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APPLICATION NUMBER:

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SUMMARY REVIEW

Division Director Summary Review

Date	April 11, 2014
From	Patricia Keegan
Subject	Division Director Summary Review
BLA #	STN BL 125477
Applicant Name	Eli Lilly and Company
Date of Submission	March 27, 2013 (received)
PDUFA Goal Date	April 23, 2014
Proprietary Name / Established (USAN) Name	Cyramza Injection\ Ramucirumab
Dosage Forms / Strength	Injection for intravenous infusion/ 100 (10mg/mL) and 500 mg (10 mg/mL)
Proposed Indication(s)	Cymraza, as a single-agent, is indicated for the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Sharon Sickafuse
Medical Officer Review	Sandra J Casak
Statistical Review	Hui Zhang
Pharmacology Toxicology Review	Gabriel S. Khasar
Quality Review (OBP)	Michele K. Dougherty
Microbiology Review	Kalavati C Suvarna
Microbiology Review	Candace Gomez-Broughton
Clinical Pharmacology Review	Lillian H Zhang
OSI	Lauren Iacono-Connors
CDTL Review	Steven Lemery
OSE/DMEPA	Jibril Abdus-Samad
OSE/DRISK	Cynthia LaCivita
QT IRT Consult Review	Dhananjay D Marathe
OPDP	Quynh-Van Tran

OND=Office of New Drugs
OBP=Office of Biologic Products
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
QT IRT=Interdisciplinary Review Team

Division Director Summary Review

1. Introduction

CYRAMZA (ramucirumab (also known as IMC-1121B and LY3009806); Eli Lilly and Company) is a recombinant human IgG 1 kappa monoclonal antibody that specifically binds to the extracellular domain of the human vascular endothelial growth factor receptor-2 (VEGFR-2). Ramucirumab effectively blocks the interaction of VEGFR-2 with its ligands, VEGF-A, VEGF-C, and VEGF-D, resulting in inhibition of VEGF-stimulated activation of both VEGFR-2 and downstream signaling pathways.

The efficacy of ramucirumab was demonstrated in a single multicenter, randomized (2:1), double-blind, placebo-controlled trial (Protocol IMCL CP12-0715/14T-IE-JVBD (REGARD) evaluating the safety and efficacy of single-agent ramucirumab. Because of concerns raised by inconsistent treatment effects in specific subsets identified during review of the REGARD trial, and to provide additional support for this single trial, FDA requested and received the high-level summary results (and limited datasets) of a second, multicenter, randomized, double-blind, placebo-controlled trial (RAINBOW) evaluating the contribution of ramucirumab to chemotherapy over chemotherapy alone. Both trials were conducted in patients with metastatic gastric/gastro-esophageal junction adenocarcinoma which had progressed following one prior chemotherapy regimen for treatment of metastatic disease and demonstrated a statistically significant, albeit modest, increase in overall survival.

The REGARD trial enrolled 355 patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the gastro-esophageal junction [GEJ]) with disease progression during or within 6 months after completion of platinum- or fluoropyrimidine-containing chemotherapy. Of these 355 patients, 236 were randomized to ramucirumab 8 mg/kg (n=238) as an intravenous infusion every 2 weeks and 117 patients to matching placebo. The trial was conducted at 119 clinical sites across 29 countries. The median age of the study population was 60 years, 70% of patients were male, 77% were White and 16% were Asian; 29% had ECOG performance status of 0 while the remainder had ECOG PS of 1. Across the study population, 91% had measurable disease, the majority, 75%, had gastric cancer and 25% had adenocarcinoma of the GEJ. The majority of patients (85%) had experienced disease progression during or following first-line therapy for metastatic disease. Prior chemotherapy for gastric cancer consisted of platinum/fluoropyrimidine combination chemotherapy (81%), fluoropyrimidine-containing chemotherapy regimens without platinum (15%), or platinum-containing chemotherapy regimens without fluoropyrimidine (4%).

The REGARD trial demonstrated a marginally, statistically significant and clinically modest effect on overall survival [hazard ratio (HR) 0.78 (95% CI 0.60, 0.998), p=0.47, stratified log-rank test] and a more statistically robust but also clinically modest effect on progression-free survival [HR = 0.48 (95% CI: 0.38, 0.62), p = < 0.0001, stratified log-rank test]. The observed

median survival was 5.2 months for the ramucirumab arm and 3.8 months for the placebo arm, corresponding to a 1.4-month increase in median survival. The observed median PFS was 2.1 months in the ramucirumab arm and 1.3 months in the placebo arm, corresponding to a 0.8-month increase in median PFS. In addition to the marginally significant effect on survival, there was an apparent lack of treatment effects certain subgroups (women and the patients accrued at North American clinical sites in exploratory subgroup analyses.

Concerns regarding the lack of robustness of the effect on survival and the apparent lack of the treatment effect in women and North Americans were addressed by submission of the summary efficacy results for overall survival, including subgroup analyses by gender and by region of the world, in a second clinical trial in the same patient population. Protocol CP12-0922/14T-IE-JVBE (RAINBOW) is a randomized (1:1) multicenter, multinational, double-blind, placebo-controlled trial that evaluated the safety and efficacy of ramucirumab 8 mg/kg every two weeks in combination with paclitaxel compared with paclitaxel alone in 665 patients with previously treated metastatic or unresectable, locally advanced gastric cancer. The final analysis of this trial demonstrated a statistically significant effect on survival [HR 0.81 (0.68, 0.96), $p = 0.02$)] and progression-free survival [HR 0.64 (0.54, 0.75), $p < 0.0001$]; the effects on overall survival were consistently observed across relevant subgroups, including women and patients enrolled at clinical sites in North America, Europe, or Australia.

The toxicity profile of ramucirumab is acceptable in the indicated patient population and is similar to other drugs whose primary mechanism of action is inhibition of angiogenesis. The safety database was of adequate size to detect adverse reactions occurring at an incidence of approximately 0.5%. The most common adverse reactions occurring in patients receiving ramucirumab, i.e., at an incidence that was 10% or higher and at a higher rate (≥2%) than in the placebo arm, were diarrhea and hypertension.

The most common serious adverse reactions (requiring medical intervention or resulting in hospitalization or death) in the ramucirumab arm were intestinal obstruction (2.1%) and anemia (3.8%). The incidence of severe (NCI CTCAE grade 3) hemorrhage was also higher for ramucirumab-treated patients (3.4% vs. 2.6%) as was the incidence of patients receiving red blood cell transfusions (11% vs. 8.7%). Additional serious adverse reactions observed in ramucirumab-treated patients that were expected based on its mechanism of action (inhibition of VEGF pathway) were serious arterial thrombotic events (observed at an incidence of 1.7% in the REGARD trial), severe hypertension (observed at an incidence of 8% in the REGARD trial), gastrointestinal perforation (observed in 0.7% of the 570 patients in the safety database) and reversible posterior leukoencephalopathy syndrome (observed<0.1% of the 570 patients in the safety database). Additional serious adverse reactions were severe infusion-related reactions, which occurred at an incidence of 5.4% (2/37) in patients who did not receive premedication, and clinical deterioration in patients with pre-existing liver disease (Child-Pugh B or C).

2. Background

Indicated Population and Available Therapy

Adenocarcinoma of the stomach and gastro-esophageal junction is the 17th most common malignancy in the United States.[1] According to the National Cancer Institute's SEER database, there will be an anticipated 21,600 new cases of gastric cancer and 10,990 deaths due to gastric cancer in 2013. The median age at diagnosis is 69 years of age, with a male predominance (2:1) and a higher incidence in non-Whites (Black, Hispanic, Native Americans) than in non-Hispanic Whites.

Based on data obtained since 2005, indicate that 5-year survival rates of 25%, supporting the need for more effective treatments. Drugs which carry an FDA-approved indication for treatment of metastatic gastric cancer are doxorubicin, docetaxel, mitomycin C, fluorouracil, and trastuzumab; however doxorubicin and mitomycin C are no longer commonly used for treatment of gastric cancer. As summarized in the NCCN Clinical Practice Guidelines,[2] current recommendations for advanced, localized gastric cancer/gastro-esophageal junction cancer consists of multi-modality approaches of surgery, pre-or post-operative chemotherapy, with or without radiotherapy. Treatment of metastatic disease consists of two- or three-drug combination chemotherapy regimens; common regimens include fluoropyrimidine and platinum, with or without epirubicin or docetaxel. Current recommendations for second-line therapy include single agent taxane, irinotecan alone or in combination with a taxane, fluoropyrimidines, or platinum; trastuzumab is indicated for patients with HER-2 overexpressing tumors.

Pre-Submission Regulatory History

Clinical development of ramucirumab was conducted under IND 011856

May 20, 2008: CMC meeting held to discuss CMC issues relating to the planned Phase 3 studies and the proposed BLA, the design of the drug-drug interaction study, and the immunogenicity assay format.

- FDA reached agreement on the adequacy of the program outlined for the qualification of an additional manufacturing suite; adequacy of the leachables assessment for containers. (b) (4); acceptability of storage conditions; need for modifications for specifications used for stability studies; .
- Imclone would provide the complete study report for the monkey PK comparability study in support of comparability assessment and introduction of Process C material in the Phase 3 trial
- FDA agreed that the proposed (b) (4) immunogenicity assay appeared to be sufficiently sensitive however a final determination would be made during review complete reports in the BLA.
- FDA confirmed that the proposed DDI study design was acceptable.

[1] http://seer.cancer.gov/statfacts/html/stomach.html - accessed on February 22, 2014.
[2] http://www nccn.org/professionals/physician_gls/pdf/gastric.pdf. accessed on February 22, 2014.

May 28, 2008: pre-Phase 3 meeting: Discussion of the REGARD study design. Key advice and agreements reached during the meeting were;

- FDA found the proposed study design, including eligibility criteria, treatment plan and control arm, and endpoints generally acceptable. Imclone agreed to clarify the timing of the primary analysis of PFS and to conduct exploratory analyses of survival in relevant subgroups and sensitivity analyses of PFS.
- FDA agreed to review ImClone's rationale for not including primary site primary site (GEJ vs. other) as a stratification variable based on date from the REAL-2 study in which the primary site was not a strong prognostic factor.
- Regarding proposed power calculations to detect significant effects on p=0.05, two-sided, FDA noted that if the trial were intended to serve as the sole trial supporting licensure, sample size calculations and .trial design should be based on a higher significance level (e.g., two-sided 0.01). FDA would accept a single pivotal study to support licensure if results show a highly statistically significant effect on survival that is internally consistent across relevant subgroups. The results of the single pivotal trial must be sufficiently robust and so compelling that it would be unethical to repeat the study.
- FDA further noted that if ImClone provides assurance that a second trial in gastric cancer is being planned for the development program in gastric cancer. The currently proposed demonstration of an effect on survival in the REGARD trial could be accepted under an SPA.

November 15, 2011: CMC meeting to discuss a comparability strategy for the proposed IMC-1121B commercial manufacturing process and raw material changes to the drug substance (DS), the primary container changes for the drug product (DP), the addition of an alternate drug product (DP) manufacturing site, and the proposed strategy for process validation and stability matrix strategy. Key advice and agreements reached were:

- FDA agreed that ImClone's approach for determining comparability was acceptable and that supporting data would need to be included in the BLA.
- FDA provided specific requests for information to be included in the comparability and stability protocols.

January 23, 2012: Type C meeting to discuss pharmacokinetic analyses intended to support labeling claims for gastric (b) (4) cancer. Key advice and agreements reached were:

- FDA agreed that Imclone's proposed population PK analysis plan was appropriate.
- FDA did not agree with the plan for an early database snapshot (when 75% of overall survival events need for the final efficacy analyses have occurred) for the major efficacy trials due to concerns regarding unblinding of the trials prior to primary analyses of efficacy. FDA stated that if analyses were performed on the data snapshot, 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.

November 14, 2012: FDA granted Fast Track Designation for the investigation of ramucirumab, as a single agent, for the treatment of patients with unresectable or metastatic gastric adenocarcinoma including adenocarcinoma of the gastroesophageal

junction that has progressed following first-line chemotherapy for the investigation of its effect on overall survival.

January 17, 2013: An interdisciplinary, pre-BLA meeting held to discuss a BLA based on the results of a single trial (REGARD). Key advice and agreements reached were

- FDA could not confirm that, based on the summary results provided, the REGARD study were sufficient to support the proposed indication. FDA noted that the study showed a modest magnitude of the treatment effect on overall survival that was not statistically robust and may not provide substantial evidence of effectiveness required for approval based on a single study. FDA also noted the more modest effect in the North American subgroup and in females. FDA advised that the application would be likely be referred to ODAC and that the top-line results of the RAINBOW trial should be submitted to the BLA during the review when they became available, but would not be required for filing. Imclone confirmed their view that the totality of the data with a significant effect on survival, a more robust effect on progression-free survival, and a favorable safety profile as compared to standard chemotherapy observed in the REGARD trial were sufficient to support the BLA, but agreed to provide the RAINBOW results when available.
- FDA stated, and Imclone agreed to provide, additional justification and clinical data in the BLA to support the necessity and effectiveness of the proposed recommendations for pre-medication in mitigating infusion-related toxicity to support inclusion of the recommendation for premedication in product labeling.
- Agreement was reached on the content of the efficacy and clinical safety, clinical pharmacology, and nonclinical pharmacology/toxicology modules for the BLA. Agreement on the quality module was to be reached during the January 23, 2013 pre BLA meeting for CMC issues.
- FDA informed Imclone that the BLA must contain either reproductive toxicology studies or an adequate scientific assessment of the reproductive effects of ramucirumab that can be used from both a scientific and regulatory perspective as an alternative to these studies.
- Imclone agreed to submit a revised timeline for a rolling BLA submission
- FDA stated that, based on available information, a REMS would not be required for filing of the BLA.

January 23, 2013: pre-BLA meeting limited to discussion of the content and format of the proposed BLA CMC meeting

March 15, 2013: Proposed schedule for rolling BLA components (schedule accepted by FDA)

History of the NDA

The BLA was submitted as a rolling application in four components as listed below. The BLA was completed with the submission received on August 23, 2013.

- March 26, 2013: First component containing Modules 2.4 and 2.6; Module 4; and related administrative items in Module 1

- April 30, 2013: Second component containing Modules 2.2, 2.5, and 2.7; Module 5; Module1 (administrative items and draft USPI labeling); and responses to OSI information requests from preBLA meeting
- June 19, 2013: Third component containing the clinical study report for Study 14T-IE-JVBK (IMCL CP12-0712)
- August 23, 2013: Fourth component containing Module 2.3; Module 3; and Module 1 (Outstanding administrative items and draft carton and container labels)

October 31, 2013: Submission containing summary results and datasets for demographics, survival, and progression-free survival for the RAINBOW trial.

December 11, 2013: 120-day safety update submission containing data from completed studies up to a database lock of July 2013

3. CMC

I concur with the conclusions reached by the quality reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Based on the compliance history of Eli Lilly, a recent inspection confirming no significant deviations from GMP, and previous approval to manufacture sterile injectable products, including therapeutic biologic products, pre-approval inspection of the drug product manufacturing facility was waived. Manufacturing site inspections for the drug substance manufacturing site, packaging sites, and all major release or critical in-process testing sites have been determined to be acceptable and there are no pending or ongoing compliance actions that preclude approval of this BLA. Stability testing supports an expiry of the drug product of (b) (4) from the date of manufacture when stored at 2-8°C.

Ramucirumab is a recombinant, human, immunoglobulin IgG1, kappa monoclonal antibody (IMC-1121B, LY3009806) that binds to VEGFR-2 (human vascular endothelial growth factor receptor-2. (b) (4) . It is manufactured in accordance with GMP to yield a pure and potent product. Ramucirumab injection is supplied in 100 mg and 500 mg single-dose vial strengths in a sterile, preservative-free liquid solution at concentration of 10 mg/ml. A claim for a categorical exclusion from the Environmental Assessment (EA) requirement has been submitted under 21CFR section 25.31(c) was granted. There are no outstanding issues that preclude approval.

The immunogenicity assays were determined to be sensitive and reliable for the detection of both binding and neutralizing anti-drug antibodies in the absence of excess drug. However, since there was insufficient data in the BLA to demonstrate the anti-drug antibody assay was capable of detecting antibodies against ramucirumab at levels of drug expected to be present in serum samples at the time of collection (drug tolerance), two post-marketing requirements were identified by the Quality and Clinical Pharmacology reviewers to further assess and characterize the immunogenicity of ramucirumab, as follows:

- To submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to ramucirumab, including procedures for the accurate detection of binding antibodies to ramucirumab in the presence of ramucirumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

- To conduct an assessment of anti-drug antibody (ADA) response to ramucirumab with a validated assay (required in PMR #1) capable of sensitively detecting ADA responses in the presence of ramucirumab levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300 patients.

Because of the limited manufacturing experience using the commercial process, FDA requested and Lilly agreed to provide additional information to fully characterize and confirm quality aspects of the drug under as described in the following postmarketing commitments

- To re-evaluate ramucirumab drug substance and ramucirumab drug product lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process.

- To confirm product stability over (b) (4) using small scale studies.

- To perform a shipping study designed to confirm validation of the commercial ramucirumab drug product shipping conditions.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval.

The BLA contained the results of pharmacodynamic studies, short-term and long-term toxicology studies in non-human primates, and toxicology studies to assess effects on wound healing. Assessment of carcinogenicity studies and genetic toxicology studies were not required to support the BLA, in accordance with ICH S6, because the indicated patient population (patients with recurrent, progressive metastatic gastric cancer) has a median survival of less than 6 months with ramucirumab treatment. Reproductive toxicology studies were not required to support the BLA based on published literature demonstrating the critical role of this pathway in embryo-fetal development. Thus product labeling will indicated that ramucirumab, which inhibits this pathway, has embroyfetal toxicity in humans.

In vitro pharmacology studies demonstrated that ramucirumab binds specifically to the human VEGFR2 receptor but not the murine homolog. Upon binding to VEGFR2, ramucirumab inhibits VEGF ligand binding to its receptor, thus resulting in inhibition of ligand-induced phosphorylation of the VEGFR2 receptor. In addition, ramucirumab inhibited inhibited VEGF-induced proliferation and migration of human cells in a murine-human xenograft model.

Short (1-month) and chronic (39-week) toxicology studies were conducted in cynomolgus monkeys. Findings included effects on bone growth (epiphyseal growth plate changes, epiphyseal thickening and osteochondropathy), renal toxicity (moderate to severe glomerulonephritis), hemorrhage, cardiac toxicity (mononuclear infiltrates and aggregates, with elevated creatine kinase), and perivascular changes in the CNS.

Special Pharmacology studies
The results of a dedicated study in monkeys evaluating effects on wound healing demonstrated delay in healing of incisions as compared to controls.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

The selected dosing regimen in the proposed product label is adequately supported by non-clinical pharmacodynamic and proof-of-concept studies and results of pharmacokinetic sampling in the major efficacy trial. The dosing regimen evaluated in the REGARD trial, ramucirumab 8 mg/kg as an intravenous infusion administered every 14 days, was chosen based on the goal of achieving serum trough concentrations of greater than 18 μg/mL; this trough concentration resulted inhibition of tumor growth in tumor xenograft models. Based on the limited pharmacokinetic sampling collected in a subgroup (n=58) of patients in the ramucirumab arm, 95% of patients achieved the target trough concentration.

The apparent mean half-life of ramucirumab following a single dose of 8 mg/kg was approximately 8 days (range 6-9 days) in Japanese patients with gastric cancer. Population pharmacokinetics did not identify clinically important differences in exposure based on age, gender, or body weight. There was no evidence that ramucirumab exposure resulted in clinically important prolongation of QTc intervals in a dedicated QT study.

Although the incidence of anti-ramucirumab antibody development was evaluated in an adequately sized population, in which the incidence of binding antibodies was 7.4% (33/443) and the incidence of neutralizing antibodies was 3% (1/33 patients with binding antibodies), the reliability of the data is uncertain given the timing of sampling and lack of sensitivity of the assay in the presence of ramucirumab concentrations likely to be present at the time of sampling. For this reason, the Quality and Clinical Pharmacology reviewers identified the two post-marketing requirements described in sections 3 and 17 of this review.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

I concur with the conclusions reached by the clinical and statistical reviewers and the cross-discipline team leader that there are no outstanding clinical issues that preclude approval.

The application relied primarily on the results of a single, randomized, multicenter, multinational trial. A more detailed discussion of the FDA interactions with Lilly/Imclone on the clinical development program is provided discussed in section 2 of this review. During the May 28, 2008 end-of-Phase 2 meeting, FDA agreed that a single pivotal study could support licensure if results show a highly statistically significant effect on survival that is internally consistent across relevant subgroups. However, during the January 17, 2013, preBLA meeting, FDA raised concerns regarding the magnitude of the treatment effects on both overall and progression-free survival, the lack of a robust statistical result for the analysis of overall survival, and the possible lack of consistent effects on survival in two relevant subgroups: women and study sites in North America. Based on this, FDA stated that the high-level results of the analysis of a second trial, the RAINBOW trial, be submitted to the BLA with datasets to verify the summary results as soon as these results became available. Thus while there is a single efficacy trial reviewed in detail, the clinical reviewers also relied on the reported efficacy findings from a second well-designed trial to establish the robustness of the treatment effects.

No concerns were raised during the review regarding the conduct of the REGARD trial or data integrity. The dosing regimen studied is supported by pharmacodynamic effects and appears to be reasonably safe and tolerated.

Major Efficacy Trial (REGARD trial)

Protocol History
The original protocol was issued on March 5, 2008. Enrollment was initiated under an amended version (submitted to IND 11856 on June 10, 2009. The trial was amended five times after initiation of accrual; changes to the statistical analysis plan are summarized below.

Protocol Design
Protocol IMCL CP12-0715/14T-IE-JVBD (REGARD) entitled, "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 Following Disease Progression on First-Line Platinum- or Fluoropyrimidine- Containing Therapy"

Key eligibility criteria were histologically- or cytologically-confirmed, measurable or evaluable, localized unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma, patients with locally-recurrent, unresectable gastric/GEJ cancer were required to have lymph node metastases. All patients were required to have had prior combination chemotherapy that included a platinum or a fluoropyrimidines component and progression during or within four months of the last dose of therapy for metastatic disease or during or within six months after the last dose of adjuvant therapy.

The protocol excluded patients deemed to have increased risks of bleeding (≥ Grade 3 hemorrhage within 3 months; uncontrolled hemorrhagic disorder; ulcer; chronic anti-platelet therapy), thromboembolic events (arterial thrombotic event within 6 months; symptomatic heart failure; unstable angina pectoris; uncontrolled thrombotic disorder), hypertension (uncontrolled or poorly controlled hypertension); or wound-healing delays (serious or non-healing wound or bone fracture; major surgery within 28 days; venous access device placement within seven days).

The primary objective of this trial was overall survival; key secondary efficacy endpoints were progression free survival (PFS), 12-week PFS, overall response rate, and duration of response.

The trial was a double-blinded, randomized (2:1), multi-center, international trial. Randomization was stratified by weight loss (≥ 10% over the preceding 3 months versus < 10%), geographic region (North America, Europe, Australia, and New Zealand (region 1)versus South and Central America, India, South Africa, Jordan, Egypt, Saudi Arabia, and Lebanon (region 2) versus Asia (region 3)), and primary tumor as a stratification factor (gastric versus GEJ site).

Treatment consisted of ramucirumab 8 mg/kg as an intravenous infusion through an in-line filter every two weeks or matching placebo until disease progression, unacceptable toxicity, decline of ECOG PS of ≥ 2 points, or withdrawal of consent. Patients in both arms also received best supportive care. Premedication was administered prior to ramucirumab/placebo at the investigator's discretion and was required in patients who had experienced prior infusion-related reactions.

Patients underwent assessments for tumor size every 6 weeks and following discontinuation of study drug, patients were followed for survival and information on subsequent anti-cancer therapy every three months for at least 18 months.

The sample size for the trial at the time of trial initiation (October 2009) of 615 patients based on the assumptions that a total of 459 deaths were required to detect an improvement in overall survival at a hazard ratio of 0.714 at a two-sided significance level of 0.05 with 90% power, if the median survival were 5 months in the placebo arm and 7 months in the ramucirumab arm. The analysis plan included one interim analysis for efficacy and three interim analyses for futility.

The protocol was amended on November 23, 2010 to decrease the sample size to 315 patients with a plan to conduct the final analysis of overall survival after 256 deaths. The interim analysis for efficacy was removed and only two interim analyses were to be conducted for futility. The revised assumptions for this analysis were that a significant effect would be detected at a hazard ratio of 0.69 and 80% power, assuming a median survival of 5 months in the placebo arm and 7.25 months in the ramucirumab arm.

The protocol was again amended on October 31, 2011, to increase the sample size to 348 patients with a plan to conduct the final analysis of overall survival after 268 deaths. One of

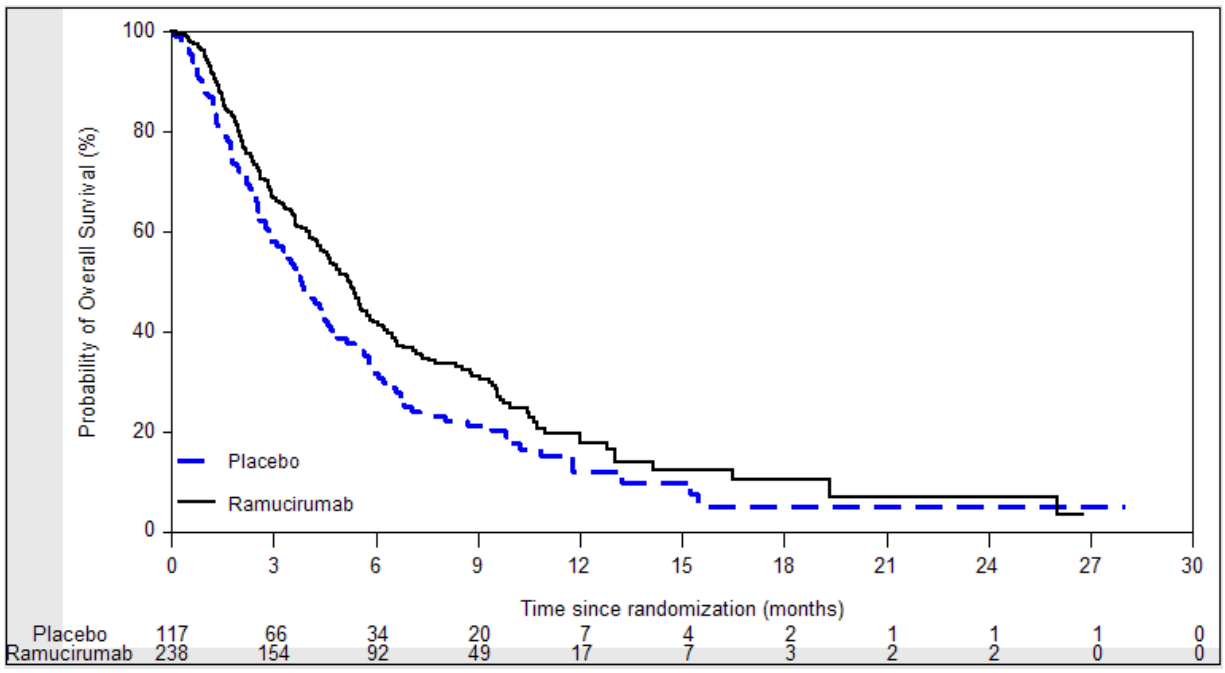
the two interim analyses for futility was dropped and this interim analysis was non-binding (i.e., study termination was optional). As noted in the statistical review, type I error was controlled at 0.05, two-sided for overall survival and progression-free survival using a gate-keeping (hierarchical testing) strategy, however type I error was not controlled for other secondary endpoints.

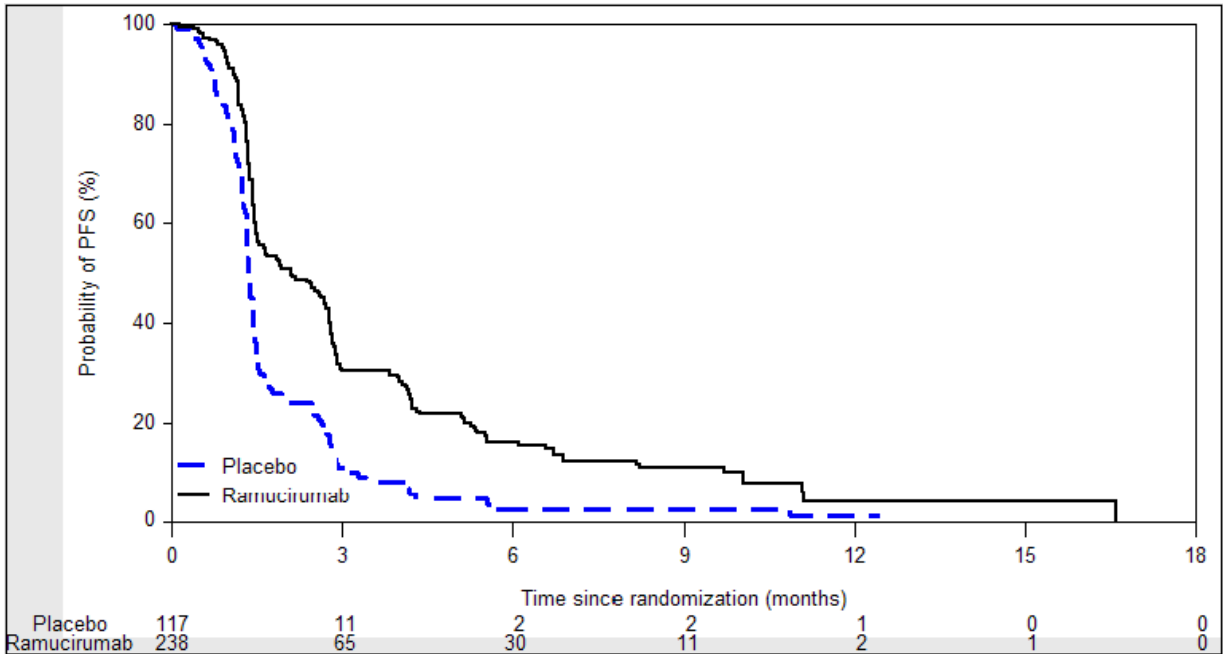
Results
The data provided in the BLA were deemed reliable based on Bioresearch Monitoring inspections conducted at three clinical study sites, selected based on the number of patients enrolled with a relatively high rate of treatment responders at these sites, and an inspection of Eli Lilly and Company, Inc., as the IND sponsor.

A total of 355 patients were randomized to ramucirumab (n=236) or placebo (n=117) at 119 clinical sites in 29 countries. The patients were randomized from October 6, 2009 through January 26, 2012. The data cut-off date for the efficacy analysis was July 25, 2012. The demographic and prognostic baseline characteristics were similar between treatment arms. The median age was 60 years and 70% of patients were men. The ethnic/racial breakdown was 77% White, of whom 17% were Hispanic or Latino. 16% Asian, 5.9% "other" and 1.7% Black. The majority of patients were enrolled from sites in region 1 (69%) followed 23% from sites in region 2, and 7% from sites in Asia (region 3). The ECOG PS was 0 for 28% of patients and 1 for 72% of patients and 17% had experienced a ≥ 105 weight loss in the preceding 3 months. Nearly all patients (91%) had measurable disease, 75% of patients had gastric cancer; and 25% had adenocarcinoma of the GEJ, and 98.3% had metastatic disease. The majority of patients (85%) experienced disease progression during or following first-line therapy for metastatic disease. Prior chemotherapy for gastric cancer consisted of platinum/fluoropyrimidine combination therapy (81%), fluoropyrimidine-containing regimens without platinum (15%), and platinum-containing regimens without fluoropyrimidine (4%). In Study 1, patients received a median of 4 doses (range 1-34) of ramucirumab or a median of 3 doses (range 1-30) of placebo.

The results of the trial primary and key secondary efficacy analyses are presented in the table, (abstracted from the draft product label) and figures (abstracted from the statistical review) below. There was one patient reported to have a complete response and 7 patients reported to have a partial response in the ramucirumab arm for an overall response rate of 3.4%.

	Ramucirumab N=238	**Placebo N=117**
Overall Survival		
Number of deaths (%)	179 (75%)	99 (85%)
Median – months (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)
Hazard Ratio (95% CI)	0.78 (0.60, 0.998)	
Stratified Log-rank p-value	0.047	
Progression-free Survival		
Number of events (%)	199 (84%)	108 (92%)
Median – months (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)
Hazard Ratio (95% CI)	0.48 (0.38, 0.62)	
Stratified Log-rank p-value	<0.001	





The statistical reviewer conducted a series of exploratory analyses based on age (<65 yrs., ≥ 65 yrs.), gender (male, female), race (White, Asian, other), and study region (1, 2 and 3). These exploratory subgroup analyses suggested a lack of treatment effect in the following subgroups:

- Females (n=107) [HR 1.43 (95% CI: 0.85, 2.40)]
- "Other" race (n=27) [HR 1.43 (95% CI: 0.45, 4.54)]
- Region 1 (n=245) [HR 0.84 (95% CI 0.70, 1.26)]

Supportive efficacy data

Study CP12-0922/I4T-IE-JVBE (RAINBOW), titled "A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase 3 Study of Weekly Paclitaxel With or Without Ramucirumab (IMC-1121B) Drug Product in Patients With Metastatic Gastric Adenocarcinoma, Refractory to or Progressive After First-Line Therapy With Platinum and Fluoropyrimidine," is a randomized (1:1), multicenter, double-blinded, placebo-controlled study that was designed to establish superior efficacy and evaluate the safety of the combination of ramucirumab plus paclitaxel over paclitaxel alone in patients with recurrent or progressive metastatic gastric adenocarcinoma following platinum- or fluoropyrimidines-based chemotherapy. Key eligibility criteria were the requirement to have progressed either during or within 4 months after the last dose of first-line therapy for locally advanced or metastatic disease, or during or within 6 months after the last dose of adjuvant therapy.

Patients were randomized to receive:

- paclitaxel 80 mg/m^2 by intravenous infusion over approximately 60 minutes on days 1, 8, and 15 of every 28-day cycle plus ramucirumab 8 mg/kg by intravenous infusion over approximately 60 minutes on days 1 and 15; or
- paclitaxel 80 mg/m^2 by intravenous infusion over approximately 60 minutes on days 1, 8, and 15 of every 28-day cycle plus matching placebo by intravenous infusion over approximately 60 minutes on days 1 and 15.

Randomization was stratified by measurable disease (yes vs. no), geographic region (Europe [including Israel]/North America/Australia vs. Asia [including East Asia - Japan, South Korea, China, Hong Kong, Taiwan - and South East Asia Malaysia, Thailand, Singapore] vs. the rest of the world), and time to progression on first-line therapy (< 6 months vs. ≥ 6 months), using a stratified permuted block randomization.

The primary objective was to demonstrate superior overall survival for ramucirumab plus paclitaxel over paclitaxel alone. Secondary efficacy objective were progression-free survival, time-to-progression, and overall response rate. Patients were assessed for tumor status every 6 weeks for the first 6 months then every 9 weeks thereafter.

The sample size of 663 patients was based on the ability to detect a significant improvement in overall survival after 510 deaths at a one-sided alpha of 0.025 and 90% power using the following assumptions: a drop-out rate of 5%, hazard ratio of 0.75, median survival of 7 months in the control arm and 9.33 months in the ramucirumab-containing arm.

Summary results

A total of 665 patients were randomized to paclitaxel plus ramucirumab (n=330) or to paclitaxel plus placebo (n=335) between December 23, 2010 and September 23, 2012. Demographic and baseline tumor characteristics for the study population were a median age of 60 years, 70% of patients were male, 77% were White and 16% were Asian, and 29% had an ECOG performance status (PS) of 0 while the remainder had an ECOG PS of 1. Across the study population, 91% of patients had measurable disease. The majority had gastric cancer (75%) and 25% had adenocarcinoma of the GEJ. The majority of patients (85%) had experienced disease progression during or following first-line therapy for metastatic disease.

Prior chemotherapy for gastric/GEJ cancer consisted of platinum/fluoropyrimidine combination chemotherapy (81%), fluoropyrimidine-containing chemotherapy regimens without platinum (15%), or platinum-containing chemotherapy regimens without fluoropyrimidine (4%).

The final analysis for overall survival was conducted after 511 deaths and as requested by FDA, the top-line results and analysis datasets were submitted to the BLA on October 31, 2013. Using the datasets provided, which contained only derived data, the statistical reviewer confirmed the reported results of a significant improvement in overall survival for patients with metastatic gastric adenocarcinoma randomized to ramucirumab plus paclitaxel as compared to paclitaxel alone. Because derived datasets were provided, the statistical reviewer could not independently generate the results from the primary (raw) data.

Using the derived datasets, the statistical reviewer confirmed the results provided in the summary report, in which the addition of ramucirumab to paclitaxel, was reported to show a statistically significant improvement in overall survival [HR 0.81 (95% CI: 0.68, 0.96); p=0.017), with a median survival was 9.63 months in the ramucirumab-containing arm and 7.36 months in the paclitaxel alone arm, corresponding to a 2.3-month increase in median survival. The trial was also reported to show a statistically significant improvement in progression-free survival [HR 0.64 (95% CI: 0.54, 0.75); p<0.0001), a reported median PFS of 4.4 months in the ramucirumab-containing arm and 2.9 months in the paclitaxel alone arm. In addition, consistent effects on survival were observed across subgroups, including women [HR 0.67 (95% CI 0.48, 0.94)] and patients enrolled at European, North American, or Australian sites [HR 0.73 (95% CI: 0.58, 0.91)].

8. Safety

Size of the database: The size of the safety database was sufficient to detect adverse drug reactions occurring at an incidence of approximately 0.5%. The safety of ramucirumab as a single agent was evaluated in 570 patients, including 236 patients with locally advanced or metastatic gastric cancer in the REGARD trial who received CYRAMZA. It should be noted that the patient population enrolled in the REGARD trial were selected to ensure lower risks of bleeding, hypertension, or impairment of wound healing than may be observed in the general population of patients with cancer.

In the REGARD trial, patients received a median of 4 doses of ramucirumab and the median duration of exposure was 8 weeks. Fourteen percent (32/236) of patients received ramucirumab for 6 months of longer. The most common adverse reactions occurring in patients receiving ramucirumab, i.e., at an incidence that was 10% or higher and at a higher rate (≥2%) than in the placebo arm, were diarrhea and hypertension. Less common, but clinically relevant adverse reactions of ramucirumab observed in the REGARD trial were headache (9% vs. 3%), neutropenia (4.7% vs. 0.9%), arterial thromboembolic events (1.7% vs. 0%), intestinal obstruction (2.1% vs. 0%), epistaxis (4.7% vs. 0.9%), and rash (4.2% vs. 1.7%). Based on laboratory monitoring, the incidence of proteinuria was also increased (8% vs. 3%).

Major safety concerns
The most common serious adverse reactions (requiring medical intervention or resulting in hospitalization or death) in the ramucirumab arm were intestinal obstruction (2.1%) and anemia (3.8%). The incidence of severe (NCI CTCAE grade 3) hemorrhage was also higher for ramucirumab-treated patients (3.4% vs. 2.6%) as was the incidence of patients receiving red blood cell transfusions (11% vs. 8.7%). Based on these findings, FDA requested that labeling contain a Boxed Warning for Hemorrhage.

Additional serious adverse reactions observed in ramucirumab-treated patients that were expected based on its mechanism of action (inhibition of VEGF pathway) were serious arterial thrombotic events (observed at an incidence of 1.7% in the REGARD trial), severe hypertension (observed at an incidence of 8% in the REGARD trial), gastrointestinal perforation (observed in 0.7% of the 570 patients in the safety database) and reversible posterior leukoencephalopathy syndrome (observed<0.1% of the 570 patients in the safety database). All of these adverse reactions are described in the Warnings and Precautions section of product labeling.

Although evidence of impaired wound healing was not observed across the safety database, at least half the population studied was selected to ensure a lower risk of such events. Based on the mechanism of action, non-clinical data suggesting that ramucirumab impairs wound healing, and the observed impairment of wound healing in patients with other drugs which inhibit the VEGF pathway, this potential risk was also included in the Warnings and Precautions section of product labeling.

The risk of infusion related reactions, which has been observed with other antibodies and proteins, was observed in a very small group of 37 patients who did not receive prophylactic premedication (antihistamines). Of the 16% (6/37) of patients who experienced an infusion-related reaction, two patients had severe symptoms and this information was included in the Warnings and Precautions section of product labeling. It is noted that this early experience may overestimate the incidence of this risk, however since nearly all patients in the safety database received premedication, the true risks are uncertain. Thus the basis for recommending premedication for all patients is based on the absence of precise estimates of this risk in patients who are not pre-medicated and not on evidence that premedication is necessary to mitigate unreasonable risks to patients.

Finally, clinical deterioration in patients with pre-existing hepatic impairment (Child-Pugh B or C) was observed in clinical studies across the development program. This information was included in the Warnings and Precautions section of product labeling.

REMS: I concur with the conclusions reached by the DRISK consult reviewer, the clinical reviewer, and cross-discipline team leader that, based on the data presented in the application, a REMS is not required to ensure safe use of ramucirumab in the indicated population.

PMRs and PMCs: I concur with the conclusions reached by the clinical reviewer and cross-discipline team leader that based on the data presented in the application, no post-marketing requirements are required to evaluate serious safety risks of ramucirumab.

9. Advisory Committee Meeting

This new molecular entity was not referred for review to the Oncologic Drugs Advisory Committee because there were the safety profile is acceptable for the treatment of patients with metastatic gastric cancer that has recurred or progressed following cisplatin- or fluoropyrimidine-based chemotherapy, the clinical trial is acceptable, based on the totality of the data including the confirmation of efficacy in the RAINBOW trial, the application did not raise significant public health questions on the role of the ramucirumab for treatment of patients with relapsed or refractory metastatic gastric adenocarcinoma, and outside expertise was not necessary since there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

On February 16, 2012, Imclone Systems LLC received orphan drug designation for treatment of gastric cancer; therefore this application is exempt from the requirements of the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

There are no unresolved regulatory issues. There were no concerns identified by the clinical reviewer regarding potential bias based on her review of financial disclosure data submitted in the BLA and the Bioresearch monitoring audits of the sponsor and selected clinical sites did not identify significant deviations from Good Clinical Practices and regulations.

12. Labeling

- Proprietary name: The proposed proprietary name, Cyramza, was determined to be acceptable by DMEPA, OPDP, and the clinical review team members.

- Physician labeling – all major labeling issues were resolved. The following summarizes agreed-upon modifications to the proposed label

    - Boxed Warning: FDA requested that labeling contain a Boxed Warning for hemorrhage. The rationale for this change is discussed in section 8 of this summary review.
    - Indications and Usage: This section was modified to reflect the population studied by added the qualifiers “metastatic” and noting the population had disease progression during (or after) fluoropyrimidine- or cisplatin-based chemotherapy.
    - Dosage and Administration
        - Extensively modified for brevity, bulleted to enhance prominence of key information, and “command” language as per FDA Guidance;

- The subsection on administration moved to the end of the section and information in this section provided information on by dosing regimen added to "recommended dose and schedule" subsection.
- The subsection on dose modifications was modified to provide information all information for a specific type of adverse reaction together (rather than based on the action to be taken);
- Information on use of an in-line filter retained because this reflects the administration method used in clinical trials however there are no data in the application to support a conclusion that use of in-line filters mitigates toxicity.

- Dosage Forms and Strengths: Added information on concentration for each strength.
- Warnings and Precautions:
  - Retitled proposed section [redacted] (b) (4) to "Hemorrhage," added data from REGARD study, and moved this to the first warning based on highest incidence when ramucirumab is used according to the product labeling.
  - Added incidence rates from the REGARD study to Arterial Thromboembolic Events subsection;
  - Added incidence rates for overall safety population to Hypertension subsection (REGARD data are provided in tabular format in Adverse Reactions section), provided information on frequency of monitoring based on clinical trial protocols, and added statements to discontinue ramucirumab in patients with hypertensive encephalopathy or crisis;
  - Added information regarding incidence on infusion-related reactions prior to routine use of premedication for context and provided directions for patient monitoring and dosing modifications for IRRs;
  - Added incidence information across the safety database on GI perforations (incidence data for REGARD trial is in section 6.1);
  - Removed exculpatory language [redacted] (b) (4) as the FDA's nonclinical toxicology reviewer disagreed with this assessment;
  - Retitled "[redacted] (b) (4)" subsection for clarity and provided a description of the findings observed in patients with Child-Pugh B or C rather than a general population.
  - Added new subsection on RPLS based on identification of one patient in clinical studies with RPLS and observation of RPLS in other drugs that inhibit the VEGF pathway
- Adverse Reactions
  - Added information describing the patient population, study design, and exposure as per FDA Guidance; removed items from the tabular listing that did not occur above background (placebo rate); deleted information [redacted] (b) (4) [redacted] (b) (4) replaced information on clinical adverse events of proteinuria and replaced with data on the more sensitive incidence rates of proteinuria based on laboratory findings; moved data on incidence of RBC transfusions next to incidence of anemia in text preceding Table 1 and deleted information [redacted] (b) (4) as not essential.

- Added new subsection (Immunogenicity) to provide information on the incidence of anti-drug antibody development.

- Use in Specific Populations
  - Revised Pregnancy and Nursing Mothers subsections and added new subsection on Males and Females of Reproductive Potential in accordance with current labeling practices as recommended by the Maternal Health Staff and the non-clinical toxicology reviewer;
  - added animal study information to the Pediatric Use subsection in accordance with current labeling practices for this subsection;
  - modified the Geriatric Use subsection for conformance to regulatory language and labeling practices in the Office of Hematology and Oncology;
  - Moved statements regarding available information on ramucirumab pharmacokinectics in patients with organ impairment to subsections titled "renal impairment" and "hepatic impairment" in accordance with current labeling practices and applicable FDA Guidance documents for these sections.
- Overdosage: Expanded this section to provide additional context and information based on clinical studies
- Description: Removed potentially promotion language on mechanism of action, which is not required in this section of labeling; provided data on inactive ingredients based on concentration which applies to both strengths; added "preservative-free" and "pH 6.0" to the product description
- Clinical Pharmacology:
  - From subsection on Mechanism of Action, removed non-essential information on VEGF pathway, promotional language (e.g., "(b) (4) and statements on mechanism that are not supported by data in the BLA
  - From subsection on Pharmacokinetics, moved information on pharmacokinetics in elderly patients and those with renal impairment to Section 8 and deleted non-essential information on pharmacokinetics in Phase 1 study.
- Nonclinical Toxicology:
  - Deleted statement (b) (4) (b) (4) and provided non-clinical information indicating that drugs with this mechanism of action impairs fertility in animals;
  - moved data on effects observed in juvenile animals to the Pediatric Use subsection (8.4); in accordance with current labeling practice and FDA Guidance documents provided dosing information in animal studies as a proportion of the recommended human dose;
  - Provided details for the wound impairment studies which put the reported results in context and identify limitations of the study.
- Clinical Studies: Included additional information on study design (important eligibility criteria; endpoints) but removed all information on (b) (4) (b) (4) ; included updated information on survival that that provided in the original BLA
- How Supplied/ Storage and Handling: edited for brevity and clarity (to clearly distinguish between diluted and undiluted products in describing storage conditions).

- Patient Counseling: Added counseling information for common adverse reactions and potential for impairment of wound healing; clarified instructions for nursing mothers.

- Carton and immediate container labels: Carton and immediate container labels have been revised as requested by the DMEPA and quality review staff and there are no outstanding issues.

- Patient labeling/Medication guide: The applicant did not submit proposed patient labeling. I concur that a Medication Guide is not required to ensure safe use. Since the product is administered under the direct supervision of a healthcare professional in a controlled setting, development of patient labeling was not requested by FDA.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I recommend approval of this application for the reasons discussed in the section below on Risk: Benefit Assessment.

- Risk Benefit Assessment
  There are no unresolved issues and all review team members recommended approval of this BLA. I recommend approval based on the evidence from both the REGARD trial, supported by the RAINBOW trial, of a statistically improvement in overall survival and in progression-free survival for a patient population for whom there are no satisfactory treatments. While the magnitude of the treatment effects on survival and PFS are modest, they may be meaningful to patients whose median survival is only 3.8 months and median progression-free survival is only 1.3 months. In addition, based on the common side effects (hypertension, diarrhea, and headache with an incidence of ≤16% each) and of the low incidence of serious adverse drug reactions of anemia (3.8%), severe bleeding (3.4%), intestinal obstruction (2.1%), the toxicity profile is acceptable to patients and physicians, given the benefits and limited survival in the indicated population of less than one year.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the recommendations of the clinical reviewer and cross-discipline team leader that a REMS is not required to ensure safe use of ramucirumab, which is administered in a healthcare setting by healthcare professionals, and which does not carry unreasonable risks for the indicated patient population.

- Recommendation for other Postmarketing Requirements and Commitments
  The rationale for the post-marketing requirements and post-marketing commitments below are summarized in Section 3 of this review

  Post-marketing requirements
  - To submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to ramucirumab, including procedures for the accurate detection of binding antibodies to ramucirumab in the presence of ramucirumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

- To conduct an assessment of anti-drug antibody (ADA) response to ramucirumab with a validated assay (required in PMR #1) capable of sensitively detecting ADA responses in the presence of ramucirumab levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300 patients.

Post-marketing commitments

- To re-evaluate ramucirumab drug substance lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

- To re-evaluate ramucirumab drug product lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

- To confirm product stability (b) (4) using small scale studies. These studies will include testing of (b) (4) for product quality (purity by (b) (4) and potency of ramucirumab).

- To perform a shipping study designed to confirm validation of the commercial ramucirumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for product quality (purity by SEC, rSDS-PAGE, nrSDS-PAGE, IEX, (b) (4), and potency of ramucirumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

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/s/

PATRICIA KEEGAN
04/11/2014