/BSC (n;%) N=236	Placebo/BSC (n;%) N=115
Subjects who experienced an AE Grade 1-2	207 (88)	88 (77)
Subjects who experienced an AE Grade 3-4	120 (51)	63 (55)
Subjects who experienced a SAE	106 (45)	51 (44)
Deaths related to an AE	35 (15)	19 (17)

At the SOC level, the most frequently affected systems ($\geq 25\%$ incidence) were gastrointestinal (placebo arm 64%, ramucirumab arm 69%), general disorders and administration sites (placebo arm 56%, ramucirumab arm 54%), metabolism and nutritional disorders (placebo arm 38%, ramucirumab arm 22%), investigations (placebo arm 18%, ramucirumab 29%), and respiratory, thoracic, and mediastinal SOC (placebo arm 27%, ramucirumab arm 25%). Table 32 summarizes all the adverse events by SOC.

Table 32 - REGARD: AEs by SOC

SOC	Ramucirumab/BSC (n, %) N=236			Placebo/BSC (n, %) N=115		
	All grades	Grades 3-4	Deaths	All grades	Grades 3-4	Deaths
Gastrointestinal disorders	162 (69)	45 (19)	5 (2)	74 (64)	21 (18)	3 (3)
General disorders	128 (54)	22 (9)	18 (8)	64 (56)	13 (11)	7 (6)
Metabolism and nutrition disorders	90 (38)	27 (11)	1 (<1)	48 (42)	15 (13)	0
Investigations*	68 (29)	23 (10)	0	21 (18)	7 (6)	0
Resp., thoracic, and mediastinal disorders	60 (25)	11 (5)	1 (<1)	31 (27)	8 (7)	0
Musculoskeletal disorders	56 (24)	4 (2)	0	26 (23)	4 (3)	0
Vascular disorders	51 (22)	19 (8)	0	23 (20)	7 (6)	0
Blood and lymphatic disorders	49 (21)	20 (8)	0	23 (20)	12 (10)	0
Nervous system disorders	48 (20)	6 (3)	0	24 (21)	2 (2)	0
Infections and infestations	40 (17)	7 (3)	3 (1)	18 (16)	8 (7)	2 (2)
Psychiatric disorders	29 (12)	4 (2)	0	16 (14)	2 (2)	0
Renal and urinary disorders	27 (11)	6 (3)	1 (<1)	14 (12)	3 (3)	0
Skin and subcutaneous tissue disorders	25 (11)	1 (<1)	0	8 (7)	0	0
Injury, poisoning, and procedural complications	23 (10)	0	1 (<1)	8 (7)	2 (2)	0
Hepatobiliary disorders	17 (7)	9 (4)	2 (1)	8 (7)	3 (3)	0
Cardiac disorders	8 (3)	0	2 (1)	7 (6)	1 (1)	0
Eye disorders	6 (3)	0	0	4 (3)	0	0
Neoplasms	7 (3)	3 (1)	1 (<1)	4 (3)	2 (2)	2 (2)
Reproductive system and breast disorders	4 (2)	1 (<1)	0	3 (3)	0	0
Ear and labyrinth disorders	4 (2)	0	0	1 (1)	0	0
Endocrine disorders	4 (2)	0	0	0	0	0
Immune system disorders	2 (1)	0	0	1 (1)	0	0
Surgical and medical procedures	2 (1)	0	0	1 (1)	1 (1)	0
Congenital, familial, and genetic disorders	2 (1)	0	0	0	0	0

* Laboratory abnormalities reported as AEs if they led to study treatment discontinuation, dose modification, or fulfilled seriousness criteria.

When grouped by high level term (HLT) level, the most frequently reported events (incidence \geq 20%) were asthenic conditions (placebo arm 41%, ramucirumab arm 36%), gastrointestinal pains (29% in each arm), nausea and vomiting (placebo arm 36%, ramucirumab arm 29%), and appetite disorders (24% in both arms). Most of the common events occurred at the same incidence rate in both arms or had a higher incidence rate among patients who received placebo. Ramucirumab-treated patients had a higher incidence rate of “physical examination procedures and organ system status” (including PTs such as physical examination, weight, temperature, , vascular hypertensive disorders and diarrhea.

Table 33 summarizes the adverse events (regardless of the outcome) by preferred term, Grades 1-5 that occurred with an incidence of 5% or more.

Table 33 - REGARD: AEs with an incidence \geq 10% (by HLT)

HLT	Ramucirumab/BSC (n, %) N=236	Placebo/BSC (n, %) N=115
Asthenic conditions	84 (36)	47 (41)
Gastrointestinal and abdominal pains	69 (29)	33 (29)
Nausea and vomiting symptoms	68 (29)	41 (36)
Appetite disorders	57 (24)	27 (24)
Musculoskeletal and connective tissue pain and discomfort	40 (17)	18 (16)
Physical examination procedures and organ system status	39 (17)	14 (12)
Gastrointestinal atonic and hypomotility disorders	38 (16)	27 (24)
Vascular hypertensive disorders	36 (15)	9 (8)
Anemias	35 (15)	17 (15)
Diarrhea (excl infective)	34 (14)	10 (9)
Gastrointestinal signs and symptoms	28 (12)	12 (11)
Edema	24 (10)	10 (9)
Breathing abnormalities	23 (10)	16 (14)
Coughing and associated symptoms	23 (10)	12 (11)
General signs and symptoms	23 (10)	9 (8)
Peritoneal and retroperitoneal disorders	23 (10)	11 (10)

At the preferred term level, the most frequently reported events (incidence \geq 20%) were fatigue (placebo arm 24%, ramucirumab arm 25%), decreased appetite (placebo arm 23%, ramucirumab arm 24%), vomiting (placebo arm 25%, ramucirumab arm 20%), nausea (placebo arm 26%, ramucirumab arm 19%), abdominal pain (placebo arm 25%, ramucirumab arm 19%), and constipation (placebo arm 23%, ramucirumab arm 15%).

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Table 34 summarizes the adverse events (regardless of the outcome) by preferred term, Grades 1-5 that occurred with an incidence of 5% or more. Table 69, in the appendices section, summarizes the adverse events by PT, Grades 1-5 that occurred with an incidence of 2-4%.

Table 34 - REGARD: AEs with an incidence $\geq 5\%$ (by PT)

PT	Ramucirumab/BSC (n, %) N=236	Placebo/BSC (n, %) N=115
Fatigue	58 (25)	28 (24)
Decreased appetite	57 (24)	26 (23)
Vomiting	47 (20)	29 (25)
Nausea	45 (19)	30 (26)
Abdominal pain	45 (19)	29 (25)
Constipation	36 (15)	26 (23)
Anemia	35 (15)	17 (15)
Hypertension	36 (15)	9 (8)
Diarrhea	34 (14)	10 (9)
Asthenia	28 (12)	19 (17)
Dysphagia	25 (11)	12 (10)
Weight decreased	27 (11)	11 (10)
Abdominal pain upper	27 (11)	5 (4)
Ascites	23 (10)	11 (10)
Dyspnea	22 (9)	15 (13)
Headache	22 (9)	4 (3)
Back pain	18 (8)	11 (10)
Edema peripheral	20 (8)	10 (9)
Cough	19 (8)	9 (8)
Insomnia	13 (6)	8 (7)
Hypokalemia	13 (6)	6 (5)
Hyponatremia	13 (6)	2 (2)
Disease progression	11 (5)	7 (6)
Hypoalbuminemia	12 (5)	6 (5)
Dyspepsia	6 (3)	7 (6)
Dysgeusia	7 (3)	6 (5)
Pain in extremity	8 (3)	6 (5)
Dizziness	4 (2)	6 (5)
Hypotension	5 (2)	6 (5)

Events observed with an increased incidence $\geq 2\%$ in the placebo arm were vomiting (placebo arm 25%, ramucirumab arm 20%), nausea (placebo arm 26%, ramucirumab arm 19%), abdominal pain (placebo arm 25%, ramucirumab arm 19%), constipation (placebo arm 23%, ramucirumab arm 15%), asthenia (placebo arm 17%, ramucirumab arm 12%), dyspnea (placebo arm 13%, ramucirumab arm 9%), back pain (placebo arm 10%, ramucirumab arm 8%), dyspepsia (placebo arm 6%, ramucirumab arm 3%), dysgeusia and pain in extremity (placebo arm 5%, ramucirumab arm 3%), and dizziness and hypotension (placebo arm 5%, ramucirumab arm 2%). Events observed with an increased incidence $\geq 2\%$ in the ramucirumab arm were hypertension (placebo arm 8%, ramucirumab arm 15%), diarrhea (placebo arm 9%, ramucirumab arm 14%), upper abdominal pain (placebo arm 4%, ramucirumab arm 11%), and headache

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(placebo arm 3%, ramucirumab arm 9%). Although there was a discrepancy for upper abdominal pain at the PT level, this discrepancy was not apparent when the analysis was conducted at the HLT level.

7.3.1 Deaths

At the time of data cutoff, 17 patients in the placebo arm (15% of the placebo safety population) and 59 patients in the ramucirumab arm (25% of the ramucirumab safety population) were alive. Most patients (64% in the placebo arm and 63% in the ramucirumab arm) died because of progression of disease. This section will focus on the deaths within 30 days of the last dose of study therapy. Table 35 summarizes the deaths in the safety population (deaths in the ITT population will be analyzed in the efficacy section) as per the time to event dataset (ADTE.xpt).

Table 35 - REGARD: Summary of deaths in the safety population (ADTE dataset)

	Ramucirumab/BSC (n, %) N=236	Placebo/BSC (n, %) N=115
All deaths	177 (75)	98 (85)
Disease progression	148 (63)	74 (64)
Adverse event	25 (11)	15 (13)
Other causes	4 (2)	9 (8)
Deaths within 30 days of last treatment dose	48 (20)	30 (26)
Disease progression	26 (11)	15 (13)
Adverse event	22 (9)	15 (13)

A total of 78 patients died within 30 days of the last treatment dose or while on treatment; however, in the adverse events dataset, there were 54 deaths that occurred secondary to an adverse event with a start date within 30 days of the last dose of study treatment (summary in Table 36), 35 in patients in the ramucirumab arm and 19 deaths in patients in the placebo arm [differences between the datasets (time-to-event dataset and adverse event dataset) were based on whether or not disease progression was an adverse event]. As such, the number of deaths differed slightly from the Applicant's analysis, where 37 subjects in the ramucirumab arm and 15 subjects in the placebo arm died within 30 days of last study drug administration. If the events of disease progression, gastric cancer, and neoplasm were subtracted, there were 26 patients (11% patients in the ramucirumab arm) and 12 patients (10% patients in the placebo arm) who experienced an adverse event with a fatal outcome.

Table 36 - REGARD: Deaths within 30 days of study drug (AE dataset)

PT	Ramucirumab/BSC N=236	Placebo/BSC N=115
Disease progression	8	5
Death	4	0
Multiorgan failure	4	1
Health deterioration	2	0
Pneumonia	2	0
Bacteremia	1	0
Cardiac arrest	1	0

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PT	Ramucirumab/BSC N=236	Placebo/BSC N=115
Cholangitis	1	0
Cholestasis	1	0
Dehydration	1	0
Dyspnea	1	1
Gastric cancer	1	0
Gastric hemorrhage	1	0
Gastrointestinal hemorrhage	1	1
Intestinal obstruction	1	0
Intestinal perforation	1	0
Large intestinal perforation	1	1
Multiple injuries	1	0
Myocardial infarction	1	0
Acute renal failure	1	0
Gastrointestinal obstruction	0	1
Lobar pneumonia	0	1
Neoplasm	0	2
Pulmonary embolism	0	2
Respiratory failure	0	2
Septic shock	0	1
Sudden death	0	1

The sponsor stated in their report that only 4 events of pneumonia, gastric hemorrhage, intestinal perforation, and myocardial infarction were related to ramucirumab and one event each of colon perforation and pulmonary embolism were attributed to placebo.

A review of the safety dataset and narratives was conducted to analyze deaths within 30 days of last study drug treatment that were not attributed to disease progression (as progression of disease, per protocol, should have not been captured as an adverse event) and all the death events with the exception of those that the investigators attributed to non-treatment related causes.

There were four deaths (all in the ramucirumab arm) with a PT of “death”. From the narratives, it appears that at least in two patients (#202-0001 #540-0002) the cause of death was disease progression (increasing ascites, sub ileus, etc.). In one subject (#540-0002), the event of death was preceded by acute general health deterioration within 48 hours of the event, and no cause of death was listed in the death certificate. Subject #702-0002, with a history of anemia and hyponatremia, experienced Grade 4 anemia, hyponatremia, and hyperkalemia, accompanied by dyspnea and hypotension 6 days after the last dose of ramucirumab and expired; the investigator attributed the death to disease progression. There was one event of sudden death in the placebo arm (subject #234-0012) in a 72 year old male patient who was found after a syncope; ECG showed an inferior acute infarct, and the patient died of cardio respiratory arrest 10 days after receiving the last placebo dose.

There were two events of general health deterioration with a fatal outcome in the ramucirumab arm. Subject #602-0005 experienced health deterioration after the 3rd dose of ramucirumab and died 27 days after this last dose. The cause of death was attributed as progressive disease. There

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was no CRF or narrative for subject #635-0005, but 12 days before the event of general health deterioration he experienced a pulmonary embolism.

There were 4 events of multiorgan failure in the ramucirumab arm. In three subjects (#111-0001 331-0002, and 401-0003) multiorgan failure appeared to have occurred after disease progression and with all other adverse events resolved. In one subject (#634-0002), multiorgan failure was likely complicated by an ongoing respiratory infection; although not conclusive, the autopsy report of his death 12 days after the second dose of ramucirumab reported progressive disease complicated with bronchoaspiration. One subject (#507-0005) experienced a Grade 4 gastric hemorrhage 9 days after one dose of placebo, and died 3 days later of multiorgan failure. A fibroscopy before his death showed massive tumor necrosis.

There was one event of fatal bacteremia in the ramucirumab arm (subject ID#412-0005). The actual cause of death was septic shock, and the blood cultures were positive for gram positive cocci, probably from a central line that was removed; this subject also experienced concomitant Grade 4 pleural effusion and had a history of pulmonary embolism during treatment. An event of Grade 5 septic shock in the placebo arm occurred in a subject (#122-0005) with progressive disease, esophageal obstruction, and esophageal candidiasis.

There was one fatal event of cardiac arrest in the ramucirumab arm (subject ID#526-0007). According to the autopsy report, this subject died as a complication of pneumonia and sepsis that developed 6 days after the second dose of ramucirumab. Subject #122-0006 died 24 days after the second dose of ramucirumab due to pneumonia that developed in the context of an urinary tract infection, Grade 2 renal failure, and ascites that required paracentesis.

There were two fatal events of biliary obstruction in the ramucirumab arm. Subject #663-0001, experienced cholangitis secondary to tumor obstruction of a biliary stent. Subject #544-0001 experienced intrahepatic mechanical biliary obstruction with multifocal liver metastases.

There was one fatal event of dehydration 12 days after a single ramucirumab dose. Subject (#139-0004) died after experiencing acute renal failure and acute lung edema secondary to dehydration. Subject #715/202-0004, also in the ramucirumab arm, died due to acute renal failure that developed after gastrointestinal hemorrhage and inappropriate secretion of antidiuretic hormone syndrome.

There was one fatal event of dyspnea per arm. Subject #601-0004 had a history of COPD and experienced dyspnea after one dose of ramucirumab because of lung compression of progressive gastric tumor and lung metastases. Subject #623-0001 in the placebo arm died of worsening carcinomatous lung lymphangitis. In addition, there were two fatal events of respiratory failure in the placebo arm. Both subjects (#217-0002 and 221-0002) had disease progression and died of respiratory failure.

There were two fatal events of gastrointestinal hemorrhage, one per arm. Subject #700-0006 in the ramucirumab arm first experienced hematemesis and melena after cycle 4, which worsened

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after cycle 4 of therapy and resulted in death; imaging revealed stable disease. Subject #513-0002 experienced fatal hematemesis after 12 days of receiving placebo.

There was no CRFs or narratives provided for subject #660-0001 in the ramucirumab arm, who died of intestinal obstruction. Subject #121-0002 experienced gastrointestinal obstruction 6 days after the fourth dose of placebo and died due to multiorgan failure attributed to disease progression.

There were two events of intestinal perforation, one per arm. Subject #664-0001 experienced colon perforation 12 days after the second dose of ramucirumab, with new peritoneal carcinomatous lesions present in CT scans. Subject #852-0007 in the placebo arm died secondary to septic shock and renal failure; fever developed after 48 hours of starting treatment and the subject had a history of colon perforation.

Subject #123-0002 in the ramucirumab arm died due to injuries sustained in a motor vehicle accident.

There were two events of fatal pulmonary embolism, both in the placebo arm. Subject #715/535-0001 died of pulmonary embolism and progression of disease 26 days after the first dose of placebo. Subject #702-0001 died suddenly after experiencing acute abnormal breathing 2 days after the first infusion of placebo and the death certificate states pulmonary embolism as the death cause; no autopsy was conducted.

It was difficult, in some cases, to establish if disease progression was the sole underlying cause of death. For example, for some events, such as intestinal obstruction, perforations, gastric hemorrhage, etc., can be both related to either disease or therapy, or both have been contributing factors.

Reviewer's comment: In summary, the leading cause of death for in both arms was disease progression. Treatment related deaths were more frequent in the ramucirumab, and although only four events were attributed by the investigators as treatment-related, it is not possible to rule out the contribution of the treatment to other events such as hemorrhages, perforations, etc.

7.3.2 Nonfatal Serious Adverse Events

The protocol's definition for a Serious Adverse Event (SAE) was any untoward medical occurrence that, at any dose resulted in death or, was life-threatening; or required inpatient hospitalization or prolongation of existing hospitalization or; resulted in persistent or significant disability/incapacity or; caused a congenital anomaly/birth defect, or; was a medically important event. For the purposes of the analysis of this section, fatal SAEs were excluded and analyzed in Section 7.3.1. The results of this reviewer's analysis differed slightly from the applicant's results due to the exclusion of the events with fatal outcomes.

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A total of 134 patients experienced 248 non-fatal SAE, 44 patients (38%) in the placebo arm and 90 (38%) patients in the ramucirumab arm. Of the 87 (non-fatal) SAEs in the placebo arm, 9 (10%) were Grade 1, 19 (22%) were Grade 2, 47 (54%) were Grade 3, and 12 (14%) were Grade 4. Of the 161 SAEs in the ramucirumab arm, 19 (12%) were Grade 1, 26 (16%) were Grade 2, 90 (56%) were Grade 3, and 26 (16%) were Grade 4.

More events in the ramucirumab arm resulted in drug delays/dose modifications (6%) than in the placebo arm (4%), and treatment was more frequently withdrawn because of these events in the ramucirumab arm (5%) than in the placebo arm (3%). More events resulted in hospitalization or prolongation of hospitalization in the placebo arm (29% vs. 20% in the placebo and ramucirumab arms, respectively); the addition of new concomitant medications or medical procedures (4% vs. 3% in the placebo and ramucirumab arms respectively); and both hospitalization or prolongation of hospitalization and addition of new concomitant medications or medical procedures (35% vs. 33% in the placebo and ramucirumab arms respectively).

As summarized in Table 37, toxicities by SOC were similar in both arms. The most frequently reported events were in the gastrointestinal system, metabolism and nutrition, and general disorders and administration conditions SOCs.

Table 37 - REGARD: Non-fatal SAEs by SOC

SOC	Ramucirumab; n (%) N=236		Placebo; n (%) N=115	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Gastrointestinal disorders	9 (4)	38 (16)	7 (6)	19 (17)
Metabolism and nutrition	3 (1)	15 (6)	1 (1)	8 (7)
General disorders	1 (<1)	13 (6)	2 (2)	7 (6)
Blood and lymphatic system	0	12 (5)	1 (1)	5 (4)
Infections	2 (1)	8 (3)	1 (1)	6 (5)
Hepatobiliary disorders	0	5 (2)	2 (2)	1 (1)
Investigations	1 (<1)	5 (2)	0	0
Nervous system disorders	2 (1)	3 (1)	0	0
Renal and urinary disorders	2 (1)	3 (1)	1 (1)	2 (2)
Neoplasms	0	3 (1)	0	2 (2)
Respiratory, thoracic and mediastinal disorders	1 (<1)	3 (1)	1 (1)	1 (1)
Vascular disorders	1 (<1)	2 (1)	2 (2)	2 (2)
Injury and procedural complications	15 (6)	0	5 (4)	2 (2)
Cardiac disorders	0	0	0	1 (1)
Endocrine disorders	1 (<1)	0	0	0
Musculoskeletal and connective tissue disorders	1 (<1)	0	0	0
Psychiatric disorders	0	1 (<1)	0	1 (1)
Reproductive system	1 (<1)	0	0	0
Surgical and medical procedures	1 (<1)	0	0	1 (1)

The incidence of SAEs by PTs was also similar between arms as shown in Table 38.

Table 38 - REGARD: Non-fatal SAEs by PT (incidence ≥ 2%)

PT	Ramucirumab; n (%)		Placebo; n (%)	
	N=236		N=115	
	All grades	Grades 3-4	All grades	Grades 3-4
Abdominal pain	10 (4)	9 (4)	3 (3)	2 (2)
Anemia	9 (4)	9 (4)	2 (2)	2 (2)
Ascites	6 (3)	5 (2)	3 (3)	3 (3)
Dysphagia	5 (2)	4 (2)	3 (3)	3 (3)
Vomiting	6 (3)	4 (2)	5 (4)	4 (3)
Dehydration	3 (1)	2 (1)	3 (3)	3 (3)
Hypoglycemia	2 (1)	2 (1)	2 (2)	2 (2)
Pneumonia	2 (1)	2 (1)	2 (2)	2 (2)
Sepsis	3 (1)	3 (1)	2 (2)	2 (2)
Decreased appetite	3 (1)	3 (1)	1 (1)	1 (1)
Fatigue	2 (1)	2 (1)	1 (1)	1 (1)
ALP increased	3 (1)	2 (1)	0	0
Acute cholecystitis	2 (1)	2 (1)	0	0
General physical health deterioration	2 (1)	2 (1)	0	0
Hematemesis	2 (1)	2 (1)	0	0
Hyperkalemia	2 (1)	2 (1)	0	0
Hyponatremia	3 (1)	3 (1)	0	0
Intestinal obstruction	4 (2)	3 (1)	0	0
Multiorgan failure	2 (1)	2 (1)	0	0
Nausea	3 (1)	2 (1)	0	0
Pain	2 (1)	2 (1)	0	0
Asthenia	0	0	4 (3)	4 (3)
Deep vein thrombosis	0	0	3 (3)	2 (2)
Acute renal failure	1 (<1)	0	2 (2)	2 (2)
Thrombocytopenia	1 (<1)	1 (1)	2 (2)	2 (2)
Constipation	0	0	2 (2)	1 (1)
Diarrhea	0	0	2 (2)	1 (1)
Fall	0	0	2 (2)	1 (1)
Pancytopenia	0	0	2 (2)	1 (1)

Although there is a protocol and regulatory definition of serious adverse event, there is certain subjectivity in the attribution of seriousness of an event, particularly in oncology trials. For example, of the 23 events of Grade 3 anemia, 7 were considered SAEs. To avoid bias in the review of adverse events, this reviewer (and the applicant) conducted additional analyses of specific adverse events known to occur following VEGF inhibition (see Sections 7.3.4 and 7.3.5 of this review).

7.3.3 Dropouts and/or Discontinuations

A total of 40 patients experienced adverse events that resulted in withdrawal from study treatment (including patients with an outcome of treatment discontinuation), 32 patients (14%) in

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the ramucirumab arm and 8 patients (7%) in the placebo arm. There was a disparity in the incidence of events that resulted in death as the cause of treatment withdrawal: 12 (5%) patients had fatal events in the ramucirumab arm and 3 (3%) patients died in the placebo arm. As analyzed in Section 7.3.1, treatment related deaths were more frequent in the ramucirumab arm, and although only four events were attributed by the investigators as treatment-related, it was not possible to rule out the contribution of the treatment to other events such as hemorrhages, perforations, etc.

Patients in the ramucirumab arm were discontinued from treatment after the occurrence of the following fatal AEs: bacteremia, cholestasis, death, disease progression (in 4 patients, disease progression should have not been reported as an AE), dyspnea, gastric cancer (should have not been reported as an AE) intestinal perforation (2), and multiorgan failure. In the placebo arm, one patient each was withdrawn from treatment after the occurrence of a fatal event of disease progression, pulmonary embolism, and respiratory failure. Because the reason for treatment discontinuation in 5 patients in the ramucirumab arm and 1 patient in the placebo arm was clearly disease-related and not due to toxicity, the incidence of fatal AEs leading to discontinuation in the ramucirumab arm was 3% (7 patients) and 2% (2 patients) in the placebo arm.

Grade 1-2 events leading to discontinuation in the ramucirumab arm were dyspepsia, hypoglycemia, inappropriate secretion of antidiuretic hormone, proteinuria, and acute renal failure. Grade 3-4 events leading to discontinuation in the ramucirumab arm were biliary sepsis, creatinine increase, cerebrovascular accident, decreased appetite, dehydration, disseminated intravascular coagulation, ECOG PS deterioration, fatigue (2), general physical health deterioration hematemesis, proteinuria, small intestinal obstruction, upper gastrointestinal hemorrhage, and weight decrease.

There was one event of Grade 2 fatigue leading to treatment withdrawal in the placebo arm. Grade 3-4 events leading to discontinuation in the placebo arm were disease progression (which should have not been included as an AE), dysphagia, gastric hemorrhage, and upper gastrointestinal hemorrhage.

7.3.4 Significant Adverse Events – Non-fatal Grade 3-4 AEs

A total of 183 patients experienced 433 non-fatal Grade 3-4 AEs, 63 patients (55%) in the placebo arm and 120 (51%) patients in the ramucirumab arm. For the purposes of this review, Grade 3 and 4 adverse events will be considered as “severe.” Of the 138 non-fatal Grade 3-4 AEs in the placebo arm, 119 (86%) were Grade 3 and 19 (14%) were Grade 4. Of the 295 non-fatal Grade 3-4 AEs in the ramucirumab arm, 263 (89%) were Grade 3 and 32 events (11%) were Grade 4.

Table 39 summarizes the non-fatal Grade 3-4 AEs by SOC. The incidence of AEs between arms was similar. A difference of at least 2% incidence with more proportional events occurring in the placebo arm was observed in the metabolism and nutrition SOC (11% and 13% in the

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ramucirumab and placebo arms, respectively), general disorders and administration conditions (10% and 12% in the ramucirumab and placebo arms, respectively), blood and lymphatic system disorders (8% and 10% in the ramucirumab and placebo arms, respectively), respiratory disorders (5% and 8% in the ramucirumab and placebo arms, respectively), infections (3% and 7% in the ramucirumab and placebo arms, respectively), and injury and procedural complications (none observed in the ramucirumab arm and 2% in the placebo arm). A difference of at least 2% incidence with more proportional events occurring in the ramucirumab arm was observed in the investigations SOC (10% vs. 6% in the ramucirumab and placebo arms, respectively) and vascular disorders SOC (8% vs. 6% in the ramucirumab and placebo arms, respectively).

Table 39 - REGARD: Non-fatal grade 3-4 AEs (by SOC)

SOC	Ramucirumab; n (%) N=236	Placebo; n (%) N=115
Gastrointestinal disorders	46 (19)	22 (19)
Metabolism and nutrition	27 (11)	15 (13)
General disorders and administration site conditions	24 (10)	14 (12)
Investigations	23 (10)	7 (6)
Blood and lymphatic system disorders	20 (8)	12 (10)
Vascular disorders	19 (8)	7 (6)
Respiratory, thoracic, and mediastinal disorders	11 (5)	9 (8)
Hepatobiliary disorders	9 (4)	3 (3)
Infections	7 (3)	8 (7)
Renal and urinary disorders	6 (3)	3 (3)
Nervous system disorders	6 (3)	2 (2)
Musculoskeletal and connective tissue disorders	4 (2)	4 (3)
Psychiatric disorders	4 (2)	2 (2)
Neoplasms	3 (1)	2 (2)
Injury and procedural complications	0	2 (2)
Cardiac disorders	0	1 (1)
Surgical and medical procedures	0	1 (1)
Reproductive system	1 (<1)	0
Skin and subcutaneous tissue disorders	1 (<1)	0

This section will review adverse events that occurred in each SOC (including the PT and HLT terms). Table 40 summarizes the PT with incidence rates $\geq 2\%$. Table 70 in the appendices section summarizes the HLT with incidences $\geq 1\%$.

Table 40 - REGARD: Non-fatal Grade 3-4 AEs by PT (incidence $\geq 2\%$)

PT	Ramucirumab; n (%) N=236	Placebo; n (%) N=115
Hypertension	17 (7)	3 (3)
Anemia	15 (6)	9 (8)
Abdominal pain	12 (5)	3 (3)
Ascites	10 (4)	5 (4)
Fatigue	10 (4)	4 (3)

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Vomiting	6 (3)	5 (4)
Decreased appetite	8 (3)	4 (3)
Hyponatremia	8 (3)	1 (1)
Asthenia	5 (2)	8 (7)
Dysphagia	5 (2)	5 (4)
Dehydration	4 (2)	4 (3)
ALP increased	4 (2)	1 (1)
Hypokalemia	5 (2)	1 (1)
Pain	4 (2)	0
Dyspnea	3 (1)	7 (6)
Back pain	3 (1)	3 (3)
ALT increased	3 (1)	2 (2)
Diarrhea	2 (1)	2 (2)
Hyperkalemia	3 (1)	2 (2)
Hypoglycemia	2 (1)	2 (2)
Pneumonia	2 (1)	2 (2)
Sepsis	3 (1)	2 (2)
Constipation	1 (<1)	3 (3)
Hyperbilirubinemia	1 (<1)	3 (3)
Thrombocytopenia	1 (<1)	3 (3)
Urinary infection	0	3 (3)
Deep vein thrombosis	0	2 (2)
Mental status changes	0	2 (2)
Peripheral edema	1 (<1)	2 (2)
Acute renal failure	1 (<1)	2 (2)

Severe events occurring with $\geq 2\%$ difference in the ramucirumab arm included pain (2% vs. none in the ramucirumab and placebo arms, respectively), hyponatremia (3% vs. 1% in the ramucirumab and placebo arms respectively), abdominal pain (5% vs. 3% in the ramucirumab and placebo arms respectively), and hypertension (7% vs. 3% in the ramucirumab and placebo arms respectively). Events occurring with $\geq 2\%$ difference in the placebo arm were asthenia (2% vs. 7% in the ramucirumab and placebo arms, respectively), dysphagia (2% vs. 4% in the ramucirumab and placebo arms, respectively), and anemia (6% vs. 8% in the ramucirumab and placebo arms, respectively).

The following paragraphs in this section of the review describe the incidence rates of severe (Grade 3 and 4) adverse events.

Severe adverse events in gastrointestinal SOC

The most frequently reported affected system was the gastrointestinal system, with 19% incidence of Grade 3 or 4 AEs in both arms. However, the distribution of the severe adverse events was slightly different between arms: abdominal pain and upper abdominal pain (HLT gastrointestinal and abdominal pains) were reported in 6% patients in the ramucirumab arm and 3% patients in the placebo arm. Gastrointestinal obstructions and stenosis (HLT) were also more frequently observed in the ramucirumab arm (3% vs. 0%); however, there were 2 events of obstructions and stenosis in the placebo arm (PT terms gastric obstruction and colonic

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obstruction), not included in this HLT. Constipation was more frequent in the placebo arm (1 event in the ramucirumab and 3 events in the placebo arm).

Severe gastrointestinal hemorrhage occurred with the same frequency in each arm (2%). Nausea/vomiting (HLT) occurred in 3% and 4% patients in the ramucirumab and placebo arms, respectively. Dysphagia occurred in 4% and 5% in the ramucirumab and placebo arms respectively; half of these patients had GEJ tumors. Ascites was observed in 4% and 5% in the ramucirumab and placebo arms respectively. There were two events of fistula (enterocutaneous fistula in the ramucirumab arm and esophageal fistula in the placebo arm). There were 2 events of diarrhea per arm and 2 events of ileus in the ramucirumab arm. Additional GI events were abdominal distention (1 event per arm) and dyspepsia (one event, ramucirumab arm).

Severe adverse events in metabolism and nutrition disorders SOC

With the exception of appetite disorders (3% incidence of decreased appetite per arm), all the other AEs in this SOC were laboratory abnormalities. Hyponatremia was the most frequent electrolyte abnormality (3% vs. 1% in the ramucirumab and placebo arms, respectively), followed by dehydration (2% vs. 3% in the ramucirumab and placebo arms, respectively). All other electrolyte and laboratory abnormalities reported (hypokalemia, hypoglycemia, hypophosphatemia, hypoalbuminemia, hypocalcemia, hypoproteinemia, and mineral deficiency) had incidence rates less than 2%.

Severe adverse events in general disorders and administration site conditions SOC

Asthenic conditions (HLT) were more frequent in the placebo arm (6% vs. 10% in the ramucirumab and placebo arms, respectively). With the exception of pain (2% in the ramucirumab arm, no events in the placebo arm) and peripheral edema (no events in the ramucirumab arm and 2% incidence in the placebo arm), all other events in this SOC (general physical health deterioration, multiorgan failure, chest pain, extravasation, generalized edema, malaise, and pyrexia) occurred with an incidence rate of 1% or less.

There was one event of a patient who experienced systemic inflammatory response, disseminated intravascular coagulopathy, hypovolemic shock, and anemia 6 days after receiving his first and last dose of ramucirumab. Although coded as Grade 3, the narrative clearly defines a Grade 4 event, with the subject requiring resuscitation. The most likely cause of the anemia and hypovolemic shock was gastrointestinal bleeding, as there are records of melena while the patient was in the ICU. The patient recovered from these events and died of multiorgan failure and disease progression 23 days later.

Severe adverse events in investigations SOC

The events in this SOC were laboratory abnormalities that were reported as AEs because they were considered by investigators as clinically relevant. Section 7.4.2, Laboratory Findings, better describes the lab abnormalities observed in the study. All the events were Grade 3.

The following were events (one each) reported in the ramucirumab arm only: bronchial aspiration, increased conjugated bilirubin, hypocalcemia, increased serum creatinine,

hyperglycemia, hypertension (blood pressure increased) ECOG PS decreased, hematocrit decreased, hepatic enzymes increased, neutropenia, RBC decreased. There was one event occurring only in the placebo arm, gamma glutamyl transferase increased. There was one event each in each arm of ALT increase, AST increase, alkaline phosphatase increase, bilirubin increase, and hemoglobin decrease and weight decrease.

Severe adverse events in Blood and lymphatic system disorders SOC

Section 7.4.2, Laboratory Findings, better describes the lab abnormalities observed in the study. Severe anemia was more frequently observed in the placebo arm (6% and 8% in the ramucirumab and placebo arms, respectively). Thrombocytopenia was also more frequently observed in the placebo arm (<1% and 3% in the ramucirumab and placebo arms, respectively). All other AEs (neutropenia, DIC, febrile neutropenia, and pancytopenia) were observed with incidence rates $\leq 1\%$.

Severe adverse events in Vascular disorders SOC

Further analyses of hypertension are summarized in Section 7.3.5, Submission Specific Primary Safety Concerns. In additional, background regarding class effect and safety concerns with other drugs targeting the same pathway can be found in Section 2.4.

All vascular events were graded as Grade 3, although as reviewed above, narrative of patient one patient described an event of hypovolemic shock that was life-threatening and required resuscitation.

There were three events of thrombosis in the placebo arm and none in the ramucirumab arm. With the exception of hypertension (7% in the ramucirumab arm and 3% in the placebo arm), all other events occurred only once per arm (hypotension, hypovolemic shock, and pallor).

Severe adverse events in Respiratory, thoracic and mediastinal disorders SOC

With the exception of dyspnea (1% vs. 6% in the ramucirumab and placebo arms, respectively), all other events (hiccups, hypoxia, pleural effusion, pulmonary embolism, and pulmonary edema) had incidence rates of $\leq 1\%$.

Severe adverse events in infections SOC

Urinary tract infections was the most common event (none in the ramucirumab arm, 3% in the placebo arm), followed by sepsis (2% per arm, PTs sepsis and biliary sepsis). Other events were (incidence $\leq 2\%$) liver abscess, lung infection, peritonitis, pneumonia, respiratory lung and infection. By HLT, there was a 2% difference in the incidence of lower respiratory infections (1% vs. 3% in the ramucirumab and placebo arms, respectively).

Severe adverse events in All other SOCs (incidence $\leq 3\%$)

In the renal and urinary SOC (3% incidence AEs in both arms), renal failure was observed in two subjects per arm. Additional events were (1 subject each) hematuria, nephrolithiasis, proteinuria, ureteric obstruction, ureteric perforation, and urinary retention in the ramucirumab arm. There was one subject with nocturia in the placebo arm.

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Central nervous system AEs observed in the ramucirumab arm were lethargy (2 subjects), cerebrovascular accident, coma, depressed level of consciousness, dizziness and hyperammonemic encephalopathy (one subject each). AEs observed in the placebo arm were peripheral sensory neuropathy and somnolence (one subject each).

The events observed in the musculoskeletal SOC were different PTs for back pain. In the HLT analysis, musculoskeletal and connective tissue pain and discomfort incidence was 1% in the ramucirumab arm and 3% in the placebo arm.

Psychiatric disorders observed in the ramucirumab arm were (one each) confusional state, insomnia, stupor, and anxiety. There were two subjects who experienced mental status changes in the placebo arm.

All events in the neoplasm SOC were related to progression of disease.

In all other SOCs, incidence rates of specific events were $\leq 1\%$ and did not appear to be drug-treatment related.

7.3.5 Submission Specific Primary Safety Concerns

As described in Section 2.4, Important Safety Issues With Consideration to Related Drugs, hypertension, gastrointestinal toxicity, proteinuria, thromboembolic events, hemorrhage, reversible posterior leukoencephalopathy (RPLS) and wound healing are consistently observed across clinical trials and in the post marketing setting following the administration of both biologic and small molecule anti-VEGF and anti-VEGFR agents (approved and investigational). The spectrum of adverse events in individual patients and different disease settings is variable and may reflect several factors: dose of the VEGF inhibitor, specificity of the inhibition of the pathway, disease factors, co-morbidities, co-targeting of other pathways, and use of concomitant chemotherapy.

The black box warning in the bevacizumab and ziv-aflibercept labels describe gastrointestinal perforation, surgery and wound healing complications, and hemorrhage. In addition to these adverse reactions, the Warnings and Precautions section of the bevacizumab label describes non-gastrointestinal fistula formation, arterial thromboembolic events, hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), and infusion reactions. The Warnings and Precautions section of the ziv-aflibercept label describes fistula formation, arterial thromboembolic events, hypertension, proteinuria, neutropenia and neutropenic complications, diarrhea and dehydration, and RPLS. Some of these additional toxicities in the Zaltrap label such as diarrhea, dehydration, etc, are classical chemotherapy-related toxicities where the incidence rate was increased following the administration of ziv-aflibercept.

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The Applicant considered the following AEs to be adverse events of special interest for ramucirumab: infusion-related reactions (IRR), hypertension, proteinuria, arterial and venous thromboembolic events, bleeding/hemorrhagic events, gastrointestinal perforation, congestive heart failure, wound healing complications, fistula, liver failure/ liver injury, and RPLS. Two of these AEs were not considered VEGF/R-related AEs: IRR and liver failure/liver injury. IRRs are considered of interest because of the observation of IRR in other monoclonal antibodies and based on the clinical experience with ramucirumab.

The applicant used a search strategy to group PTs in a manner similar to the SMQ strategy used in the MedDRA dictionary; for some AE groupings, like arterial thromboembolic events, there was no defined SMQ. For other AE groupings, like hypertension, Lilly modified the SMQ to exclude terms that were not relevant to this application (such as eclampsia, HELLP syndrome) and/or add terms that were not included in the original SMQ definition. This reviewer also searched the database to expand the Applicant's grouping and include some relevant terms such as essential hypertension, etc. Table 41 lists the PTs included in the MedDRA "hypertension" SMQ and the Applicant's grouping. Table 72 displays the MedDRA narrow SMQ analysis (using the MAED instrument) of the REGARD database.

Table 41 - Hypertension MEdDRA SMQ vs. AESI grouping

MedDRA SMQ PTs	Applicant's AEs of special interest PTs
Accelerated hypertension	
Blood pressure ambulatory increased	
Blood pressure diastolic increased	
Blood pressure inadequately controlled	
Blood pressure increased	
Blood pressure management	
Blood pressure orthostatic increased	
Blood pressure systolic increased	
Diastolic hypertension	
Eclampsia	
Endocrine hypertension	
Essential hypertension	
Gestational hypertension	
HELLP syndrome	
Hyperaldosteronism	
Hypertension	Hypertension
Hypertension neonatal	
Hypertensive angiopathy	
Hypertensive cardiomegaly	
Hypertensive cardiomyopathy	
Hypertensive crisis	Hypertensive crisis
Hypertensive emergency	
Hypertensive encephalopathy	
Hypertensive heart disease	
Hypertensive nephropathy	
Labile hypertension	
Malignant hypertension	

MedDRA SMQ PTs	Applicant's AEs of special interest PTs
Malignant hypertensive heart disease	
Malignant renal hypertension	
Maternal hypertension affecting fetus	
Mean arterial pressure increased	
Metabolic syndrome	
Neurigenic hypertension	
Orthostatic hypertension	Orthostatic hypertension
Pre-eclampsia	
Pre hypertension	Pre hypertension
Primary hyperaldosteronism	
Procedural hypertension	
Renal hypertension	
Renovascular hypertension	
Retinopathy hypertensive	
Secondary hyperaldosteronism	
Secondary hypertension	
Systolic hypertension	
Withdrawal hypertension	
PTs with relevant investigations abnormal: aldosterone, catecholamines, blood pressure measurements, etc.	Blood pressure diastolic increased Blood pressure increased
Diuretic therapy	
Ectopic aldosterone secretion	
Ectopic rennin secretion	
Tyramin reaction	

Hypertension

The REGARD study used the NCI CTCAE version 4.0 dictionary for grading toxicities. The following are the dictionary definitions:

- Grade 1: pre-hypertension (systolic BP 120-139 mm Hg or diastolic BP 80-89 mm Hg).
- Grade 2: Stage 1 hypertension (systolic BP 140-159 mm Hg or diastolic BP 90-99 mm Hg); medical intervention indicated; recurrent or persistent (≥ 24 hrs) or symptomatic increase by > 20 mmHg (diastolic) or to $> 140/90$ if previously within normal limits; monotherapy may be indicated.
- Grade 3: Stage 2 hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated.
- Grade 4: life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
- Grade 5: death.

Hypertension was more common in subjects receiving ramucirumab than in subjects receiving placebo. There were 9 subjects (8%) who experienced hypertension in the placebo arm (3% Grade 3) and 39 subjects (17%) in the ramucirumab arm who experienced hypertension or increased blood pressure. Grade 3 hypertension was observed in 18 subjects (8%) in the

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ramucirumab arm. There were no Grade 4-5 events of hypertension or reversible posterior leukoencephalopathy in this study.

There were no treatment discontinuations related to hypertension, and there were four dose delays related to hypertension management in the ramucirumab arm.

Although only 48 subjects (14%) in the safety population experienced hypertension, 43% of subjects in the ramucirumab arm and 40% subjects in the placebo arm received antihypertensive therapy, including diuretics, peripheral vasodilators, beta-blocking agents, calcium channel antagonists, and renin-angiotensin agents. No definite conclusions can be drawn from the concomitant medication use as these agents have multiple, non-hypertension related indications. The incidence of hypertension in the REGARD study is consistent with the known class effect and epidemiology of the studied population (see Section 2.4).

Infusion-related reactions (IRR)

Premedication was not mandated in the REGARD study and the recommendations regarding premedication for IRR changed in several protocol amendments. Premedication use was balanced between arms and administered at least at 1 time point for 183 patients (78%) in the ramucirumab arm and 92 patients (80%) in the placebo arm. The majority of patients who received premedication received H1 antagonists, either alone or in combination with one or more additional agents.

For the purposes of this analysis, the Applicant searched the database for the following preferred terms: allergic reaction, anaphylactic reaction, anaphylaxis, drug hypersensitivity, hypersensitivity, and IRR. This analysis did not consider other adverse events that may have been related to an IRR occurring during the first 24 hours after infusions such as hypertension/hypotension, chest pain, dyspnea, etc, and as such, was restricted in scope to events that were clearly identified by the investigators as infusion reactions.

There was one event of a Grade 1 allergic reaction in one subject 11 days after his 8th ramucirumab dose, which did not reoccur upon rechallenge. Two patients in the placebo arm experienced Grade 1 IRR, and in one of them was secondary to diphenhydramine administered as premedication on study Day 1 (verbatim term: “reaction to premedication [diphenhydramine]”).

Proteinuria

Although the incidence of proteinuria was similar between arms (2.6% in the placebo arm and 2.9% in the ramucirumab arm), the only Grade 3 event occurred in the ramucirumab arm. In addition, there were two treatment discontinuations (ID #4300007 and 4570001) because of Grade 2 and 3 proteinuria as a consequence of proteinuria in the ramucirumab arm.

Unless otherwise indicated, proteinuria was assessed every 6 weeks (3 cycles). A comprehensive analysis of proteinuria was complicated based on issues in the laboratory assessments dataset (excluding pretreatment assessments). For example, data for two patients

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(ID#5320009 in the placebo arm and #4300007 in the ramucirumab) contained numerical data without units or type of assessment (24-hour collection, single sample, etc). In 18 (8%) patients in the ramucirumab arm and 4 (3%) patients in the placebo arm, the urine analysis for proteinuria was considered “positive” or “+++” (presumably dipstick) in the dataset.

As summarized in Section 2.4 and Table 2, the incidence of proteinuria in bevacizumab studies ranged from 15-35%, and Grade 3-4 proteinuria from 0.7-15% with almost all studies below 2%. The incidence of proteinuria with ziv-aflibercept in subjects with metastatic colorectal cancer was 41% in the placebo/FOLFIRI arm and 62% in the ziv-aflibercept/FOLFIRI arm, and Grade 3-4 events were reported in 1% subjects in the placebo arm and 8% subjects in the aflibercept arm, including 2 patients with nephrotic syndrome.

The incidence of proteinuria in the REGARD study appeared to be lower than with other VEGF/R biologic products; however, the lab datasets results were consistent with the incidence and difference between arms with other VEGFR monoclonal antibodies. Additionally, the addition of chemotherapy may increase the risk of proteinuria (this would be the first approval of a monoclonal antibody targeting the VEGF pathway in cancer that would administered as a single agent).

Arterial thrombotic events

No arterial thromboembolic events were observed in the placebo arm. The following events occurred in the ramucirumab arm (some of which occurred in the same patient, see below): Grade 2 angina pectoris, cerebral ischemia, and myocardial ischemia, Grade 4 cerebrovascular accident, and the fatal events of myocardial infarction and cardiac arrest. Subject 5900001 experienced both events of Grade 2 angina pectoris and Grade 5 myocardial infarction. Subject 5520001 experienced a Grade 4 cerebrovascular accident, discontinued treatment and died approximately 100 days after the event of unknown causes. Both subjects had diagnosis of hypertension before study entry (controlled). The event of fatal cardiac arrest (subject 5260007) occurred in the context of pneumonia and septic shock. One subject experienced Grade 2 cerebral ischemia and myocardial ischemia on day 254 of Study entry.

Although a firm conclusion regarding arterial thrombotic events cannot be made based on the low incidence of events in the REGARD trial (and confounding factors), anti-VEGF therapies have been associated with ATEs.

Venous thromboembolic events (VTE)

The association between cancer and venous thromboembolism, including deep vein thrombosis and pulmonary embolism is well established. Neoplasms are associated with activation of the coagulation system, and this prothrombotic state may be further exacerbated by chemotherapy, hormone therapy, and surgery. Population-based case-control studies (Khorana 2013) indicate a 2-year cumulative incidence of 0.6% to 7.8%, depending on the population studied.

Eight subjects (7%) in the placebo arm and 9 subjects (4%) in the ramucirumab arm experienced venous thromboembolic events. There were 3 events each of deep venous thrombosis per arm, 2

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events of embolism (subjects 2440001 and 6370002, site unspecified, CFRs for these two subjects not provided) in the ramucirumab arm, two events of thrombosis (one per arm), and one event of venous limb thrombosis in the placebo arm.

The NCI CTCAE version 4.0 dictionary changed the grading for thromboembolic events: Grade 3 is defined as “thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated”, and Grade 4 is defined as “life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated”. There were 3 events (2 fatal) of pulmonary embolism in the placebo arm and 3 events of pulmonary embolism in the placebo arm. All non-fatal pulmonary embolism events were Grade 3, and in one subject in the placebo arm (4250004) it was preceded by a peripheral (axillary) thrombosis.

In conclusion, it appears that although VEGF/R inhibition is a known risk for VTE, the addition of ramucirumab to the treatment of gastric cancer in second line did not increase the risk of VTE when compared to placebo. Consideration should be given to the fact that patient eligibility was restricted so patients who had experienced any arterial thromboembolic events within 6 months prior to randomization were excluded from participation in this study.

Bleeding/hemorrhagic events

Bleeding/hemorrhagic events were more frequent in the ramucirumab arm (16% incidence) than in the placebo arm (11%). There was one event of fatal gastric/gastrointestinal hemorrhage per arm. Grade 4 events were gastric hemorrhage (placebo arm) and hematemesis (ramucirumab arm). Grade 3 events in the ramucirumab arm were hematemesis, gastrointestinal hemorrhage (2 subjects), and hematuria; the only Grade 3 event in the placebo arm was an upper gastrointestinal hemorrhage.

The majority of events were Grade 1-2; the incidence of Grade 1-2 bleeding/hemorrhagic events in the ramucirumab arm was 12% vs. 8% in the placebo arm. Grade 1-2 events in the ramucirumab arm were epistaxis (5%), hematemesis (3%), hematuria (2 subjects), hemoptysis (2 subjects), gingival bleeding, hemorrhage, hemorrhoidal hemorrhage, melena, nail bed bleeding, petechiae, and rectal hemorrhage (one subject per event). Grade 1-2 events in the placebo arm were hematemesis (3%), hematuria (2 subjects), epistaxis, gastrointestinal hemorrhage, hematoma, hemoptysis, and vaginal hemorrhage (one subject per event).

In the REGARD study, as expected, subjects in the ramucirumab arm experienced more hemorrhagic events than patients in the placebo arm; however, the incidence of serious, life-threatening or fatal events of hemorrhages were not increased. Patient who had experienced any Grade 3-4 gastrointestinal bleeding within 3 months prior to randomization or on anticoagulation therapy with unresected primary tumors or local tumor recurrence following resection were not eligible for participation in the study.

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Gastrointestinal perforations

Three instances of gastrointestinal perforation were observed, all fatal. Patient 5760002 presented with symptoms of intestinal perforation 8 days after his 5th dose of ramucirumab and subsequently died after surgery (with massive intestinal necrosis and a cecum perforation) of multiorgan failure and sepsis. Patient 6640001 experienced colonic perforation 11 days after the second ramucirumab dose and died 22 days after the last study dose administration. On the placebo arm, patient 8520007 received a single dose of placebo and experienced colonic perforation and acute renal failure 3 days after receiving placebo; his death occurred 13 days after the placebo administration.

Liver injury/failure

The Applicant and FDA are following ramucirumab's potential for liver toxicity. Following an internal safety data committee unblinded review of 28 cases from Study CP12-0919, JVBF (a multicenter, randomized, double-blind, Phase 3 study of ramucirumab vs. best supportive care as second-line treatment in patients with HCC following first-line treatment with sorafenib), an imbalance was found in events searched under the hepatic disorders SMQ. In the JVBF study, the estimated exposure to ramucirumab was 208 patients. These events occurred in 22 cases in 20 patients, (9.6%) in the investigational arm compared to 6 cases in 6 patients (2.9%) in the placebo arm.

As per FDA request, Lilly submitted to the IND an aggregated safety report for non-HCC cancers identified using the same search criteria described above. Following the unblinded review of 13 cases from non-HCC cancer studies (the estimated exposure to ramucirumab was 2004 patients and to placebo was 1502 patients), an imbalance in the number of serious adverse events for the ramucirumab treated groups (11 cases, 0.55%) compared with the placebo groups (2 cases, 0.13%) was found.

FDA review of the cases concluded that overall, these events did not appear to show that ramucirumab caused direct drug-induced liver failure, but rather ramucirumab can exacerbate sequelae of cirrhosis (e.g., exacerbate encephalopathy, increase ascites, or possibly cause hepatorenal syndrome). It is unclear if these events were related to fluid shifts or some other mechanism.

The IDMC recommended that patients with cirrhosis at a level of Child-Pugh Class B (or worse) or cirrhosis with a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis should not be further enrolled on Study JVBF; the IDMC also recommended discontinuing study drug (ramucirumab or placebo) for patients with new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis. Regarding non-HCC patients, all serious hepatic events were confounded by the use of simultaneous known hepatotoxic drugs or liver metastatic disease. Follow-up aggregated reports (last report submitted and reviewed 7/10/2013) continue to show an imbalance of the same magnitude in the HCC study, while the differences in the non-HCC studies are of a lesser magnitude.

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In the REGARD study, twenty six patients (11%) in the ramucirumab arm and 8 patients (7%) in the placebo arm experienced a laboratory abnormality or liver toxicity reported as an adverse event flagged by the sponsor as “hepatotoxicity”. The events were combinations of ALT/AST, bilirubin, and alkaline phosphatase increases, plus the following terms: jaundice, cholestatic jaundice, hepatic failure, hepatic function abnormal, and liver disorder. There was an additional event of hepatic infection in each arm that was not included in this query.

As summarized in Table 42, Grade 3-4 events were similar in frequencies between arms (8% and 7% in the ramucirumab and placebo arms, respectively).

Table 42 - REGARD: Grade 3-4 liver toxicity

PT	Ramucirumab (n=236) N; (%)	Placebo (n=115) N; (%)
ALT increased	3 (1.27)	1 (0.86)
AST increased	3 (1.27)	2 (1.73)
BI conjugated increased	1 (0.30)	0
ALP increased	4 (1.69)	1 (0.86)
BI increased	3 (1.27)	1 (0.86)
Hepatic enzymes increased	1 (0.30)	0
Hepatic failure	1 (0.30)	0
Hepatic function abnormal	0	0
Hyperbilirubinemia	1 (0.30)	3 (2.60)
Jaundice	1 (0.30)	0
Jaundice cholestatic	1 (0.30)	0
Liver disorder	1 (0.30)	0
Transaminase increases	0	0

After reviewing the narratives and CRFs, it appeared that in the REGARD study, most cases of Grade 3-4 liver events in both arms were related to disease progression.

Table 43 summarizes FDA’s review of the SMQ search (using the MAED instrument) for the HLTs and HGLTs involving liver events.

Table 43 - REGARD: SMQ (HTLs and HGLTs) for hepatic dysfunction terms

	Ramucirumab/BSC; n (%) N=236	Placebo/BSC; n (%) N=115
HTL		
Blood duct inflammation and infection	1 (<1)	1 (1)
Cholecystitis and cholelithiasis	2 (1)	0
Cholestasis and jaundice	9 (4)	5 (4)
Hepatic and Hepatobiliary disorders	2 (1)	0
Hepatic enzymes and function abnormalities	1 (<1)	0
Hepatic failure and associated disorders	1 (<1)	0
Hepatic infections	1 (<1)	1 (1)
Hepatic signs and symptoms	2 (1)	1 (1)
Liver function analysis	15 (6)	5 (4)

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	Ramucirumab/BSC; n (%) N=236	Placebo/BSC; n (%) N=115
Obstructive bile disorders	1 (<1)	1 (1)
HLGT		
Hepatic and Hepatobiliary abnormalities	14 (6)	6 (5)
Hepatobiliary investigations	15 (6)	5 (4)

In conclusion, liver toxicity does not appear to be a concern in the REGARD study population.

Congestive heart failure

There was one event of cardiac failure in a patient (425-0005) in the ramucirumab arm with a history of coronary artery disease, aortic, mitral, and tricuspid regurgitation, left bundle branch block, tachycardia, and mild cardiac enlargement. The event occurred after Cycle 3 and no action was taken with regard to ramucirumab; the patient continued to receive study drug for an additional 9 cycles, discontinuing due to PD.

Reversible Posterior Leukoencephalopathy Syndrome

No events of RPLS were observed in the REGARD study. However, there were two events of RPLS in the global safety database in patients receiving ramucirumab in combination with FOLFIRI for the treatment of metastatic colorectal carcinoma.

One patient, a 63 year old woman, was diagnosed with Grade 2 RPLS while experiencing hypertension, and improved after treatment withdrawal. The second patient, a 73 year old man, was initially diagnosed as having a Grade 4 RPLS, but the diagnosis was later changed to cerebral infarction.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Almost all patients in both arms experienced AEs, but Grade 1-2 AEs were more frequent in the ramucirumab arm (88%) than in the placebo arm (77%). Table 44 summarizes the Grade 1-2 AEs by PT with an incidence $\geq 5\%$. AEs that were observed with an incidence increased (at least 3%) in the ramucirumab arm were diarrhea (14% vs. 7% in the ramucirumab and placebo arms respectively), upper abdominal pain (10% vs. 4% in the ramucirumab and placebo arms respectively), headache (9% vs. 3% in the ramucirumab and placebo arms respectively), and epistaxis (5% vs. 1% in the ramucirumab and placebo arms respectively). AEs that were observed with an incidence increased (at least 3%) in the placebo arm were nausea (18% vs. 26% in the ramucirumab and placebo arms, respectively), vomiting (17% vs. 21% in the ramucirumab and placebo arms, respectively), constipation (15% vs. 20% in the ramucirumab and placebo arms, respectively), abdominal pain (14% vs. 23% in the ramucirumab and placebo arms respectively), dizziness (1% vs. 5% in the ramucirumab and placebo arms respectively), and dyspepsia (2% vs. 6% in the ramucirumab and placebo arms respectively).

Table 44 - REGARD: Grade 1-2 AEs (by PT), incidence ≥ 5%

PT	Ramucirumab/BSC N (%) ; N=236	Placebo/BSC N (%) ; N=115
Decreased appetite	49 (21)	22 (19)
Fatigue	48 (20)	24 (21)
Nausea	42 (18)	30 (26)
Vomiting	41 (17)	24 (21)
Constipation	35 (15)	23 (20)
Abdominal pain	33 (14)	26 (23)
Diarrhea	32 (14)	8 (7)
Asthenia	23 (10)	11 (10)
Weight decreased	24 (10)	10 (9)
Abdominal pain upper	24 (10)	5 (4)
Headache	22 (9)	4 (3)
Cough	19 (8)	9 (8)
Anemia	20 (8)	8 (7)
Dyspnea	18 (8)	8 (7)
Edema peripheral	19 (8)	8 (7)
Dysphagia	20 (8)	7 (6)
Hypertension	19 (6)	6 (5)
Back pain	15 (6)	8 (7)
Ascites	13 (6)	6 (5)
Insomnia	12 (5)	8 (7)
Hypoalbuminemia	11 (5)	5 (4)
Epistaxis	11 (5)	1 (1)
Dysgeusia	7 (3)	6 (5)
Dizziness	3 (1)	6 (5)
Dyspepsia	5 (2)	7 (6)

The results of an HLT analysis (summary in the appendices section, Table 73), supported the analysis by PTs; however, the incidence rate of hypertension was increased in the HLT analysis and increases the incidence of hypertension (11% vs. 8% in the ramucirumab and placebo arms respectively).

In summary, although there are some differences in the incidences of Grade 1-2 adverse events between arms, it does not appear to be a clinically meaningful difference, and the AEs observed in excess in the ramucirumab arm were expected (hypertension, epistaxis) as a class effect.

7.4.2 Laboratory Findings

Hematologic parameters

Table 45 summarizes the hematological effects observed throughout the REGARD study.

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Table 45 - REGARD: Hematological toxicity summary

Parameter	Ramucirumab/BSC N (%); N=236	Placebo/BSC N (%); N=115
Hemoglobin		
Within or above normal	28 (12)	15 (13)
Grade 1	120 (51)	50 (43)
Grade 2	76 (32)	39 (34)
Grade 3	12 (5)	11 (10)
WBC		
Grade 1	23 (10)	12 (10)
Grade 2	13 (6)	4 (3)
Grade 3	2 (1)	3 (3)
Grade 4	0	1 (1)
ANC		
Grade 1	19 (8)	6 (5)
Grade 2	13 (6)	8 (7)
Grade 3	3 (1)	2 (2)
Grade 4	2 (1)	0
PLT		
Grade 1	78 (33)	29 (25)
Grade 2	6 (3)	1 (1)
Grade 3	4 (2)	3 (2)
Grade 4	1 (<1)	1 (1)

As depicted in Figure 12, the median hemoglobin levels in the ramucirumab were higher throughout the study (e.g., median Hb in the ramucirumab arm in Cycle 1 was 10.80 mmol/L and 6.70 mmol/L in the placebo arm). Median hemoglobin values did not change significantly in each arm, and in each arm the fluctuations were not marked.

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Figure 12 - REGARD: Median Hemoglobin (mmol/L) in the first 10 cycles

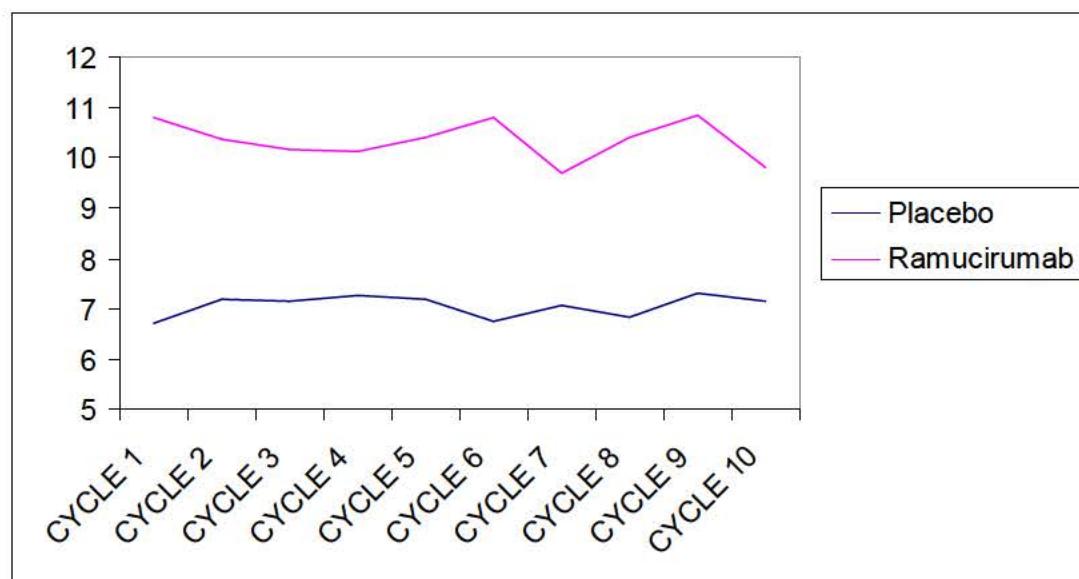


Table 46 summarizes hemoglobin (by CTCAE 4.0) shifts during the first 180 days of treatment. This exploratory analysis may include patients who dropped out of treatment more than 30 days before the lab value was assessed (i.e., patients who received only 3 cycles of therapy but had follow-up assessments or unscheduled assessments before day 180).

Table 46 - REGARD: Hemoglobin shift (by CTCAE v 4.0) in the first 180 days

Baseline	Ramucirumab/BSC (N=232)				Placebo/BSC (N=110)			
	Shift during treatment; n (%)				Shift during treatment; n (%)			
	WLN	Grade 1	Grade 2	Grade 3	WLN	Grade 1	Grade 2	Grade 3
WNL	28 (12)	23 (10)	1 (<1)	1 (<1)	15 (14)	7 (6)	4 (4)	3 (3)
Grade 1	7 (3)	91 (39)	48 (21)	6 (3)	4 (4)	36 (33)	18 (16)	6 (5)
Grade 2	1 (<1)	6 (3)	15 (6)	5 (2)	1 (1)	1 (1)	14 (13)	0
Grade 3	0	0	0	0	0	0	0	1 (1)

The proportion of patients in the placebo arm who shifted from normal hemoglobin or Grade 1 anemia to Grade 3 anemia was higher in the placebo arm (8% in the placebo arm versus 4% in the ramucirumab arm). These values do not exactly match the ones in Table 45, as the shift table was based on a subset of the population; however, in both analyses patients in the placebo arm had lower hemoglobin levels. The increased incidence of anemia in the placebo arm cannot be explained by overt hemorrhage (overall hemorrhages incidence 16% in the ramucirumab arm and 11% in the placebo arm), perforations or other clinically defined events.

As expected, ramucirumab did not result in significant changes in total white blood cell counts (WBC). More patients in the ramucirumab arm experienced Grade 2 toxicity (6% vs. 3% in the ramucirumab and placebo arms respectively), but more patients in the placebo arm experienced

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Grade 3 toxicity (1% vs. 3% in the ramucirumab and placebo arms respectively). As absolute neutrophil counts (ANC) are a fraction of the total WBC count, there were no marked differences between arms. More patients in the ramucirumab arm experienced Grade 1 neutropenia, 8% vs. 5%. Table 47 summarizes the shift in ANC values as per CTCAE v 4.0.

Table 47 - REGARD: ANC shift (by CTCAE v 4.0) in the first 180 days

Baseline	Ramucirumab/BSC (N=213)					Placebo/BSC (N=108)			
	Shift during treatment; n (%)					Shift during treatment; n (%)			
	WLN	Grade 1	Grade 2	Grade 3	Grade 4	WLN	Grade 1	Grade 2	Grade 3
WNL	176 (83)	8 (4)	10 (4)	0	2 (1)	88 (81)	3 (3)	3 (3)	1 (1)
Grade 1	4 (2)	6 (3)	0	0	0	3 (3)	0	1 (1)	1 (1)
Grade 2	1 (<1)	0	0	1 (<1)	0	2 (2)	0	1 (1)	0

The administration of ramucirumab did not result in thrombocytopenia. Although as summarized in Table 45, there was an increased proportion of patients in the ramucirumab arm who experienced a mild decrease in platelet counts (Grade 1), these were subjects who were previously exposed to myelotoxic regimens. There were only 7 patients (4 in the ramucirumab arm and 3 in the placebo arm) who experienced Grade 3 thrombocytopenia and one patient per arm with Grade 4 thrombocytopenia (in one event, thrombocytopenia occurred at the day 30 assessment and in the other patient at the end of therapy assessment).

In summary, ramucirumab did not result in significant myelotoxicity. Although the median hemoglobin values were different in both arms, the treatment did not change the values over time (random differences in baseline values).

Coagulation lab parameters

For patients to be enrolled in the protocol, coagulation function must have been adequate as defined by International Normalized Ratio (INR) ≤ 1.5 and a partial thromboplastin time (PTT) ≤ 5 seconds above the ULN (unless receiving anticoagulation therapy). Patients on full-dose anticoagulation must have been on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If receiving warfarin, the patient must have had an INR ≤ 3.0 and no active bleeding (i.e., no bleeding within 14 days prior to the first dose of study therapy) or pathological condition present that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices). Patients on anticoagulation therapy with unresected primary tumors or local tumor recurrence following resection were not eligible.

Table 48 summarizes the results post-baseline of coagulation parameter assessments.

Table 48 - REGARD: Coagulation parameters summary

Parameter	Ramucirumab/BSC N (%); N=231	Placebo/BSC N (%); N=114
INR		
Grade 1	40 (17)	16 (14)
Grade 2	0	3 (3)

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Parameter	Ramucirumab/BSC N (%); N=231	Placebo/BSC N (%); N=114
Grade 3	0	2 (1)
aPTT		
Grade 1	35 (15)	12 (11)
Grade 2	5 (2)	2 (2)
Grade 3	2 (1)	0

In summary, there were no clinically significant differences in the toxicity observed in coagulation parameters between arms.

Hepatic function parameters

Table 49 summarizes the incidence of hepatic lab parameters toxicity.

Table 49 - REGARD: Hepatic function parameters summary

Parameter	Ramucirumab/BSC N (%); N=236	Placebo/BSC N (%); N=115
ALT		
Grade 1	71 (30)	28 (24)
Grade 2	10 (4)	2 (2)
Grade 3	6 (3)	7 (6)
Grade 4	0	0
AST		
Grade 1	85 (36)	37 (32)
Grade 2	17 (7)	4 (3)
Grade 3	8 (3)	6 (5)
Grade 4	1 (<1)	0
Bilirubin		
Grade 1	27 (11)	11 (10)
Grade 2	12 (5)	5 (4)
Grade 3	10 (4)	6 (5)
Grade 4	9 (4)	1 (1)
ALT and/or AST >3 xULN AND BIT >2 xULN (met lab criteria for Hy's law)		
	9 (4)	5 (4)
ALP		
Grade 1	71 (30)	44 (38)
Grade 2	36 (15)	17 (15)
Grade 3	26 (11)	12 (10)
Grade 4	1 (<1)	0

All patients had normal bilirubin levels at baseline with the exception of 7 patients in each arm (3% in the ramucirumab arm and 6% in the placebo arm).

Refer to Section 7.3.5 above that describes the potential adverse effects of ramucirumab in patients with hepatocellular cancer / cirrhosis. As a result of this signal, several changes in the HCC protocol were implemented, restricting eligibility to subjects with Child Pugh A-B7, no

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history of hepatic encephalopathy, etc. The Investigator's Brochure was revised, and all investigators have been notified of the potential ramucirumab liver toxicity.

In order to further explore ramucirumab toxicity in the setting of gastric cancer, the lab dataset was queried to search for subjects with concomitant \geq Grade 2 increase of serum bilirubin levels and \geq Grade 3 transaminases increases (*laboratory criteria for Hy's law*). Nine patients in the ramucirumab arm (3.8%) and 5 patients in the placebo arm (4.3%) were found. Table 50 summarizes the dataset and CRFs data (when available).

Table 50 - REGARD: Summary of events meeting laboratory criteria for Hy's law

Ramucirumab arm
#1370003: (no CRF) Grade 3 ALT/BI at Cycle 3 and end of treatment evaluation.
#1380002: Grade 3 ALT/BI at Cycle 3 and end of treatment (progressive disease) evaluation ALT/BI.
#2330001: Grade 2 BI and Grade 3 AST at Cycle 8. Follow up of bilirubin showed further increases
#2450001: Grade 2 BI and Grade 3 ALT at Cycle 3 and 4. Grade 4 bilirubin and Grade 3 ALT/AST at the end of treatment (progressive disease).
#2470001: Grade 3 AST and bilirubin at the end of treatment evaluation.
#5080001: Grade 3 AST and Grade 2 bilirubin at the end of treatment evaluation
#5330002: Grade 3 AST and Grade 2 bilirubin at the 30-day follow-up evaluation
#5440001: Grade 3 AST and Grade 2 bilirubin in Cycle 3; worsening (progressive disease) to Grade 4 AST and Grade 3 ALT and bilirubin at the end of treatment evaluation (2 weeks later).
#6060005: Progressive bilirubin increase since Cycle 2; Grade 4 bilirubin and Grade 3 ALT/AST at the 30-day follow-up evaluation (progressive disease).
Placebo arm
#1000003: Grade 3 ALT/AST and bilirubin at the end of treatment (progressive disease). Clinical jaundice and edema.
#4300008: Grade 3 ALT/AST and bilirubin at the end of treatment evaluation.
#4560002: Grade 2 bilirubin and Grade 3 ALT/AST at the 30-day follow-up evaluation.
#5080007: Grade 3 ALT/AST and bilirubin at the end of treatment evaluation.
#6020006: Grade 3 ALT/AST/bilirubin at the end of treatment evaluation

Although there was a concomitant increase of bilirubin and ALT/AST, in all cases it appeared that progressive disease was the underlying cause. Furthermore, the incidence of severe hepatic laboratory impairment was slightly increased in the placebo arm. Thus there was no evidence from this trial that these cases satisfied all criteria for Hy's law.

Renal function

Serum creatinine was assessed every two weeks. There were only three patients who presented with Grade 3 serum creatinine levels, all in the ramucirumab arm (one of these patients, #202007, discontinued treatment after this finding). This analysis was inconsistent with the adverse event analysis, where two patients presented with Grade 3 acute renal failure in the placebo arm, and in the ramucirumab arm one patient had Grade 3 acute renal failure, an additional patient had Grade 3 renal failure, and a third patient had acute renal failure with fatal outcome (Grade 5). the laboratory finding corresponded to the clinical event in only one of these cases (ID#6050003). Although there were inconsistencies between these analyses, there

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was no excess of renal toxicity in the ramucirumab arm, and in most patients renal failure was associated with dehydration and progression of disease.

Unless otherwise indicated, proteinuria was assessed every 6 weeks (3 cycles). The dataset contained (excluding pretreatment assessments) data for two patients (ID#5320009 in the placebo arm and #4300007 in the ramucirumab) with numerical data, but no units or type of assessment were described (24-hour collection, single sample, etc).

In 18 (8%) patients in the ramucirumab arm and 4 (3%) patients in the placebo arm, the urine analysis for proteinuria was considered “positive” or “+++” (presumably dipstick) in the dataset. At least two patients in the ramucirumab arm (#4300007 and 4570001) discontinued treatment because of Grade 2 or 3 proteinuria. In the Applicant’s analysis, proteinuria was reported for 7 patients in the ramucirumab arm (the above described Grade 3 event and 6 events of \leq Grade 2) and three patients in the placebo arm.

Because patients with gastric/GEJ tumors are often malnourished, have limited oral intake, vomiting, etc, electrolyte disturbances are a common occurrence. Grade 3 hyponatremia was observed in 29 (12%) patients in the ramucirumab arm and 14 (12%) patients in the placebo arm. Grade 4 hyponatremia (less than 120 mEq/L) was observed in 7 (3%) patients in the ramucirumab arm and 1 (1%) patient in the placebo arm. There were 16 patients (7%, only one patient with Grade 4) with Grade 3-4 hypokalemia in the ramucirumab arm and 3 patients (3%, 2 patients Grade 4) with Grade 3-4 hypokalemia in the placebo arm.

7.4.3 Vital Signs

There were no events of fever \geq 38.5 C immediately after ramucirumab or placebo infusions (there was a pre-infusion event). No significant shifts (less than 1%) were observed between pre- and post-infusion arterial pulse (first 6 cycles analyzed).

Table 51 and Table 52 summarize the shifts in blood pressure assessments throughout the study. For grading hypertension, the CTCAE dictionary for hypertension considered the blood pressure assessment, clinical findings, and therapeutic measures taken. Therefore, although the incidence of hypertension differed between the AE dataset and the blood pressure assessment data, the shift analysis was consistent with the findings in the adverse events analysis (hypertension incidence increased in the ramucirumab arm: 17% vs. 8% in the placebo arm), as expected in a VEGF inhibitor.

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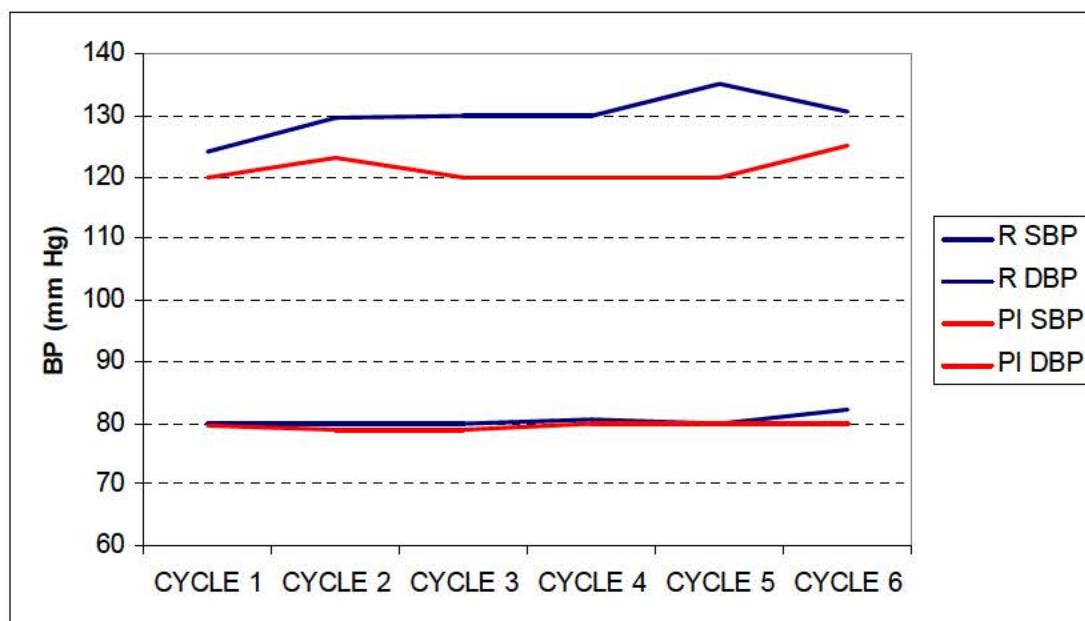
Table 51 - REGARD: Systolic blood pressure shift during treatment

Baseline	Ramucirumab/BSC (N=236)			Placebo/BSC (N=114)		
	Shift during treatment; n (%)			Shift during treatment; n (%)		
	< 140 mm Hg	140-160 mmHg	> 160 mmHg	< 140 mm Hg	140-160 mmHg	> 160 mmHg
< 140 mm Hg	109 (46)	81 (34)	11 (5)	68 (59)	26 (23)	1 (1)
140-160 mmHg	3 (1)	15 (6)	12 (5)	6 (5)	8 (7)	3 (3)
> 160 mmHg	0	3 (1)	2 (1)	0	2 (2)	0

Table 52 - REGARD: Diastolic blood pressure shift during treatment

Baseline	Ramucirumab/BSC (N=236)			Placebo/BSC (N=114)		
	Shift during treatment; n (%)			Shift during treatment; n (%)		
	< 90 mm Hg	90-100 mmHg	> 100 mmHg	< 90 mm Hg	90-100 mmHg	> 100 mmHg
< 90 mm Hg	115 (49)	86 (36)	8 (3)	77 (66)	25 (22)	3 (3)
90-100 mmHg	6 (3)	15 (6)	6 (3)	5 (4)	3 (3)	0
> 100 mmHg	0	0	0	0	0	1 (1)

Figure 13 shows an exploratory analysis of median blood pressure (the upper curves are the median of the maximal systolic pressure recorded per subject, and the lower curves are the maximal diastolic pressure recorded per subject in the first 6 cycles of treatment; ramucirumab arm is in blue and placebo arm is in red (data tabulation can be found in the appendices section, Table 74).

Figure 13 - REGARD: Median blood pressure Cycles 1-6 by treatment arm

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This graph shows a finding that is consistent among biologic VEGF inhibitors, where most of the hypertension is diagnosed within the first 3 cycles. In the REGARD study, by Cycle 3, there is a 10 mm Hg difference in the median systolic blood pressure in the ramucirumab arm (130 mm Hg vs. 120 mm Hg). In the ramucirumab arm, the median systolic blood pressure peaked at Cycle 5 (135 mm Hg). There were no significant changes in the diastolic blood pressure. To further analyze the timing of the blood pressure increases throughout treatment, an analysis by categories (i.e., systolic below 140 mm Hg, between 140-160 mm Hg, and above 160 mm Hg) was conducted and the results summarized in Table 53 and Table 54.

Table 53 - REGARD: Systolic blood pressure (mm Hg) by cycle

	Ramucirumab – N (%)				Placebo – N (%)			
	N	<140	140-160	> 160	N	<140	140-160	> 160
CYCLE 1	231	182 (79)	45 (19)	3 (1)	112	92 (82)	19 (17)	1 (1)
CYCLE 2	212	158 (75)	43 (20)	11 (5)	99	81 (82)	18 (18)	0
CYCLE 3	193	134 (69)	49 (25)	10 (5)	79	67 (85)	11 (13)	1 (1)
CYCLE 4	122	85 (70)	29 (24)	8 (7)	36	28 (78)	7 (20)	1 (3)
CYCLE 5	99	58 (59)	37 (37)	4 (4)	25	22 (88)	2 (8)	1 (4)
CYCLE 6	96	60 (63)	33 (34)	3 (3)	23	17 (74)	6 (26)	0

Table 54 - REGARD: Diastolic blood pressure (mm Hg) by cycle

	Ramucirumab – N (%)				Placebo – N (%)			
	N	<90	90-100	> 100	N	<90	90-100	> 100
CYCLE 1	231	195 (84)	33 (14)	2 (1)	112	101 (90)	10 (9)	1 (1)
CYCLE 2	212	172 (81)	34 (16)	6 (3)	99	86 (87)	13 (13)	0
CYCLE 3	193	141 (73)	49 (25)	3 (2)	79	71 (90)	8 (10)	0
CYCLE 4	122	85 (70)	37 (30)	0	36	33 (92)	3 (8)	0
CYCLE 5	99	65 (66)	32 (49)	2 (2)	25	23 (92)	2 (8)	0
CYCLE 6	96	68 (71)	26 (27)	2 (2)	23	18 (78)	5 (22)	0

In this analysis (acknowledging the limitation imposed by the small number of patients in the placebo arm, particularly after Cycle 3), both the systolic and diastolic blood pressure peaked in the ramucirumab arm after Cycle 3.

7.4.4 Electrocardiograms (ECGs)

Patients had baseline assessments of ventricular function (MUGA scans) and electrocardiograms. Patients were not assessed periodically for these parameters, and the impact of ramucirumab on electric cardiac toxicity comes from other studies, and a QTc dedicated study, 7I4T-IE-JVBK.

Study JVBK, entitled “A Study to Evaluate the Relationship between Ramucirumab (IMC-1121B) Therapy and Corrected QT (QTc) Interval Changes in Patients with Advanced Cancer”, was a multicenter, open-label, single-active arm, monotherapy study that enrolled 68 patients with advanced solid tumors. 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. The

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first 16 patients enrolled in the study received 1 dose of moxifloxacin (400 mg orally [PO]), an antibiotic associated with mild QTc prolongation, followed by a 1-week washout period to assess the assay sensitivity in this patient population.

FDA analysis of the results of study JVBK (please refer to D. Marathe, K. Krudys, Q.Dang, M. Fizman and N. Stockbridge's review) concluded that no significant QTc prolongation effect of ramucirumab (10 mg/kg/3 weeks) was detected in this study. The largest upper bounds of the 2-sided 90% CI for the mean difference between ramucirumab (10 mg/kg/3 weeks) and placebo were below 10 ms. There was no statistically significant relationship between ramucirumab concentrations and Δ QTcF. The 10-mg/kg every 3 weeks dose selected for this QT study produces Cmax values (mean Cmax of 571 μ g/mL at Cycle 3- third dose) which are higher than that with the intended therapeutic dose of 8 mg/kg every 2 weeks (geometric mean Cmax of 282 μ g/mL and maximum individual Cmax of 318 μ g/mL at Cycle 2- third dose).

The interdisciplinary review team for QT studies also agreed with the Applicant's proposed label language in Section 12.2.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted or reported.

7.4.6 Immunogenicity

Eli Lilly submitted immunogenicity data from 10 clinical studies (551 patients receiving ramucirumab and 106 patients receiving placebo). Among patients who received ramucirumab, there were 2.4% who had antibodies (ADA) to ramucirumab at baseline. Five percent had transient positive samples and 7 patients (1.3%) had persistent ADA-positive samples. Twenty one patients receiving ramucirumab (3.8%) were positive for ADA at follow-up. Neutralizing antibodies were observed in one patient.

Five patients (4.7%) in the placebo group had positive samples for ADA. Two of the 5 patients had transient positive ADA samples, while 1 of the 5 had persistent ADA positive samples. Three patients had ADA-positive samples at baseline. Ramucirumab PKs appeared to be lower in patients with treatment-emergent ADA, but the limited data pairing PK samples and immunogenicity samples precluded definitive conclusions.

In the REGARD study, 6 patients (3%) in the ramucirumab arm and 1 patient (1%) in the placebo arm developed ADA: none were associated with infusion-related reactions. Eli Lilly acknowledged that although there were scheduled assessments of the presence of ADA at the end of study and 30 day follow-up, there were few long term samples (>6 months) collected. Lilly attributed the failure to obtain the samples to the nature of the patient population and the short overall survival in the patient populations for the study.

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No evaluation of the effect of immunogenicity on efficacy can be conducted because of the small number of patients available for such an analysis. It appeared that immune-related reactions were not correlated with the presence of antibodies against ramucirumab.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This study administered a single ramucirumab dose for all patients, 8 mg/kg.

7.5.2 Time Dependency for Adverse Events

Patients in the ramucirumab arm received a median of 4 courses of therapy (8 weeks), while patients in the placebo arm received a median of 3 courses of treatment (6 weeks). This number of cycles is consistent with the time for disease progression observed in the REGARD study, and also with findings in other clinical studies in patients with previously treated metastatic gastric cancer. In the COUGAR-2 study (Ford H., 2014), 168 patients were randomized to receive docetaxel or best supportive care for the second line treatment of gastric/GEJ carcinoma. The median number of cycles for patients receiving docetaxel was 3 (range 1-6), and only 19% of patients received the planned 6 cycles of therapy. As in the REGARD study, the main reason (65%) for discontinuation was progressive disease. However, discontinuations due to intolerable toxicity were observed in 31% of patients and death in 15% of patients.

The following analysis of adverse events with $\geq 10\%$ incidence was limited to the first 55 days of treatment (equivalent to 4 cycles) because the drop in number of patients receiving placebo was marked. Only 35 patients received 4 cycles (25 patients received 5 cycles), making comparisons between arms less reliable (i.e., any adverse event will be over represented in percentages) and increasing the chances of random findings.

Table 55 and Table 56 summarize the most frequent adverse event (PT) by bi-weekly period (equivalent to cycles) by arm.

Table 55 - REGARD: Most frequent AEs by Cycle, ramucirumab arm

PT	Days 1-13 N=236 (%)	Days 14-27 N= 217 (%)	Days 28-41 N= 187 (%)	Days 42-55 N=122 (%)
Fatigue	20 (8)	20 (9)	14 (7)	9 (7)
Vomiting	19 (8)	12 (6)	15 (8)	3 (2)
Nausea	17 (7)	7 (3)	11 (6)	5 (4)
Constipation	13 (6)	9 (4)	7 (4)	6 (5)
Decreased appetite	14 (6)	13 (6)	16 (9)	9 (7)
Abdominal pain	13 (6)	11 (5)	5 (3)	4 (3)
Diarrhea	12 (5)	8 (4)	8 (4)	8 (7)
Hypertension	11 (5)	11 (5)	10 (5)	13 (11)

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Dyspnea	7 (3)	5 (2)	6 (3)	1 (1)
Ascites	6 (3)	7 (3)	4 (2)	3 (2)
Abdominal pain upper	7 (3)	8 (4)	1 (1)	2 (2)
Asthenia	5 (2)	8 (4)	5 (3)	7 (6)
Anemia	5 (2)	9 (4)	7 (4)	4 (3)
Dysphagia	3 (1)	11 (5)	8 (4)	3 (2)
Weight decreased	1 (<1)	6 (3)	5 (3)	5 (4)

In the ramucirumab arm, it did not appear that the incidence (note that this analysis was exploratory as the same patient may have been counted in several periods) changed with time. Regarding hypertension (please see complete analysis in Section 7.3.5, Table 51, Table 52, Table 53, and Table 54), the incidence in the ramucirumab arm was 17% (8% Grade 3). The increased rate observed in the third cycle appeared to be explained by both existing and new incident cases. Characteristically, 75% of hypertensive events observed in patients exposed to biologic proteins inhibiting VEGF occurred within the first 3 cycles.

Table 56 - REGARD: Most frequent AEs by Cycle, placebo arm

PT	Days 1-14 N=115	Days 14-27 N= 101	Days 28-41 N= 74	Days 42-55 N= 35
Fatigue	14 (12)	8 (8)	8 (11)	2 (6)
Vomiting	5 (4)	13 (13)	7 (9)	0
Nausea	6 (5)	14 (14)	5 (7)	1 (3)
Constipation	12 (10)	9 (9)	5 (7)	5 (14)
Decreased appetite	9 (8)	9 (9)	9 (12)	4 (11)
Abdominal pain	8 (7)	11 (11)	8 (11)	5 (14)
Diarrhea	3 (3)	0	2 (3)	3 (9)
Hypertension	4 (3)	5 (5)	3 (4)	1 (3)
Dyspnea	2 (2)	5 (5)	6 (8)	3 (9)
Ascites	1 (1)	7 (7)	3 (4)	1 (3)
Abdominal pain upper	0	1 (1)	0	2 (6)
Asthenia	7 (6)	6 (6)	2 (3)	1 (3)
Anemia	2 (2)	5 (5)	3 (4)	5 (14)
Dysphagia	5 (4)	5 (5)	4 (5)	2 (6)
Weight decreased	1 (1)	2 (2)	3 (4)	2 (6)

Because there were fewer patients in the placebo arm (particularly in the fourth period), events by time in the placebo arm were difficult to interpret. Most of the adverse events described are common to the disease itself, and progression of disease can contribute to the increasing incidence.

7.5.3 Drug-Demographic Interactions

Age

Sixty five patients (35%) in the ramucirumab arm and 45 patients (39%) in the placebo arm were 65 years of age or older. Table 57 summarizes the incidence of AEs by SOC in patients younger than 65 years old and 65 years of age or older.

Table 57 - REGARD: AEs by age group (by SOC)

SOC	Ramucirumab/BSC; n (%) N=236		Placebo/BSC; n (%) N= 115	
	≤ 64 y.o. (n=154)	≥ 65 y.o. (n=82)	≤ 64 y.o. (n=70)	≥ 65 y.o. (n=45)
Blood and lymphatic system disorder	38 (25)	9 (11)	14 (20)	9 (20)
Cardiac disorders	5 (3)	3 (4)	4 (6)	3 (7)
Congenital disorders	2 (1)	0	0	0
Ear and labyrinth disorders	3 (2)	0	1 (1)	0
Endocrine disorders	4 (3)	0	0	0
Eye disorders	4 (3)	3 (4)	1 (1)	3 (7)
Gastrointestinal disorders	102 (66)	27 (33)	47 (67)	27 (60)
General disorders and administration site conditions	82 (53)	29 (35)	35 (50)	29 (64)
Hepatobiliary disorders	9 (6)	4 (5)	4 (6)	4 (9)
Immune system disorders	1 (1)	0	1 (1)	0
Infections	22 (14)	8 (10)	10 (14)	8 (18)
Injury and procedural complications	15 (10)	4 (5)	4 (6)	4 (9)
Investigations	41 (27)	8 (10)	13 (19)	8 (18)
Metabolism and nutrition disorders	54 (35)	19 (23)	29 (41)	19 (42)
Musculoskeletal and connective tissue disorders	40 (26)	6 (7)	20 (29)	6 (13)
Neoplasms	5 (3)	2 (2)	2 (3)	2 (4)
Nervous system disorders	30 (19)	13 (16)	11 (16)	13 (29)
Psychiatric disorders	17 (11)	7 (9)	9 (13)	7 (16)
Renal and urinary disorders	17 (11)	6 (7)	8 (11)	6 (13)
Reproductive disorders	3 (2)	2 (2)	1 (1)	2 (4)
Respiratory, thoracic and mediastinal	28 (18)	12 (15)	19 (27)	12 (27)
Skin and subcutaneous disorders	16 (10)	3 (4)	5 (7)	3 (7)
Surgical and medical procedures	1 (<1)	0	1 (1)	0
Vascular disorders	36 (23)	7 (9)	16 (23)	7 (16)

Although when analyzed by SOC it does not appear than the administration of ramucirumab is increasing the incidence of AEs in the older population, an analysis by PT shows some differences by age group. Table 58 summarizes the most frequently observed AEs (incidence \geq 10%) discriminated by age and severity of the events. Older patients receiving ramucirumab experienced more frequent (differences of at least 3%) fatigue (30% vs. 21% in younger patients), decrease appetite (29% vs. 21%), upper abdominal pain (15% vs. 10%), weight decrease (16% vs. 10%), dyspnea (17% vs. 5%), and cough (12% vs. 6%). In the placebo group, older patients experienced more nausea (31% vs. 23%), decrease appetite (24% vs. 21%), abdominal pain (27% vs. 24%), constipation (27% vs. 20%), asthenia (22% vs. 13%), dyspnea (16% vs. 11%), and peripheral edema (13% vs. 7%). In summary, in both groups asthenia/fatigue, decreased appetite, and dyspnea were more frequently observed in the older population, but no differences between the ramucirumab arm and the placebo arm were found, supporting the hypothesis that the increased incidence in these AEs was probably related to the interaction disease-age.

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Table 58 - REGARD: AEs by age group (by PT, incidence ≥ 10%)

PT	Ramucirumab/BSC; n (%) N=236				Placebo/BSC; n (%) N= 115			
	≤ 64 y.o. (n=154)		≥ 65 y.o. (n=82)		≤ 64 y.o. (n=70)		≥ 65 y.o. (n=45)	
	All grades	Grade 3-5	All grades	Grade 3-5	All grades	Grade 3-5	All grades	Grade 3-5
Vomiting	37 (24)	5 (3)	10 (12)	1 (1)	18 (26)	3 (4)	11 (24)	2 (4)
Fatigue	33 (21)	5 (3)	25 (30)	5 (6)	17 (24)	4 (6)	11 (24)	0
Nausea	32 (21)	3 (2)	13 (16)	0	16 (23)	0	14 (31)	0
Decreased appetite	33 (21)	5 (3)	24 (29)	3 (4)	15 (21)	2 (3)	11 (24)	2 (4)
Abdominal pain	29 (19)	9 (6)	16 (20)	3 (4)	17 (24)	3 (4)	11 (27)	0
Anemia	28 (18)	14 (9)	7 (9)	1 (1)	11 (16)	5 (7)	6 (13)	4 (9)
Constipation	25 (16)	0	11 (13)	1 (1)	14 (20)	3 (4)	12 (27)	0
Hypertension	24 (16)	11 (7)	12 (15)	6 (7)	5 (7)	1 (1)	4 (9)	2 (4)
Diarrhea	23 (15)	2 (1)	11 (13)	0	7 (10)	1 (1)	3 (7)	1 (2)
Dysphagia	20 (13)	5 (1)	5 (6)	0	7 (10)	3 (4)	5 (11)	2 (4)
Asthenia	18 (12)	4 (1)	10 (12)	1 (1)	9 (13)	5 (7)	10 (22)	3 (7)
Back pain	15 (10)	3 (2)	3 (4)	0	10 (14)	3 (4)	1 (2)	0
Ascites	16 (10)	7 (5)	7 (9)	3 (4)	9 (13)	4 (6)	2 (4)	1 (2)
Abdominal pain upper	15 (10)	3 (3)	12 (15)	0	3 (4)	0	2 (4)	0
Headache	15 (10)	0	7 (9)	0	3 (4)	0	1 (2)	0
Weight decrease	14 (9)	1 (1)	13 (16)	2 (2)	9 (13)	1 (1)	2 (4)	0
Dyspnea	8 (5)	2 (1)	14 (17)	2 (2)	8 (11)	3 (4)	7 (16)	4 (9)
Cough	9 (6)	0	10 (12)	0	5 (7)	0	4 (9)	0
Peripheral edema	13 (8)	0	7 (9)	1 (1)	5 (7)	0	6 (13)	4 (9)

Table 59 summarizes the AEs with fatal outcomes by age group and arm. There were no identifiable trends regarding a type of toxicity with fatal outcome. Older patients in the placebo arm experienced more AEs with fatal outcome (13% vs. 10% in younger patients), and no differences were found between arms.

Table 59 - REGARD: AEs with fatal outcomes by age group

PT	Ramucirumab/BSC; n (%) N=236		Placebo/BSC; n (%) N= 115	
	≤ 64 y.o. (n=154)	≥ 65 y.o. (n=82)	≤ 64 y.o. (n=70)	≥ 65 y.o. (n=45)
Total deaths*	17 (11)	10 (12)	7 (10)	6 (13)
Death	4	0	0	0
Multiorgan failure	3	1	0	1
Pneumonia	2	0	0	0
Cholestasis	1	0	0	0
Gastric cancer	1	0	0	0
Gastrointestinal hemorrhage	1	0	0	1
General physical deterioration	1	1	0	0
Intestinal obstruction	1	0	0	0

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PT	Ramucirumab/BSC; n (%) N=236		Placebo/BSC; n (%) N= 115	
	≤ 64 y.o. (n=154)	≥ 65 y.o. (n=82)	≤ 64 y.o. (n=70)	≥ 65 y.o. (n=45)
Intestinal perforation	1	0	0	0
Multiple injuries	1	0	0	0
Acute renal failure	1	0	0	0
Bacteriemia	0	1	0	0
Cardiac arrest	0	1	0	0
Cholangitis	0	1	0	0
Dehydration	0	1	0	0
Dyspnea	0	1	0	1
Gastric hemorrhage	0	1	0	0
Gastrointestinal obstruction	0	0	1	0
Large intestine perforation	0	1	0	1
Lobar pneumonia	0	0	1	0
Myocardial infarction	0	1	0	0
Neoplasm	0	0	1	1
Pulmonary embolism	0	0	2	0
Respiratory failure	0	0	1	1
Septic shock	0	0	1	0
Sudden death	0	0	0	1

* excluding disease progression

Gender

The efficacy of ramucirumab by gender appeared to differ in the REGARD trial (HR for male patients 0.676 [95% CI 0.499; 0.916] and the HR for female patients is 1.431 [95% CI 0.852, 2.405]). To further explore differences that can contribute to this difference, demographics and AEs by gender were analyzed (Table 13).

Median age of women receiving ramucirumab was 60 years old, the same as men receiving ramucirumab, but 6 years older than women receiving placebo. Women in the ramucirumab arm had a higher incidence of gastric tumors when compared with women in the placebo arm (93% vs. 82%), and had higher incidence of diffuse histology when compared with women in the placebo arm (49% vs. 34%). Some of these factors may have contributed to the differences in outcomes. Importantly, this differential subgroup effect was not observed in the RAINBOW trial. Thus the effect observed in the REGARD trial was likely a chance finding related to imbalances in prognostic factors at baseline.

Table 60 summarizes the AEs by SOC by gender.

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Table 60 - REGARD: AEs by gender (by SOC)

SOC	Ramucirumab/BSC; n (%)		Placebo/BSC; n (%)	
	Males (n=169)	Females (n=67)	Males (n=77)	Females (n=38)
Gastrointestinal disorders	117 (69)	45 (67)	47 (61)	27 (71)
General disorders and administration site conditions	89 (53)	39 (58)	43 (56)	21 (55)
Metabolism and nutrition disorders	64 (38)	26 (39)	27 (35)	21 (55)
Investigations	47 (28)	21 (31)	13 (17)	8 (21)
Musculoskeletal and connective tissue disorders	42 (25)	14 (21)	15 (19)	11 (29)
Respiratory disorders	41 (24)	14 (21)	20 (26)	11 (29)
Blood and lymphatic system disorders	38 (22)	11 (16)	13 (17)	10 (26)
Vascular disorders	35 (21)	16 (24)	16 (21)	7 (18)
Nervous system disorders	28 (17)	20 (30)	12 (16)	12 (32)
Infections	28 (17)	12 (18)	11 (14)	7 (18)
Psychiatric disorders	23 (14)	6 (9)	9 (12)	7 (18)
Renal disorders	16 (9)	11 (16)	7 (9)	7 (18)
Injury and procedural complications	15 (9)	8 (12)	5 (6)	3 (8)
Hepatobiliary disorders	14 (8)	3 (4)	6 (8)	2 (5)
Skin and subcutaneous tissue disorders	13 (8)	12 (18)	6 (8)	2 (5)
Cardiac disorders	7 (4)	1 (1)	6 (8)	1 (3)
Neoplasms	6 (4)	1 (1)	3 (4)	1 (3)
Ear and labyrinth disorders	4 (2)	0	1 (1)	0
Endocrine disorders	4 (2)	0	0	0
Eye disorders	2 (1)	4 (6)	1 (1)	3 (8)
Procedures	1 (1)	1 (1)	1 (1)	0
Congenital disorders	2 (1)	0	0	0
Immune system disorders	1 (1)	1 (1)	0	1 (3)
Reproductive disorders	0	4 (6)	2 (2)	1 (3)

Overall, women experienced a higher incidence of nervous system and renal/urinary tract disorders SOCs. Four patients (one female) in the ramucirumab arm experienced Grade 3 events in the nervous system SOC (depressed level of consciousness, dizziness, and two events of lethargy) and 2 patients (both females) experienced Grade 4 coma and hyperammonemic encephalopathy. In the placebo arm, Grade 3 events (one female) were somnolence and peripheral sensory neuropathy. All other events were Grade 1-2, and most of them were headaches (ramucirumab arm 8% and 12% incidence in males and females respectively, and placebo arm 5% and 3 % in males and females respectively).

Grade 3-4 events in the renal/urinary system SOC were more frequent in the ramucirumab arm: there was one event each of hematuria, nephrolithiasis, proteinuria, renal failure, acute renal failure, ureteric obstruction, and ureteric perforation. Only one patient in the placebo arm experienced a Grade 3 event (acute renal failure). Grade 1-2 events in the ramucirumab arm included dysuria, proteinuria (2), urinary retention, urinary tract obstruction, renal failure, chronic renal failure, and acute renal failure. Grade 1-2 events in the placebo arm included

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dysuria (2), hydronephrosis, proteinuria, chronic renal failure, strangury, urinary incontinence, and urinary retention (2).

In the ramucirumab arm, women experienced higher incidences ($\geq 3\%$) when compared to men in the same arm of general conditions and administration site disorders, investigation abnormalities, injury and procedural complications, vascular disorders, skin disorders, eye disorders and reproductive disorders. Men in the ramucirumab experienced more respiratory disorders, blood disorders, musculoskeletal disorders, psychiatric disorders, hepatobiliary disorders, and cardiac disorders. Table 61 summarizes the incidences of AEs by preferred term by gender and arm.

Table 61 - REGARD: AEs by gender (by PT, incidence $\geq 10\%$)

PT	Ramucirumab/BSC; n (%) N=236				Placebo/BSC; n (%) N= 115			
	Males (n=169)		Females (n=67)		Males (n=77)		Females (n=38)	
	All Grades	Grades 3-5	All Grades	Grades 3-5	All Grades	Grades 3-5	All Grades	Grades 3-5
Decreased appetite	43 (25)	6 (4)	14 (21)	2 (3)	17 (22)	4 (5)	9 (24)	0
Fatigue	40 (24)	7 (4)	18 (27)	3 (4)	16 (21)	4 (5)	12 (32)	0
Abdominal pain	37 (22)	8 (5)	8 (12)	4 (6)	15 (19)	1 (1)	14 (37)	2 (5)
Nausea	33 (20)	2 (1)	12 (18)	1 (1)	17 (22)	0	13 (34)	1 (1)
Anemia	29 (17)	12 (7)	6 (9)	3 (4)	9 (12)	4 (5)	8 (21)	5 (13)
Vomiting	29 (17)	3 (2)	18 (27)	3 (4)	17 (22)	2 (3)	12 (32)	3 (8)
Constipation	27 (16)	1 (1)	9 (13)	0	21 (27)	2 (3)	5 (13)	1 (3)
Diarrhea	26 (15)	1 (1)	8 (12)	1 (1)	4 (5)	0	6 (16)	2 (5)
Hypertension	24 (14)	9 (5)	12 (18)	8 (12)	5 (6)	2 (3)	4 (11)	1 (3)
Dysphagia	21 (12)	3 (3)	4 (6)	2 (3)	9 (12)	4 (5)	3 (8)	1 (3)
Weight decreased	20 (12)	3 (2)	7 (10)	0	8 (10)	1 (1)	3 (8)	0
Abdominal upper pain	21 (12)	2 (1)	6 (9)	1 (1)	3 (4)	0	2 (5)	0
Asthenia	21 (12)	2 (1)	7 (10)	3 (4)	15 (19)	6 (8)	4 (11)	2 (5)
Cough	17 (10)	0	2 (3)	0	6 (8)	0	3 (8)	0
Dyspnea	14 (8)	3 (2)	8 (12)	1 (1)	11 (14)	6 (8)	4 (11)	1 (3)
Peripheral edema	12 (7)	1 (1)	8 (12)	0	8 (10)	2 (3)	2 (5)	0
Ascites	11 (7)	4 (2)	12 (18)	6 (9)	4 (5)	2 (3)	7 (18)	3 (8)
Headache	14 (8)	0	8 (12)	0	2 (3)	0	2 (5)	0
ALP increased	4 (2)	2 (1)	4 (6)	2 (3)	1 (1)	1 (1)	1 (3)	0
Back pain	15 (9)	2 (1)	3 (4)	1 (1)	6 (8)	1 (1)	5 (13)	2 (5)
Dysgeusia	4 (2)	0	3 (4)	0	0	0	6 (16)	0
Insomnia	11 (7)	1 (1)	2 (3)	0	4 (5)	0	4 (11)	0

Although there were some differences in the incidences of AEs by PT, differences $\geq 3\%$ in Grade 3-5 AEs in the ramucirumab arm were found in the following terms: anemia (males 7%, females 4%), hypertension (males 5%, females 12%), asthenia (males 1%, females 4%), and

ascites (males 2%, females 9%). However, in the placebo arm, Grade 3-5 anemia was reported in 5% men and 13% women, and asthenia in 8% men and 5% women.

In the placebo arm, men experienced more frequent Grade 3-5 asthenia and dyspnea. As in the ramucirumab arm, women experienced more frequent Grade 3-5 anemia and ascites.

Table 62 summarizes the AEs with fatal outcomes by gender. The most frequent cause of death in all subgroups was progression of disease. Death not listed as being due to progressive disease in the ramucirumab arm were 11% in men and 10% in women. Death not listed as being due to progressive disease in the placebo arm were 13% in men and 14% in women. However, as reviewed above in Section 7.3.1, it was difficult, in some cases, to establish if disease progression was the sole underlying cause of death. With certain toxicities, such as neutropenic sepsis, it was clear that the patient's death was associated with subsequent chemotherapy. However, some events, such as intestinal obstruction, perforations, gastric hemorrhage, etc, can be both related to either disease or therapy, or both may have been contributing factors.

Table 62 - REGARD: AEs with fatal outcome by gender

PT	Ramucirumab/BSC; N=236		Placebo/BSC; N= 115	
	Males (n=169)	Females (n=67)	Males (n=77)	Females (n=38)
Bacteremia/septic shock	1	0	1	0
Cardiac arrest	1	0	0	0
Cholangitis/cholestasis	2	0	0	0
Death/sudden death	2	2	1	0
Dehydration	1	0	0	0
Disease progression	5	4	3	4
Dyspnea/respiratory failure	0	1	3	0
Gastric hemorrhage	2	0	1	0
Gastrointestinal obstruction	1	0	1	0
Health deterioration	2	0	0	0
Intestinal perforation	2	0	1	0
Pneumonia	1	1	1	0
Multiorgan failure	1	3	1	0
Multiple injuries	1	0	0	0
Myocardial infarction	1	0	0	0
Pulmonary embolism	0	0	1	1
Renal failure	1	0	0	0
Total number of deaths	24 (14%)	11 (16%)	14 (18%)	5 (14%)

In summary, women in the ramucirumab experienced a similar incidence of AEs with fatal outcome; however, women in the placebo arm experienced more deaths related to disease progression.

Geographic Area

Geographic area was a stratification factor for randomization. Although the HR for the primary endpoint was below 1 in all three geographic strata, patients in the North America, Europe,

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Australia, and New Zealand region appeared to have a smaller magnitude of benefit when exposed to ramucirumab (HR for survival in this region is 0.896 [95% CI 0.667, 1.205], South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia HR is 0.464 [95% CI 0.265, 0.813], and the HR in the Asia region is 0.694 [95% CI 0.265, 1.818]). To further explore if there is any difference in toxicities that may have contributed to these differences in outcome, toxicity was analyzed by geographic region. Some subgroups were too small (e.g., there were only 18 patients in the ramucirumab arm and 8 patients in the placebo arm enrolled in Asia) and toxicity may be overrepresented.

Table 63 summarizes the AEs by body system analyzed by geographic region, where NA includes North America, Europe, Australia, and New Zealand, LA includes South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia, and AS is Asia.

Table 63 - REGARD: AEs by geographic region (by SOC)

SOC	Ramucirumab/BSC N=236; n (%)			Placebo/BSC N= 115, n (%)		
	NA N=164	LA N=54	AS N=18	NA N=78	LA N=29	AS N=8
Blood and lymphatic disorders	27 (16)	15 (28)	7 (39)	14 (18)	8 (28)	1 (13)
Cardiac disorders	7 (4)	1 (2)	0	5 (6)	2 (7)	0
Congenital and genetic disorders	1 (1)	0	1 (6)	0	0	0
Ear and labyrinth disorders	4 (2)	0	0	1 (1)	0	0
Endocrine disorders	3 (2)	1 (2)	0	0	0	0
Eye disorders	5 (3)	1 (2)	0	3 (4)	1 (3)	0
Gastrointestinal disorders	111 (68)	38 (70)	13 (72)	46 (59)	22 (76)	6 (75)
General disorders and administration site conditions	85 (52)	31 (57)	12 (67)	47 (60)	13 (45)	4 (50)
Hepatobiliary disorders	12 (7)	3 (6)	2 (11)	4 (5)	2 (7)	2 (25)
Immune disorders	1 (1)	1 (2)	0	0	1 (3)	0
Infections	26 (16)	7 (13)	7 (39)	11 (14)	7 (24)	0
Injury and procedural complications	16 (10)	4 (7)	3 (17)	8 (10)	0	0
Investigations	47 (29)	15 (28)	6 (33)	11 (14)	8 (28)	2 (25)
Metabolism and nutrition disorders	63 (38)	17 (31)	10 (56)	31 (40)	12 (41)	5 (63)
Musculoskeletal disorders	39 (24)	12 (22)	5 (28)	16 (21)	8 (28)	2 (25)
Neoplasms	3 (2)	1 (2)	3 (17)	4 (5)	0	0
Nervous system disorders	34 (21)	10 (19)	4 (22)	19 (24)	4 (14)	1 (13)
Psychiatric disorders	18 (11)	6 (11)	5 (28)	12 (15)	4 (14)	0
Renal and urinary disorders	17 (10)	5 (9)	5 (28)	7 (9)	6 (21)	1 (13)
Reproductive system disorders	3 (2)	1 (2)	0	2 (3)	0	1 (13)
Respiratory, thoracic and mediastinal disorders	47 (29)	10 (19)	3 (3)	21 (27)	10 (34)	0
Skin and subcutaneous tissue disorders	13 (8)	8 (15)	4 (22)	5 (6)	1 (3)	2 (2)
Surgical and medical procedures	2 (1)	0	0	1 (1)	0	0
Vascular disorders	38 (23)	9 (17)	4 (22)	16 (21)	5 (17)	2 (25)

In the North America/Europe/Australasia region patients in the ramucirumab experienced an increased incidence of gastrointestinal disorders (68% vs. 59% in the ramucirumab and placebo arms respectively) and investigation abnormalities when compared with patients in the placebo arm (29% vs. 14% in the ramucirumab and placebo arms respectively). However, when analyzed by PT, the majority of gastrointestinal events were Grade 1-2, and there were no significant differences in the incidences between Grade 3-5 events that support a difference in outcomes (see Table 64).

Table 64 - REGARD: Grade 3-5 gastrointestinal AEs in the North American region (incidence ≥ 2%)

PT	Ramucirumab N=164; n (%)	Placebo N=78; n (%)
Abdominal pain	8 (5)	2 (3)
Ascites	7 (4)	3 (4)
Dysphagia	5 (3)	5 (6)
Vomiting	4 (2)	3 (3)
Intestinal obstruction	4 (2)	0
Constipation	1 (1)	2 (3)
Gastric hemorrhage**	5 (3)	3 (1)

* Includes the terms intestinal obstruction and large intestinal obstruction

** Gastric hemorrhage includes the terms gastric hemorrhage, gastrointestinal hemorrhage, upper gastrointestinal hemorrhage, and hematemesis.

Similar results were obtained when analyzing the investigations SOC. The majority of events were Grades 1-2. Grade 3 events were observed at higher incidence in the ramucirumab arm (12%) when compared to the placebo arm (5%), but there was not a single cause or predominant type of investigation. Events were weight decreased, ALT/AST increase, bilirubin increase, ECOG PS deterioration, etc. There were no Grade 4-5 events in this SOC.

In conclusion, it does not appear that the (possible) differences in outcome in the North American region were related to excess toxicity in the ramucirumab arm. Notably, these differences in effect were not replicated in the RAINBOW trial.

7.5.4 Drug-Disease Interactions

There are several prognostic disease characteristics that can affect outcome in patients with gastric cancer including histology, differentiation grade, presence of peritoneal metastases. The Applicant selected location of the primary tumor (gastric [including tumors of the gastric cardia that extend into the GEJ] vs. GEJ [including tumors of the distal esophagus that extend into the GEJ, and tumors involving the GEJ when precise identification of the organ of origin is not possible]) as a stratification factor. For overall survival, the HR of ramucirumab vs. placebo is 0.823 (95% CI 0.608, 1.114) for the gastric tumors and 0.756 (95% CI 0.472, 1.211) for the GEJ tumors. This section will focus on the safety analysis by location of tumor. Table 65 summarizes the adverse events by arm and tumor location.

Table 65 - REGARD: AEs by tumor location (by SOC)

SOC	Ramucirumab/BSC N=236; n (%)		Placebo/BSC N= 115, n (%)	
	Gastric N= 176	GEJ N= 60	Gastric N= 86	GEJ N= 29
Blood and lymphatic disorders	38 (22)	11 (18)	19 (22)	4 (14)
Cardiac disorders	7 (4)	1 (2)	6 (7)	1 (3)
Congenital and genetic disorders	1 (1)	1 (2)	0	0
Ear and labyrinth disorders	2 (1)	2 (3)	0	1 (3)
Endocrine disorders	0	4 (7)	0	0
Eye disorders	6 (3)	0	2 (2)	2 (7)
Gastrointestinal disorders	115 (65)	47 (78)	57 (66)	17 (59)
General disorders and administration site conditions	94 (53)	34 (57)	45 (52)	19 (66)
Hepatobiliary disorders	10 (6)	7 (12)	7 (8)	1 (3)
Immune disorders	2 (1)	0	1 (1)	0
Infections	29 (16)	11 (18)	12 (14)	6 (21)
Injury and procedural complications	18 (10)	5 (8)	5 (6)	3 (10)
Investigations	53 (30)	15 (25)	17 (20)	4 (14)
Metabolism and nutrition disorders	60 (34)	30 (50)	37 (43)	11 (38)
Musculoskeletal disorders	40 (23)	16 (27)	16 (19)	10 (34)
Neoplasms	4 (2)	3 (5)	1 (1)	3 (10)
Nervous system disorders	32 (18)	16 (27)	18 (21)	6 (21)
Psychiatric disorders	19 (11)	10 (17)	10 (12)	6 (21)
Renal and urinary disorders	18 (10)	9 (15)	11 (13)	3 (10)
Reproductive system disorders	3 (2)	1 (2)	3 (3)	0
Respiratory, thoracic and mediastinal disorders	43 (24)	17 (28)	22 (26)	9 (31)
Skin and subcutaneous tissue disorders	19 (11)	6 (10)	5 (6)	3 (10)
Surgical and medical procedures	1 (1)	1 (2)	1 (1)	0
Vascular disorders	35 (20)	16 (27)	16 (19)	7 (24)

Overall, patients with gastric tumors had an increased incidence of blood and lymphatic disorders and investigations abnormalities. Patients with GEJ tumors had increased incidence rates of infections, musculoskeletal disorders, psychiatric disorders, respiratory disorders, and vascular disorders.

In the ramucirumab arm, patients with GEJ tumors had an increased incidence ($\geq 3\%$) of gastrointestinal disorders, hepatobiliary disorders, musculoskeletal disorders, metabolism and nutrition disorders, nervous system disorders, psychiatric disorders, respiratory disorders, and vascular disorders. Of these SOCs, only musculoskeletal disorders, respiratory disorders, and vascular disorders AEs were also more frequently observed in the placebo arm with GEJ tumors. Table 66 summarizes the AEs by preferred term by tumor location. Because of the small numbers of patients, only events that occurred in at least 2 patients are listed.

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Table 66 - REGARD: Grade 3-5 AEs by tumor location (by PT, at least 2 patients per event)

PT	Ramucirumab N=236; n (%)		Placebo N=115; (n %)	
	Gastric N=176	GEJ N=60	Gastric N=86	GEJ N=29
Anemia	12 (7)	3 (5)	6 (7)	3 (10)
Hypertension	10 (6)	7 (12)	2 (2)	1 (3)
Abdominal pain	11 (6)	1 (2)	3 (3)	0
Ascites	8 (5)	2 (3)	5 (6)	0
Fatigue	7 (4)	3 (5)	1 (1)	3 (10)
Decreased appetite	6 (3)	2 (3)	1 (1)	3 (10)
Hyponatremia	6 (3)	2 (3)	1 (1)	0
Dehydration	5 (3)	0	2 (2)	2 (7)
Vomiting	6 (3)	0	3 (3)	2 (7)
Multi-organ failure	3 (2)	3 (5)	1 (1)	0
Hypokalemia	3 (2)	2 (3)	1 (1)	0
Asthenia	4 (2)	1 (2)	7 (8)	1 (3)
Dyspnea	3 (2)	1 (2)	6 (7)	1 (3)
Back pain	3 (2)	0	1 (1)	2 (7)
Pulmonary embolism	3 (2)	0	2 (2)	1 (3)
Dysphagia	2 (1)	3 (5)	3 (3)	2 (7)
General deterioration	1 (1)	3 (5)	1 (1)	0
Pain	1 (1)	3 (5)	0	0
ALT increase	1 (1)	2 (3)	1 (1)	0
AST increase	1 (1)	2 (3)	2 (2)	0
Intestinal obstruction	2 (1)	2 (3)	0	0
Pneumonia	2 (1)	2 (3)	1 (1)	1 (3)
Sepsis	2 (1)	1 (2)	1 (1)	1 (3)
Hiccups	2 (1)	0	0	1 (3)
Hyperbilirubinemia	1 (1)	0	3 (3)	0
Thrombocytopenia	1 (1)	0	3 (3)	0
Lethargy	0	2 (3)	0	0
Neutropenia	0	2 (3)	0	0
Mental status changes	0	0	0	2 (7)
Urinary tract infection	0	0	1 (1)	2 (7)

Patients with GEJ tumors in the ramucirumab arm experienced an increased incidence rate ($\geq 3\%$) of Grade 3-5 hypertension, dysphagia, pain, and general deterioration. Patients with gastric tumors in the ramucirumab arm experienced an increased incidence rate ($\geq 3\%$) of Grade 3-5 of abdominal pain, dehydration, and vomiting.

In the placebo arm, patients with GEJ tumors appeared to have experienced excess toxicity when compared with patients with gastric tumors; however, due to the small number of patients with GEJ tumors the toxicity is likely overestimated.

In conclusion, with the exception of hypertension, the increased incidence of some toxicities appeared to be related to tumor location (i.e., dysphagia is more common in GEJ tumors, while

abdominal pain is more frequent in gastric tumors). As expected, hypertension was observed more frequently in patients in the ramucirumab arm, but with higher incidence in patients with GEJ tumors.

7.5.5 Drug-Drug Interactions

The REGARD study administered ramucirumab or placebo to all subjects without concomitant chemotherapy. No DDI analyses were conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No animal studies have been performed to test ramucirumab for potential carcinogenicity or genotoxicity, following ICH S6 and ICH S9 guidance.

7.6.2 Human Reproduction and Pregnancy Data

Reproductive and developmental toxicity studies of ramucirumab have not been conducted. Eli Lilly based the decision of not conducting these studies on meeting with FDA and ICH S9 guidance, which emphasizes that literature reviews of anticancer pharmaceuticals and science-based assessments can be alternatively used, and that no pre-clinical studies are necessary for marketing approval.

It is known that disruption of VEGF/VEGFR signaling and angiogenesis can impair the proper functioning and/or development of tissues critical for embryo-fetal development leading to embryo-fetal lethality and teratogenicity; Eli Lilly included a review of the literature supporting this statement (please see Dr. Kashar and Dr. Helms Pharmacology/toxicology review).

Lilly proposed a Pregnancy Category C for ramucirumab. Women are advised to avoid the use of ramucirumab if pregnant and only use if the potential benefit to the mother justifies the potential risk to the fetus or its postnatal development. Women of child bearing potential or women who become pregnant during ramucirumab treatment should be counseled of the potential risk for maintaining pregnancy, risk to the fetus, or risk to postnatal development. Based on the half-life of ramucirumab, the label states that pregnancy should be avoided while receiving ramucirumab and for at least 3 months after the last dose of ramucirumab.

7.6.3 Pediatrics and Assessment of Effects on Growth

Ramucirumab was granted orphan designation for the treatment of gastric/GEJ cancer; thus PREA requirements are waived. No studies have been conducted in pediatric patients.

As expected and observed in other products targeting VEGF, monkey toxicology studies showed bone growth plate pathology, although this pathology is generally not considered relevant to an adult patient population with fused bone growth plates. In cynomolgus monkeys, anatomical pathology revealed thickening and osteochondropathy on the epiphyseal growth plate at all doses tested (5-50 mg/kg). The lowest weekly dose tested in the cynomolgus monkey was 1.2 times the recommended dose of ramucirumab as a single-agent (8 mg/kg every 2 weeks).

The ramucirumab label states that safety and effectiveness of ramucirumab in pediatric patients have not been established. In animal studies, effects on epiphyseal growth plates were identified

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / 120-day Safety Update

On December 12, 2013, Eli Lilly submitted the 120-day safety update (STN 125477/0.16). The AE dataset contained data for the 14 patients who were on treatment at the time of the initial data cut-off, all receiving ramucirumab. At the time of study data cut off there was one patient still receiving placebo; this patient was unblinded and discontinued treatment and therefore there were no AEs to report (from this patient).

There were 174 AEs recorded for these 14 patients. There was one fatal event (pulmonary sepsis). There was one Grade 4 event (worsening anorexia, same patient). Grade 3 events were hyponatremia (3 patients), hypertension (4 patients), neutropenia, vomiting, anemia, asthenia, hospitalization, and one event each (all in the same patient) of ALT/AST/bilirubin increase.

Most events were Grade 1-2. Table 67 summarizes the most commonly observed Grade 1-2 events (at least 2 patients). The complete listing can be found in Table 75 in the Appendices section.

Table 67 - REGARD: Most common Grade 1-2 AEs in the 120-day safety update

Preferred Term	N
Abdominal pain	4
Abdominal pain upper	4
Anemia	3
Asthenia	4
Cough	4
Decreased appetite	6

Diarrhea	3
Epistaxis	2
Fatigue	2
Hypertension	3
Influenza	2
Nausea	2
Peripheral edema	2
Pyrexia	2
Respiratory disorder	2
Thrombocytopenia	3
Vomiting	2
Weight decreased	2

The safety data analyzed in the 120-day safety update in the REGARD study was consistent with the toxicity profile described above in the safety analysis.

The 120-day safety update also included a brief discussion of 3 phase 1 or 2 studies (I4T-IE-JVCA, I4T-IEJVCC, and I4T-IE-JVBX, all in combination with docetaxel or paclitaxel) that had data cutoffs between 31 December 2012 and 31 July 2013 and therefore were not included in the integrated summary of safety. The 4-month safety update on REGARD as well the additional ramucirumab studies reported were consistent with the safety profile submitted in the BLA. No new safety findings that may be included in the label were identified.

8 Postmarket Experience

Not applicable for this new molecular entity.

9 Appendices

Table 68 - REGARD: Study flowchart (modified from the submission)

Procedure	Pre-Treatment Evaluations ^a	Every 2 Weeks ^a	Every 6 Weeks	End of Therapy	30 day Follow-Up ^c	Extended Follow-Up
Eligibility assessments						
Informed consent	X ^d					
Medical/oncologic history	X					
Pregnancy test	X ^e		X ^s	X	X	
ECG	X ^f					
ECOG PS	X	X		X	X	
Concomitant medications	X ^g	X		X	X	
Echocardiogram / MUGA	X ^h					
Safety assessments						
Physical exam	X ⁱ	X ⁱ		X ⁱ	X ⁱ	
Vital signs	X	X ^p		X	X	
Adverse events	X ^j	X		X	X	X ^w
Laboratory tests						
Hematology profile	X	X ^q		X	X	
Coagulation profile	X		X	X	X	
Chemistry profile	X	X		X	X	
Urinalysis ^k	X ^k		X ^k	X ^k	X ^k	
Anti-ramucirumab antibody assessment	X ^l		X ^t		X ^t	
24-hour urine collection	X ^m					
Efficacy / Anti-tumor activity assessments						
Imaging (CT/MRI)	X ⁿ		X ^u	X ^u		X ^u
Tumor assessments	X ⁿ		X ^u	X ^u		X ^u
Tumor tissue	X ^o	X ^r				
EORTC-QLQ-C30			X ^v			
Survival information						X ^x
Clinical drug supplies						
Administer ramucirumab or placebo		X ^y				

- a. Pretreatment evaluations performed within 14 days prior to randomization, unless otherwise specified.
- b. Cycles were defined as every 2 weeks with no break between cycles.
- c. End of therapy evaluations performed at discontinuation of ramucirumab / placebo. Patients were to be followed for at least 30 days following cessation of ramucirumab / placebo for safety. A follow-up evaluation was to be conducted no less than 30 days and no more than 45 days after last dose of ramucirumab / placebo.
- d. Consent was required prior to any study-specific treatment evaluations.
- e. Negative serum pregnancy test required within 7 days of randomization.
- f. ECG was to be obtained within 28 days of randomization.
- g. Included all medications taken within 30 days prior to the first dose of ramucirumab or placebo.
- h. Required only for patients who received prior anthracycline therapy (within 28 days of randomization).
- i. Screening physical exam required within 14 days of randomization. Height and BSA performed only during pre-treatment evaluation.
- j. Pre-existing toxicities were to be recorded as part of the pre-treatment medical history.
- k. Twenty-four hour urine collection required if ≥ 2+ proteinuria on dipstick or routine urinalysis.
- l. Baseline immunogenicity sample also used to assess biomarkers including VEGF, soluble VEGFR-1, and soluble VEGFR-2 and were to be collected within 21 days prior to the first dose of ramucirumab or placebo

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- m. Only required in serum creatinine is 1.5 times the upper limit of normal
- n. Baseline imaging within 14 days of randomization and every 6 weeks (+/- 3 days) until documented progression
- o. Previously archived tumor tissue, if available, will be collected prior to the first dose of study therapy
- p. Included temperature, pulse rate, respiration rate, and blood pressure (performed before and after each infusion).
- q. If the hemoglobin decrease to < 9 g/dL and there are signs or symptoms of bleeding, a hematology profile was to be obtained weekly until the hemoglobin was ≥ 9 g/dL and bleeding signs or symptoms have resolved or adequately investigated.
- r. Collected if tumor tissue obtained at any time during the study as routine clinical care.
- s. Every 6 weeks or in accordance with local regulations, whichever was of shorter duration.
- t. Anti-product ant body samples were collected from all patients prior to cycle 4 and cycle 7 infusions and at the 30 day follow-up visit. Samples were also collected at the time of an infusion reaction, at the time of the resolution of the infusion reaction, and 30 days following the event.
- u. Imaging studies of all sites of known disease were obtained every six weeks (+/- three days) until documented progression.
- v. Performed prior to the infusion of cycles 4, 6, and 10 only.
- w. Adverse events considered at least possibly related to ramucirumab / placebo were to be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
- x. OS was followed every two months until the required 268 events were reported. Subsequently, all patients remaining on study were to be followed at least one year from their date of discontinuation of IP.
- y. In order to allow flexibility with patient schedules, infusions were permitted within 3 days before or 3 days after each scheduled infusion. Deviations were discouraged and required sponsor (or designee) approval.

Table 69 - REGARD: AEs with an incidence 2-4% (by PT)

PT	Ramucirumab/BSC N=236		Placebo/BSC N=117	
	N	%	N	%
Abdominal pain upper	27	11	5	4
Hyponatremia	13	6	2	2
Dehydration	12	5	4	3
Pyrexia	10	4	5	4
Abdominal distension	9	4	4	3
Hematemesis	9	4	3	3
Thrombocytopenia	10	4	3	3
Alanine aminotransferase increased	9	4	2	2
Aspartate aminotransferase increased	9	4	2	2
Mucosal inflammation	9	4	1	1
Neutropenia	9	4	1	1
Pain	10	4	1	1
Rash	9	4	1	1
Dyspepsia	6	3	7	6
Dysgeusia	7	3	6	5
Pain in extremity	8	3	6	5
Anxiety	7	3	3	3
Arthralgia	8	3	4	3
Depression	6	3	3	3
Hiccups	6	3	3	3
Hypocalcemia	7	3	3	3
Musculoskeletal pain	7	3	3	3
Neuropathy peripheral	6	3	3	3
Proteinuria	7	3	3	3
Renal failure acute	6	3	4	3
Blood alkaline phosphatase increased	8	3	2	2
Blood bilirubin increased	6	3	1	1
Medication error	7	3	1	1
Multi-organ failure	6	3	1	1
Musculoskeletal chest pain	7	3	1	1

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PT	Ramucirumab/BSC N=236		Placebo/BSC N=117	
	N	%	N	%
Nasopharyngitis	6	3	0	0
Dizziness	4	2	6	5
Hypotension	5	2	6	5
Pneumonia	5	2	3	3
Pulmonary embolism	4	2	3	3
Chills	4	2	2	2
Fall	4	2	2	2
Hyperkalemia	4	2	2	2
Pleural effusion	5	2	2	2
Productive cough	4	2	2	2
Dry mouth	4	2	1	1
Dry skin	5	2	1	1
General physical health deterioration	5	2	1	1
Jaundice	4	2	1	1
Lethargy	4	2	1	1
Oral candidiasis	4	2	1	1
Pruritus	4	2	1	1
Underdose	4	2	1	1
Blood creatinine increased	4	2	0	0
Death	4	2	0	0
Hypophosphatemia	5	2	0	0
Intestinal obstruction	5	2	0	0
Weight increased	5	2	0	0
Urinary tract infection	2	1	5	4
Deep vein thrombosis	3	1	3	3
Flatulence	2	1	3	3
Hyperbilirubinemia	3	1	3	3
Myalgia	2	1	4	3
Tachycardia	3	1	4	3
Urinary retention	2	1	3	3
Dysuria	2	1	2	2
Gastrointestinal hemorrhage	3	1	2	2
Hematuria	3	1	2	2
Hypoglycaemia	3	1	2	2
Hypomagnesemia	2	1	2	2
Joint swelling	2	1	2	2
Non-cardiac chest pain	3	1	2	2
Sepsis	3	1	2	2

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Table 70 - REGARD: Non-fatal Grade 3-4 AES (by HLT), incidence ≥ 1%

HLT	<i>Ramucirumab; n (%)</i> <i>N=236</i>		<i>Placebo; n (%)</i> <i>N=115</i>	
	<i>Number of subjects</i>	<i>%</i>	<i>Number of subjects</i>	<i>%</i>
Vascular hypertensive disorders NEC	17	7.2	3	2.61
Asthenic conditions	15	6.36	12	10.43
Anemias NEC	15	6.36	9	7.83
Gastrointestinal and abdominal pains (excl oral and throat)	14	5.93	3	2.61
Peritoneal and retroperitoneal disorders	10	4.24	5	4.35
Nausea and vomiting symptoms	8	3.39	5	4.35
Appetite disorders	8	3.39	4	3.48
Potassium imbalance	8	3.39	3	2.61
General signs and symptoms NEC	8	3.39	1	0.87
Sodium imbalance	8	3.39	1	0.87
Liver function analyses	7	2.97	4	3.48
Gastrointestinal stenosis and obstruction NEC	6	2.54	0	0
Gastrointestinal signs and symptoms NEC	5	2.12	5	4.35
Physical examination procedures and organ system status	5	2.12	2	1.74
Non-site specific gastrointestinal hemorrhages	5	2.12	1	0.87
Pain and discomfort NEC	5	2.12	0	0
Total fluid volume decreased	4	1.69	4	3.48
Tissue enzyme analyses NEC	4	1.69	1	0.87
Breathing abnormalities	3	1.27	7	6.09
Musculoskeletal and connective tissue pain and discomfort	3	1.27	4	3.48
Cholestasis and jaundice	3	1.27	3	2.61
Sepsis, bacteremia, viremia and fungemia NEC	3	1.27	2	1.74
Disturbances in consciousness NEC	3	1.27	1	0.87
Pulmonary thrombotic and embolic conditions	3	1.27	1	0.87
Neutropenias	3	1.27	0	0
Pneumothorax and pleural effusions NEC	3	1.27	0	0
White blood cell analyses	3	1.27	0	0
Lower respiratory tract and lung infections	2	0.85	3	2.61
Diarrhea (excl infective)	2	0.85	2	1.74
Renal failure and impairment	2	0.85	2	1.74

HLT	Ramucirumab; n (%) N=236		Placebo; n (%) N=115	
	Number of subjects	%	Number of subjects	%
Vascular hypertensive disorders NEC	17	7.2	3	2.61
Asthenic conditions	15	6.36	12	10.43
Gastrointestinal atonic and hypomotility disorders NEC	1	0.42	3	2.61
Thrombocytopenias	1	0.42	3	2.61
Edema NEC	1	0.42	2	1.74

Table 71 - Preferred terms included in the adverse events of special interest (copied from applicant's submission)

Adverse Drug Reactions of Special Interest Composite Term	MedDRA Preferred Terms
Infusion-related reactions	Infusion-related reaction; anaphylactic reaction; drug hypersensitivity; hypersensitivity; allergic reaction; anaphylaxis
Hypertension	Blood pressure diastolic increased; blood pressure increased; hypertension; hypertensive crisis; orthostatic hypertension; prehypertension
Proteinuria	Protein urine present; nephritic syndrome; proteinuria; urine protein, quantitative
Arterial thromboembolic events	Acute coronary syndrome; acute myocardial infarction; angina pectoris; arterospasm coronary; cardiac arrest; cardio-respiratory arrest; coronary artery disease; myocardial infarction; cerebral ischemia; embolic stroke; transient ischemic attack; embolism arterial; femoral artery occlusion; ischemia; arterial thrombosis; cerebral circulatory failure; cerebral infarction; cerebrovascular accident; ECG sings of myocardial ischemia; intestinal ischemia; myocardial ischemia; peripheral vascular disorder; retinal ischemia; troponin I increased
Venous thromboembolic events	Catheter thrombosis; pulmonary embolism; deep vein thrombosis; embolism; jugular vein thrombosis; pelvic venous thrombosis; subclavian vein thrombosis; thrombosis; vena cava thrombosis; atrial thrombosis; portal vein thrombosis; superior vena caval occlusion; thrombosis in device; venous thrombosis; venous thrombosis limb
Bleeding/hemorrhagic events	Ear hemorrhage; conjunctival hemorrhage; eye hemorrhage; retinal hemorrhage; scleral hemorrhage; anal hemorrhage; duodenal ulcer hemorrhage; gastric varices hemorrhage; gastrointestinal hemorrhage; gingival bleeding; hematemesis; hematocchezia; hemorrhoidal hemorrhage; melena; mouth hemorrhage; rectal hemorrhage; upper gastrointestinal hemorrhage; catheter site hematoma; catheter site hemorrhage; infusion site hematoma; infusion site hemorrhage; injection site hemorrhage; mucosal hemorrhage; incision site hemorrhage; post procedural hematoma; post procedural hemorrhage; muscle hemorrhage; uterine hemorrhage; vaginal hemorrhage; epistaxis; hemoptysis; pulmonary hemorrhage; ecchymosis; hemorrhage subcutaneous; petechiae; hematoma; hemorrhage; wound hemorrhage; abdominal wall hematoma; anastomotic hemorrhage; blood urine; bloody discharge; diarrhea hemorrhagic; duodenitis hemorrhagic

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Adverse Drug Reactions of Special Interest Composite Term	MedDRA Preferred Terms
	gastric hemorrhage; hemothorax; hepatic hemorrhage; injection site hematoma; intra-abdominal hematoma; intra-abdominal hemorrhage; intracranial tumor hemorrhage; large intestinal hemorrhage; laryngeal hemorrhage; lower gastrointestinal hemorrhage; Mallory-Weiss syndrome; nail bed bleeding; occult blood positive; esophageal hemorrhage; esophageal varices hemorrhage; periorbital hematoma; peritoneal hemorrhage; post-procedural hematuria; procedural hemorrhage; respiratory tract hemorrhage; retroperitoneal hemorrhage; skin hemorrhage; small intestinal hemorrhage; spinal cord hemorrhage; subarachnoid hemorrhage; ulcer hemorrhage; vessel puncture site hematoma; vitreous hemorrhage
Gastrointestinal perforation	Gastrointestinal perforation; intestinal perforation; appendicitis perforated; diverticular perforation; duodenal perforation; gastric perforation; large intestine perforation; esophageal perforation; small intestinal perforation
Congestive heart failure in patients who received ramucirumab in combination with mitoxantrone or following prior anthracycline therapy	Cardiac failure; cardiac failure acute; cardiac failure congestive; diastolic dysfunction; ejection fraction; ejection fraction decreased; hypertensive cardiomyopathy; left ventricular dysfunction; multiple gated acquisition scan abnormal; right ventricular dysfunction; ventricular dysfunction
Liver injury/failure	Acute graft versus host disease in liver; acute hepatic failure; acute yellow liver atrophy; alanine aminotransferase; alanine aminotransferase abnormal; alanine aminotransferase increased; allergic hepatitis; ammonia abnormal; ammonia increased; aspartate aminotransferase; aspartate aminotransferase abnormal; aspartate aminotransferase increased; asterixis; autoimmune hepatitis; bile output abnormal; bile output decreased; biliary cirrhosis; biliary cirrhosis primary; biliary fibrosis; bilirubin conjugated abnormal; bilirubin conjugated increased; bilirubin excretion disorder; biopsy liver abnormal; blood bilirubin increased; blood bilirubin unconjugated increased; Child-Pugh-Turcotte score increased; cholemia; cholestasis; cholestatic liver injury; cholestatic pruritus; chronic hepatic failure; chronic hepatitis; coma hepatic; gallbladder varices; gamma-glutamyltransferase abnormal; gamma-glutamyltrasnferase increased; gastric varices; gastric varices hemorrhage; graft-versus host disease in liver; granulomatous liver disease; hepatectomy; hepatic artery flow decreased; hepatic atrophy; hepatic calcification; hepatic cirrhosis; hepatic congestion; hepatic encephalopathy; hepatic encephalopathy prophylaxis; hepatic enzyme abnormal; hepatic enzyme decreased; hepatic enzyme increased; hepatic failure; hepatic fibrosis; hepatic function abnormal; hepatic hydrothorax; hepatic infiltration eosinophilic; hepatic lesion; hepatic necrosis; hepatic pain; hepatic sequestration; hepatic steatosis; hepatic vascular resistance increased; hepatitis; hepatitis acute; hepatitis cholestatic; hepatitis chronic active; hepatitis chronic persistent

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Table 72 - REGARD: Narrow SMQ analyses (MAED)

<i>SMQ (Narrow Search)</i>	<i>Ramucirumab (N=236)</i>		<i>Placebo (N=115)</i>		<i>Ramucirumab vs. Placebo</i>	
	<i>N</i>	<i>%</i>	<i>N</i>	<i>%</i>	<i>RR</i>	<i>P-value</i>
(1) Acute renal failure	8	3.39	4	3.48	0.975	1
(1) Cardiac failure	2	0.85	0	0	2.447	1
(1) Hepatic disorders	47	19.92	18	15.65	1.272	0.381
(2) Drug related hepatic disorders - comprehensive search	47	19.92	18	15.65	1.272	0.381
(3) Drug related hepatic disorders - severe events only	26	11.02	11	9.57	1.152	0.853
(4) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	26	11.02	11	9.57	1.152	0.853
(3) Liver related investigations, signs and symptoms	41	17.37	17	14.78	1.175	0.646
(3) Cholestasis and jaundice of hepatic origin	9	3.81	5	4.35	0.877	0.779
(3) Liver-related coagulation and bleeding disturbances	1	0.42	0	0	1.468	1
(2) Liver infections	0	0	1	0.87	0.163	0.328
(1) Acute pancreatitis	1	0.42	0	0	1.468	1
(1) Agranulocytosis	1	0.42	2	1.74	0.244	0.251
(1) Angioedema	4	1.69	0	0	4.405	0.308
(1) Hematopoietic cytopenias	22	9.32	7	6.09	1.531	0.409
(2) Hematopoietic cytopenias affecting more than one type of blood cell	0	0	2	1.74	0.098	0.107
(2) Hematopoietic erythropenia	1	0.42	0	0	1.468	1
(2) Hematopoietic leukopenia	12	5.08	2	1.74	2.924	0.157
(2) Hematopoietic thrombocytopenia	11	4.66	3	2.61	1.787	0.562
(1) Peripheral neuropathy	7	2.97	5	4.35	0.682	0.538
(1) Depression and suicide/self-injury	8	3.39	3	2.61	1.299	1
(2) Depression (excl suicide and self injury)	8	3.39	3	2.61	1.299	1
(1) Hemorrhages	32	13.56	13	11.3	1.199	0.613
(2) Hemorrhage terms (excl laboratory terms)	32	13.56	13	11.3	1.199	0.613
(1) Hyperglycemia/new onset diabetes mellitus	3	1.27	1	0.87	1.462	1
(1) Interstitial lung disease	1	0.42	0	0	1.468	1
(1) Ischemic heart disease	2	0.85	0	0	2.447	1
(2) Myocardial infarction	1	0.42	0	0	1.468	1
(2) Other ischemic heart disease	2	0.85	0	0	2.447	1
(1) Taste and smell disorders	8	3.39	6	5.22	0.65	0.399
(1) Cardiac arrhythmias	1	0.42	2	1.74	0.244	0.251
(2) Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)	1	0.42	2	1.74	0.244	0.251

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SMQ (Narrow Search)	Ramucirumab (N=236)		Placebo (N=115)		Ramucirumab vs. Placebo	
	N	%	N	%	RR	P-value
(3) Bradyarrhythmias (incl conduction defects and disorders of sinus node function)	1	0.42	2	1.74	0.244	0.251
(4) Disorders of sinus node function	0	0	1	0.87	0.163	0.328
(4) Conduction defects	1	0.42	1	0.87	0.487	0.549
(1) Cerebrovascular disorders	2	0.85	0	0	2.447	1
(2) Central nervous system hemorrhages and cerebrovascular conditions	2	0.85	0	0	2.447	1
(3) Ischemic cerebrovascular conditions	2	0.85	0	0	2.447	1
(3) Hemorrhagic cerebrovascular conditions	1	0.42	0	0	1.468	1
(1) Retroperitoneal fibrosis	2	0.85	2	1.74	0.487	0.6
(1) Shock	2	0.85	1	0.87	0.975	1
(2) Shock-associated circulatory or cardiac conditions (excl torsade de pointes)	1	0.42	0	0	1.468	1
(2) Hypovolemic shock conditions	1	0.42	0	0	1.468	1
(2) Toxic-septic shock conditions	0	0	1	0.87	0.163	0.328
(1) Embolic and thrombotic events	15	6.36	8	6.96	0.914	0.821
(2) Embolic and thrombotic events, arterial	1	0.42	0	0	1.468	1
(2) Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous	4	1.69	3	2.61	0.65	0.687
(2) Embolic and thrombotic events, venous	10	4.24	6	5.22	0.812	0.786
(1) Malignancies	8	3.39	6	5.22	0.65	0.399
(2) Malignant or unspecified tumors	3	1.27	4	3.48	0.365	0.223
(3) Malignant tumors	3	1.27	3	2.61	0.487	0.398
(3) Tumors of unspecified malignancy	0	0	1	0.87	0.163	0.328
(2) Malignancy related conditions	1	0.42	0	0	1.468	1
(2) Malignancy related therapeutic and diagnostic procedures	4	1.69	2	1.74	0.975	1
(1) Extrapyramidal syndrome	1	0.42	0	0	1.468	1
(2) Parkinson-like events	1	0.42	0	0	1.468	1
(1) Gastrointestinal perforation, ulceration, hemorrhage or obstruction	37	15.68	13	11.3	1.387	0.33
(2) Gastrointestinal obstruction	16	6.78	4	3.48	1.949	0.326
(2) Gastrointestinal ulceration	1	0.42	0	0	1.468	1
(2) Gastrointestinal perforation	5	2.12	2	1.74	1.218	1
(2) Gastrointestinal hemorrhage	15	6.36	7	6.09	1.044	1
(1) Oropharyngeal disorders	16	6.78	5	4.35	1.559	0.475
(2) Oropharyngeal infections	6	2.54	2	1.74	1.462	1
(2) Oropharyngeal allergic conditions	1	0.42	0	0	1.468	1
(2) Gingival disorders	1	0.42	0	0	1.468	1
(2) Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic	11	4.66	3	2.61	1.787	0.562
(1) Thrombophlebitis	2	0.85	0	0	2.447	1

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SMQ (Narrow Search)	Ramucirumab (N=236)		Placebo (N=115)		Ramucirumab vs. Placebo	
	N	%	N	%	RR	P-value
(1) Acute central respiratory depression	3	1.27	4	3.48	0.365	0.223
(1) Biliary disorders	18	7.63	8	6.96	1.096	1
(2) Functional, inflammatory and gallstone related biliary disorders	17	7.2	8	6.96	1.035	1
(3) Biliary system related investigations, signs and symptoms	13	5.51	6	5.22	1.056	1
(3) Gallbladder related disorders	2	0.85	0	0	2.447	1
(3) Bile duct related disorders	2	0.85	2	1.74	0.487	0.6
(3) Site unspecified biliary disorders	9	3.81	5	4.35	0.877	0.779
(2) Infectious biliary disorders	4	1.69	1	0.87	1.949	1
(1) Pulmonary hypertension	1	0.42	0	0	1.468	1
(1) Noninfectious encephalopathy/delirium	1	0.42	0	0	1.468	1
(1) Accidents and injuries	6	2.54	2	1.74	1.462	1
(1) Extravasation events (injections, infusions and implants)	1	0.42	0	0	1.468	1
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	137	58.05	67	58.26	0.996	1
(2) Gastrointestinal nonspecific inflammation	3	1.27	0	0	3.426	0.554
(2) Gastrointestinal nonspecific dysfunction	7	2.97	7	6.09	0.487	0.243
(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	135	57.2	65	56.52	1.012	0.909
(1) Hyponatremia/SIADH	14	5.93	2	1.74	3.411	0.102
(1) Ischemic colitis	1	0.42	1	0.87	0.487	0.549
(1) Hemodynamic edema, effusions and fluid overload	48	20.34	22	19.13	1.063	0.887
(1) Hypertension	38	16.1	9	7.83	2.057	0.044
(1) Thyroid dysfunction	3	1.27	0	0	3.426	0.554
(2) Hypothyroidism	3	1.27	0	0	3.426	0.554
(1) Hearing and vestibular disorders	4	1.69	1	0.87	1.949	1
(2) Hearing impairment	3	1.27	1	0.87	1.462	1
(2) Vestibular disorders	1	0.42	0	0	1.468	1
(1) Conjunctival disorders	2	0.85	1	0.87	0.975	1
(1) Lacrimal disorders	3	1.27	1	0.87	1.462	1
(1) Periorbital and eyelid disorders	1	0.42	1	0.87	0.487	0.549
(1) Ocular infections	1	0.42	0	0	1.468	1
(1) Ocular motility disorders	0	0	1	0.87	0.163	0.328
(1) Pregnancy and neonatal topics	2	0.85	0	0	2.447	1
(2) Congenital, familial and genetic disorders	2	0.85	0	0	2.447	1

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Table 73 - REGARD: Grade 1-2 AEs with an incidence ≥ 3% (by HLT)

HLT	Ramucirumab/BSC N=236		Placebo/BSC N=115	
	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Asthenic conditions	74	31.36	39	33.91
Nausea and vomiting symptoms	66	27.97	39	33.91
Gastrointestinal and abdominal pains (excl oral and throat)	58	24.58	31	26.96
Appetite disorders	52	22.03	24	20.87
Musculoskeletal and connective tissue pain and discomfort	38	16.1	16	13.91
Gastrointestinal atonic and hypomotility disorders NEC	37	15.68	25	21.74
Physical examination procedures and organ system status	36	15.25	12	10.43
Diarrhea (excl infective)	33	13.98	9	7.83
Vascular hypertensive disorders NEC	27	11.44	9	7.83
Anemias NEC	26	11.02	13	11.3
Gastrointestinal signs and symptoms NEC	26	11.02	12	10.43
Edema NEC	24	10.17	8	6.96
Coughing and associated symptoms	23	9.75	12	10.43
Headaches NEC	22	9.32	4	3.48
Breathing abnormalities	20	8.47	13	11.3
Peritoneal and retroperitoneal disorders	17	7.2	7	6.09
Liver function analyses	14	5.93	3	2.61
Protein metabolism disorders NEC	14	5.93	5	4.35
Potassium imbalance	13	5.51	5	4.35
Flatulence, bloating and distension	11	4.66	7	6.09
Nasal disorders NEC	11	4.66	1	0.87
Febrile disorders	10	4.24	5	4.35
Joint related signs and symptoms	10	4.24	6	5.22
Mucosal findings abnormal	10	4.24	1	0.87
Pain and discomfort NEC	10	4.24	4	3.48
Upper respiratory tract infections	10	4.24	2	1.74
Rashes, eruptions and exanthems NEC	9	3.81	1	0.87
Sensory abnormalities NEC	9	3.81	6	5.22
Thrombocytopenias	9	3.81	0	0
Urinary abnormalities	9	3.81	5	4.35
Feelings and sensations NEC	8	3.39	3	2.61
Sodium imbalance	8	3.39	1	0.87
Total fluid volume decreased	8	3.39	1	0.87
Non-site specific gastrointestinal hemorrhages	7	2.97	4	3.48
Peripheral neuropathies NEC	7	2.97	4	3.48
Dyspeptic signs and symptoms	6	2.54	8	6.96
Bladder and urethral symptoms	5	2.12	5	4.35

HLT	Ramucirumab/BSC N=236		Placebo/BSC N=115	
	<i>Number of subjects</i>	<i>Proportion (%)</i>	<i>Number of subjects</i>	<i>Proportion (%)</i>
Lower respiratory tract signs and symptoms	5	2.12	4	3.48
Vascular hypotensive disorders	5	2.12	6	5.22
Neurological signs and symptoms NEC	4	1.69	8	6.96
Rate and rhythm disorders NEC	3	1.27	4	3.48
Muscle pains	2	0.85	4	3.48

Table 74 - REGARD: Median blood pressure (mm Hg) by arm

	Ramucirumab		Placebo	
	Systolic	Diastolic	Systolic	Diastolic
Cycle 1	124	80	120	79.5
Cycle 2	129.5	80	123	79
Cycle 3	130	80	120	79
Cycle 4	130	80.5	120	80
Cycle 5	135	80	120	80
Cycle 6	130.5	82	125	80

Table 75 - REGARD: Grade 1-2 AEs 120-day safety update (ramucirumab patients)

Preferred Term	N
Abdominal pain	4
Abdominal pain upper	4
ALT increased	1
Anemia	3
Anxiety	1
Arthralgia	1
Ascites	1
AST increased	1
Asthenia	4
ALP increased	1
Chloride increased	1
Blood pressure increased	1
Chest pain	1
Conduction disorder	1
Cough	4
Decreased appetite	6
Depression	1
Diarrhea	3
Dizziness	1
Dry mouth	1
Dysphonia	1
Dyspnea	1
Epistaxis	2
Erectation	1

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Fall	1
Fatigue	2
Feeling cold	1
Folliculitis	1
Gastritis	1
Headache	1
Hypersensitivity	1
Hypertension	3
Hypoacusis	1
Hypomagnesemia	1
Hyponatremia	1
Hypothyroidism	1
Influenza	2
Joint swelling	1
Leukocytosis	1
Lymph node pain	1
Mean cell volume increased	1
Memory impairment	1
Muscle mass	1
Nasopharyngitis	1
Nausea	2
Nephrostomy	1
ANC decrease	1
Nocturia	1
Peripheral edema	2
Pain in extremity	1
Parkinson's disease	1
Pelvic pain	1
Pneumonia	1
Protein decreased	1
Pruritus	1
Pyogenic granuloma	1
Pyrexia	2
Respiratory disorder	2
Sinusitis	1
Somnolence	1
Thrombocytopenia	3
Thrombophlebitis superficial	1
Upper respiratory tract infection	1
Visual acuity reduced	1
Vomiting	2
Weight decreased	2
WBC decreased	1
Xeroderma	1

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Ramucirumab/Cyramza®

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Clinical Review

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9.2 Labeling Recommendations

As of the completion date of the review, labeling discussions were ongoing. The following table summarizes Lilly's proposal and the clinical team's proposal. At this time, labeling has not yet been sent to Lilly, and further changes may be made based on internal discussion at FDA and with Lilly. The final labeling will be part of the action package.

Section 1: Indications and Usage

Original language

CYRAMZA™ as a single-agent is indicated for the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy.

Proposed language

Clinical Review

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Ramucirumab/Cyramza®

CYRAMZA™ as a single-agent is indicated for the treatment of patients with advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy with fluoropyrimidine and cisplatin.

Section 1: Warnings and Precautions

(b) (4)

(b) (4)

6 Adverse Reactions

Throughout the label, “REGARD” has been changed to “Study 1”.

Table 1 with adverse events has been revised to show the round incidence instead of showing decimals.

The term ^{(b) (4)} was revised to gastrointestinal perforations, as there was at least one event of intestinal perforation.

Section 14 Clinical Studies

14. 1 Gastric Cancer

(b) (4)

(b) (4)

Section 17 Patient Counseling Information

Proposed language

Addition of the following bullets based on class effect:

- That CYRAMZA can cause severe bleeding. Advise patients to contact their health care provider for bleeding or symptoms of bleeding including lightheadedness.

(b) (4)

(b) (4)

9.3 Advisory Committee Meeting

This application was not referred to ODAC because outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion. The clinical study design was acceptable and the application did not raise significant safety or efficacy issues in the intended population.

APPEARS THIS WAY ON ORIGINAL

9.4 Clinical Investigator Financial Disclosure Review

Application Number: 125477/0

Submission Date(s): Rolling submission, clinical module April 30 2013.

Applicant: Eli Lilly

Product: Ramucirumab

Reviewer: Sandra J. Casak

Date of Review: 6/13/2013

Covered Clinical Study (Name and/or Number): REGARD (JVBD)

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>591</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>none</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>none</u> Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: <u>none</u> Significant equity interest held by investigator in sponsor of covered study: <u>none</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>2</u>		
Is an attachment provided with the	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation)

reason:		from applicant)
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Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements).

The REGARD study is a double-blind randomized Phase 3 study of ramucirumab vs. placebo for the second line treatment of patients with advanced or metastatic gastric or gastroesophageal carcinoma with overall survival as the primary endpoint. The study was conducted in 119 centers in 29 countries, and no center enrolled more than 13 patients; only 3 centers enrolled 10 or more patients. Therefore, no center appeared to drive the study results.

In addition (see below), one of the centers where an investigator had a conflict of interest enrolled only (b) (4) subject and the results of the study in the second site with an investigator with disclosable financial interests favored the placebo arm.

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

There were two sub-investigators who did not provide the requested information despite multiple attempts from the Applicant before they left the site after completing training. The sites where these investigators treated subjects enrolled (b) (4) patients.

There were two investigators who received honoraria from the Applicant One investigator from (b) (6) received 34,100.00 USD and one investigator from (b) (6) received 27,725 USD. A total of 43 patients from 16 sites were enrolled in the U.S., (b) (4), (b) (6); the HR was 1.54, not favoring the ramucirumab treatment arm. Only (b) (6) was enrolled in (b) (6).

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/s/

SANDRA J CASAK

01/17/2014

STEVEN J LEMERY

01/17/2014

I agree with the major recommendations described in the clinical review. A separate CDTL review will follow.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125477

Applicant: Eli Lilly

Stamp Date: August 23, 2013

Drug Name: Ramucirumab

BLA Type: initial submission

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (<i>i.e.</i> , Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			x	BLA- 351(a)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i> , appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Location in submission:			x	Not needed, single dose proposed.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: CP12-0715 (REGARD) 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	x			A second study on second line metastatic gastric or GEJ adenocarcinoma has been conducted, comparing paclitaxel/cisplatin ±

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Junction Adenocarcinoma (GEJ) Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy. Indication: Ramucirumab is indicated for the treatment of patients with metastatic gastric or GEJ adenocarcinoma following disease progression on first-line platinum- or fluoropyrimidine containing combination therapy.				ramucirumab. Enrollment is complete and high-level results of the study are expected during the review cycle.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (e.g., QT interval studies, if needed)?	x			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested)	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?		x		
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Orphan drug designation
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?		x		
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Sandra J. Casak

September 18, 2013

Reviewing Medical Officer

Date

Steven Lemery

Clinical Team Leader

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA J CASAK
09/20/2013

STEVEN J LEMERY
09/20/2013