CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125477Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	14 Mar 2014
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
BLA #	125477
Applicant	Eli Lilly and Company
Date of Submission	23 Aug 2013 (complete application with final Module of rolling submission)
PDUFA Goal Date	23 Apr 2014
Proprietary Name / Established Name	Cyramza / ramucirumab
Dosing Regimen	8 mg/kg intravenously every two weeks
Proposed Indication(s)	Treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy
Recommended:	*Approval contingent upon reaching agreement on labeling, PMRs, and PMCs*

Table of Contents

Table of Figures

Table of Tables

1. Introduction

FDA received the complete Biologics License Application (BLA) 125477 from Eli Lilly and Company (Lilly) on 23 Aug 2013 requesting marketing authorization (regular approval) for ramucirumab (proposed trade-name Cyramza) for the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy.

Disclaimer: Any data or information described below that Lilly does not own (for example, summary data from other drugs used to treat patients with metastatic gastric cancer or other cancers) is included for descriptive purposes only. This information was not relied upon or necessary to make a decision regarding this application.

The primary issue considered during the *initial* review of Module 5 of this BLA (clinical module as submitted on 30 Apr 2013) was whether the results of a single adequate and well controlled clinical trial (JVBD) provided substantial evidence of effectiveness to support the approval of ramucirumab.

FDA Guidance (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998) states that reliance on a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome and confirmation of the results in a second trial would be practically or ethically impossible.

JVBD was a randomized (2:1), multicenter, multinational, double-blind, placebo-controlled trial where patients with (previously treated unresectable and locally advanced or previously treated metastatic) gastric cancer or gastroesophageal junction cancer received ramucirumab (8 mg/kg every two weeks) plus best supportive care or placebo plus best supportive care (generally until disease progression or unacceptable toxicity). Table 1 (data obtained from the statistical review) summarizes the efficacy results from JVBD. The results demonstrated a statistically significant improvement in overall survival (OS). Nevertheless, the improvement was of a modest magnitude (median improvement in survival of 1.4 months) and the p value was just under 0.05.

Table 1 Summary of OS efficacy results (JVBD)

	Ramucirumab N = 238	**Placebo N = 117**
# of events	179	99
Median (in mos.)	5.2	3.8
Stratified HR (95% CI)	0.776 (0.603, 0.998)	
p-value (two-sided)	0.0473	

In addition to the modest effect on OS, JVBD showed potential imbalances in treatment effects by geographic region and gender. Most concerning regarding approval consideration was the point estimate for the treatment effect among women [HR = 1.43 (0.85, 2.41)]. Although there were potential reasons to explain this subgroup effect (e.g., there was a larger proportion of

women with diffuse histology who received ramucirumab compared to placebo), this reviewer would have reservations whether to approve ramucirumab (a new molecular entity) based on a single trial demonstrating a modest six week improvement in overall survival, with a p value of 0.047, and the potential for detrimental survival among women.

Based on the modest effects observed in JVBD, one could argue that a second trial of ramucirumab could ethically be conducted, especially to further evaluate the effects of ramucirumab in women. Additionally, the second study could further evaluate the treatment effects of ramucirumab in the North American subgroup (the point estimate for the hazard ratio in this subgroup was closer to one than the ITT point estimate).

Ultimately, during the clinical review, on 30 Oct 2013, Lilly was able to strengthen the application by submitting survival data (including datasets) from a second study, JVBE. JVBE was a randomized (1:1) multicenter, multinational, double-blind, placebo-controlled trial that evaluated ramucirumab (same dose and schedule as JVBD) in combination with paclitaxel versus placebo in combination with paclitaxel as a treatment for patients (n = 665) with previously treated metastatic or unresectable, locally advanced gastric cancer. After 516 events (deaths) were observed in JVBE, patients in the ramucirumab arm lived a median 2.3 months longer than patients in the placebo arm [HR = 0.807 (0.678, 0.962), p = 0.017)]. The results were supported by a modest effect on progression free survival [HR 0.635 (0.536, 0.752), p < 0.0001]. *Comment: Lilly submitted the datasets in standardized [SDTM (CDISC) / ADaM] formats which facilitated FDA's ability to rapidly review clinical data during the review cycle.*

Importantly, JVBE provided results showing that ramucirumab appears effective in women [HR point estimate for OS was 0.67 (0.48, 0.94)] and in patients enrolled in the region that included the United States.

Based on the results of study JVBE, this reviewer agrees that this application contained substantial evidence from adequate and well controlled *trials* that ramucirumab can (modestly) prolong survival when administered to patients with previously treated, metastatic gastric cancer.

2. Background

2.1 Disease and therapy related issues

Lilly requested marketing authorization for ramucirumab for the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy. In general, because metastatic gastric cancer is an incurable disease, the goal of treatment for these patients is to prolong life and/or improve quality of life.

Oncologists treat patients with metastatic gastric cancer with cytotoxic chemotherapy and with trastuzumab (for patients with tumors that overexpress HER2). For brevity, this review will not focus on supportive treatment of patients with gastric cancer; however, this reviewer acknowledges that a multidisciplinary approach is necessary to help improve the life-altering

symptoms of such patients (for example, due to gastrointestinal obstruction, thromboembolic events, hemorrhage, pain, weight loss, anorexia, nausea, and depression).

FDA approved trastuzumab for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease on 20 Oct 2010. FDA approved trastuzumab based on an improvement in overall survival when trastuzumab was added to a fluoropyrimidine (capecitabine or 5-fluorouracil) and cisplatin. Trastuzumab improved overall survival by a median 2.5 months [HR = 0.73 (0.60, 0.91), p = 0.0038].

On 22 Mar 2006, FDA approved docetaxel in combination with cisplatin and fluorouracil (CF) for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease. FDA approved docetaxel based on an improvement on time to progression and on overall survival. The hazard ratio described in the product label for overall survival is 0.77 [(0.62, 0.96), p = 0.0201]. The hazard ratio appeared to be a better estimate of overall survival compared to the median difference of 0.6 months, because the KM curves appeared to converge at the median and then separate.

In addition to trastuzumab and docetaxel which are both approved in the first-line setting, older (FDA) approvals for metastatic gastric cancer include fluorouracil, doxorubicin, and mitomycin C. In general, patients with previously treated metastatic disease receive single-agent therapy [for example, with irinotecan or a taxane (both off-label)] or best supportive care. Many such patients cannot receive cytotoxic therapy due to underlying performance status.

2.2 U.S. regulatory history

The following summarizes the pertinent regulatory history and meetings held in relation to this BLA. (b) (4)

20 May 2008 (Type B meeting between FDA and ImClone): FDA and ImClone held this meeting to discuss manufacturing issues, an immunogenicity assay, and issues related to the design of a drug-drug interaction study. ImClone requested FDA advice regarding plans to support comparability of two different manufacturing processes [Process B (b) (4) ; and Process C (b) (4) and plans to support the use of drug substance (DS) from Process C in randomized (phase 3) clinical trials. FDA agreed with the design of a proposed monkey study to assess the pharmacokinetics (PKs) of material manufactured using the different processes; however, FDA stated that that the Agency would review the results of the monkey PK study prior to determining whether human PK data would be necessary.

FDA provided advice regarding stability studies including adding a potency bioassay as a stability test, reporting percentages of aggregates and fragments in HPLC acceptance criteria, and testing for sub-visible particulates.

During the meeting, FDA agreed with a proposed DDI study plan to determine the relative effect of docetaxel on the pharmacokinetics of ramucirumab and provided advice regarding the immunogenicity assay which would be reviewed in full after submission of a BLA.

28 May 2008 (Type B meeting between FDA and ImClone): ImClone requested this meeting to reach agreement on the design of a proposed trial, CP12-0715, entitled "A Phase 3, Randomized, Double-Blinded Study of IMC1121B 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 Combination Therapy." During the meeting, FDA agreed that ImClone could enroll patients with GEJ tumors and that use of a placebo was acceptable provided that patients received adequate informed consent regarding (alternative) standard treatments. FDA also agreed with ImClone's approach regarding the conduct of futility assessments (at 25%, 50%, and 75% of OS events) and that the IDMC charter was acceptable. FDA agreed with ImClone's approach to conduct a single interim analysis following the observance of 75% of the planned events.

During the meeting, FDA recommended stratification of the trial based on an additional variable (i.e., gastroesophageal junction tumor versus other); however, ImClone provided a report (from the REAL-2 study) suggesting that the site of tumor was not a strong prognostic factor for overall survival in previously treated patients. FDA agreed to review the REAL-2 study results prior to making a decision regarding whether the approach was acceptable.

FDA also communicated to ImClone that for a single pivotal study to support licensure, the results should show a highly statistically significant effect (a p value of less than 0.01 was suggested during the meeting) on survival that is internally consistent across relevant subgroups and that the results of the single pivotal trial must be sufficiently robust and so compelling that it would be unethical to repeat the study. FDA stated that the acceptability of study CP12-0715 as a single trial to support the approval of IMC-1121B as second-line therapy in metastatic or GEJ adenocarcinoma will be contingent upon the magnitude and robustness of the effect. Alternatively, FDA stated that a second trial in gastric cancer (either first- or second- line) could generate sufficient supportive evidence if conducted at the 0.05 significance level.

07 Apr 2009 (letter to ImClone): FDA sent a letter to ImClone based on an amendment to the IND submitted on 4 Feb 2009 regarding a new DS manufacturing site and an additional drug product manufacturing facility. FDA requested information regarding viral clearance steps during production and information regarding the identity (b) (4) of ramucirumab. FDA stated that products manufactured from processes B and C appeared pharmacokinetically comparable.

29 Oct 2009 (letter to ImClone): FDA sent this letter in response to questions posed by ImClone regarding protocol IMCL-CP12-0712: "A Study to Evaluate the Relationship Between Ramucirumab (IMC-1121B) Therapy and Corrected QT (QTc) Interval Changes in Patients with Advanced Cancer." In the letter, FDA recommended revising the study to evaluate the highest therapeutic dose of ramucirumab (i.e., 20 mg/kg every three weeks). FDA

stated that co-administration of moxifloxacin was not required. FDA agreed with the proposed timing, intervals, and analyses of ECGs during the study.

27 May 2010 (Type B meeting between FDA and ImClone): ImClone requested this meeting to reach agreement on the design of a proposed trial, CP12-0922, entitled "A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel With or Without Ramucirumab Drug Product in Patients with Metastatic Gastric Adenocarcinoma, Refractory to or Progressive after First-Line Therapy with Platinum and Fluoropyrimidine." ImClone stated that patients in the trial would receive paclitaxel (80 mg/m^2 on days 1, 8, and 15 of each 28 day cycle) plus either placebo or ramucirumab (8 mg/kg) every other week. The proposed primary endpoint was overall survival. FDA stated that the overall design of the randomized (1:1) study appeared acceptable to support a BLA. However, FDA reiterated advice regarding approval based on one study conferred during the 28 May 2008, Type B meeting.

23 Sep 2010 (letter to ImClone): FDA sent this letter to ImClone in reference to an amendment dated 6 Apr 2019 to protocol IMCL-CP12-0715 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 Combination Therapy." In the letter, FDA recommended changes to the protocol in order to make claims based on progression free survival (i.e., to continue imaging assessments following the initiation of new anticancer therapy).

15 Nov 2011 (Type C meeting between FDA and ImClone): ImClone requested this meeting to discuss a comparability strategy for the proposed ramucirumab (IMC-1121B) commercial manufacturing processes and (b) (4) changes to the drug substance (DS), the primary container changes for the drug product (DP), and the addition of an alternate drug product (DP) manufacturing site. ImClone planned on submitting information from two processes (C1 and C2) in the BLA with process validation to be performed on Process C1. ImClone proposed Process C1 as the initial commercial material; this material differed from Process C0 material used in Phase 2 and Phase 3 clinical trials in that Process C1 included (b) (4) The only proposed change in Process C2 was a change (b) (4) . In general, FDA found ImClone's comparability assessment as acceptable; however, FDA requested that ImClone assess additional parameters as "critical quality attributes" (b) (4) FDA requested real-time and accelerated stability data in the comparability package.

During the meeting, FDA also provided advice regarding the proposed analytic characterization program; agreed with the proposed stability approach to support Process C1; provided advice regarding data necessary to support Process C2; agreed to the planned approach for viral control and the viral validation program using two challenge viruses

including (b) (4); and provided comments regarding the approach to validation of drug product manufacturing processes.

23 Jan 2012 (Type C meeting between ImClone and FDA): During this meeting, FDA confirmed that ImClone's proposed population PK strategy appeared sufficient to support planned BLAs in gastric (b) (4) cancer. However, FDA did not agree with ImClone's plan for an early PK database "snapshot" at 75% of events because unblinding of the trial could potentially jeopardize the integrity of the trial. ImClone stated that no unblinded safety or efficacy data would be evaluated in the population PK analysis. FDA stated that ImClone would need to provide a summary of steps taken to ensure integrity including evidence that the analysis plans for primary and key secondary endpoints were finalized prior to the conduct of the population PK analysis.

16 Feb 2012 (letter to ImClone): FDA granted orphan-drug designation (#11-3597) for the "treatment of patients with gastric cancer."

29 Jun 2012 (letter to ImClone): FDA responded to an ImClone request for a waiver from conducting a nonclinical reproductive and developmental toxicity study in a pharmacologically responsive species due to scientific and regulatory reasons (including knowledge of the biological pathway and available non-clinical ramucirumab data). FDA stated that the Agency would consider the request following review of data/information submitted to the IND; however, FDA stated that ImClone cannot rely on product-specific published literature describing results of studies from other biological drugs.

18 Sep 2012 (letter to ImClone): FDA sent a letter to ImClone regarding an (b) (4) method and data requested by the Agency during a 15 Nov 2011 CMC meeting. FDA provided advice regarding data and studies necessary to support stability and shelf-life across manufacturing processes.

14 Nov 2012 (Fast Track letter): 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. FDA granted Fast Track designation based on the plan to investigate the effect of ramucirumab on overall survival.

17 Jan 2013 (Type B, pre-BLA meeting between ImClone and FDA): The major issue discussed during this meeting was whether the results from the single JVBD study were sufficient to support the proposed indication. FDA stated that the trial showed a modest effect on overall survival and that the results were not robust as discussed in FDA guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf, accessed 01 Oct 2013). FDA also identified the modest effect observed in the North American subgroup. FDA stated that the Agency may request advisory committee advice regarding whether the Agency should wait for the results of Study JVBE (also in gastric cancer), which if positive, would confirm the results of Study JVBD. FDA encouraged ImClone to submit the results of the JVBE trial; however, FDA stated that the results of the JVBE trial would not be required for filing. FDA agreed to meet with ImClone if the top-line

results from JVBE became available during the review of a BLA (based on data from the JVBD trial) in order to determine which top-line data from JVBE should be submitted in the BLA.

During the meeting, FDA and ImClone agreed that the BLA would contain the following:

- Integrated Summaries of Safety and Effectiveness (ISS and ISE) as described in FDA Guidance Documents (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf, and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf).
- Case report forms only from completed studies.
- Financial disclosure information from Study JVBD (as other studies were not considered a "covered study").

The contents of a complete application were discussed; however, agreement on the contents of a complete application was not reached because the pre-BLA CMC meeting was yet to be held and because additional discussion was required regarding the clinical pharmacology sections of the BLA. FDA and ImClone held a preliminary discussion regarding the need for a REMS and concluded that a REMS did not appear necessary to ensure the safe use of ramucirumab for the proposed indication. FDA also did not anticipate the need for a MedGuide because ramucirumab will be administered in infusion centers and prescribed by oncologists who routinely obtain informed consent prior to administering anti-cancer therapeutics. FDA stated that the Agency would consider the application for priority review; however, FDA stated that priority review designation would be determined when the BLA is received.

During the meeting, FDA stated that the Agency would not object to a proposal to initiate an expanded access program (for ramucirumab) as long as the program did not interfere with recruitment in the ongoing JVBE trial.

23 Jan 2013 (Type B, CMC pre-BLA meeting between ImClone and FDA): ImClone requested this meeting to seek agreement regarding the structure and contents of Modules 2.3 and 3 (Quality) of their BLA. A subsequent telephone conference was held on 25 Jan 2013; the minutes from both conferences were contained in a single document.

In addition to discussing the structure of the application, ImClone and FDA discussed requirements for the preparation of a new working cell bank, validation approach to (b) (4) during drug substance manufacturing, drug substance and drug product release specifications, approach to (b) (4) method in release and stability testing with an (b) (4) method (b) (4) testing methods for endotoxin, and the proposed stability package. FDA stated that ImClone should be prepared to submit a simple stability update if requested during the review of the BLA.

During the meeting, FDA requested that ImClone provide gels and chromatograms generated during stability studies in sections 3.2.S.7 and 3.2.P.9 of the application. FDA also requested

that ImClone submit a batch record from one lot from each site where drug product is manufactured. Finally, FDA stated that based on the information provided in the pre-BLA briefing package, no deficiencies were identified that would result in a refuse-to-file action.

15 Mar 2013 (letter to ImClone): FDA (DMEPA) sent a letter stating that the proposed proprietary name of Cyramza was conditionally acceptable.

26 Mar 2013 (letter to ImClone): FDA sent a letter to ImClone that granted a rolling review of the proposed BLA based on agreements on the contents of a complete application reached during meetings held on 17 Jan 2013 and on 23 Jan 2013 and in an email dated 21 Feb 2013 regarding the proposed clinical pharmacology sections of the BLA.

10 Oct 2013 (telephone conference with Lilly in reference to high-level results of Study JVBE): During this meeting Lilly provided high level results of Study JVBE, a second randomized clinical trial that confirmed the results observed in Study JVBD. FDA informed Lilly that these top-line results would strengthen the application and FDA previously agreed to review this information during the pre-BLA meeting held on 17 Jan 2013. FDA requested that Lilly provide the following in the BLA:

- Overall survival and demographic datasets to allow the Agency to replicate Lilly's findings of overall survival in the intent-to-treat population and in relevant subgroups.
- Copies of meeting minutes between ImClone and FDA in reference to the JVBE trial.
- Copies of the protocol, all amendments, and statistical analysis plan for the JVBE trial.
- Brief report describing the major efficacy findings.
- Safety information only if the safety information would strengthen the Warnings and Precautions Section of the label and/or would change the risk/benefit assessment of ramucirumab for use in the current application.

During the meeting, Lilly informed FDA that they will plan on submitting a BLA based on the results of JVBE in 2014.

19 Dec 2013 (Mid-Cycle communication meeting with Lilly): FDA advised Lilly that the Agency issued a warning letter to the (b) (4) manufacturing site on (b) (4) In response, Lilly proposed revising Section 3.2.P.3.1 of the BLA, withdrawing the (b) (4) manufacturing site and listing the Lilly manufacturing site as the sole DP manufacturing site. Lilly stated that the Lilly manufacturing site will be able to supply the U.S. market if ramucirumab is approved. FDA agreed during the meeting that this revision to the BLA would not constitute a major amendment.

During the meeting, FDA requested that Lilly provide information, if available, regarding the incidence of bleeding in patients who received ramucirumab while taking NSAIDS (as NSAID use was an exclusion criterion in Trial JVBD).

11 Feb 2014 (Late-Cycle meeting with Lilly): See Section 11.5 of this review for a summary of items discussed during the Late-Cycle Meeting.

2.3 Application history

The following table summarizes the contents of amendments submitted to the BLA.

Table 2 Amendments to BLA 125477 (as of the date of the completion of this review)

Date of Submission	Purpose of Submission
26 Mar 2013	Original BLA submission. This submission contained Modules 4, associated sections of Module 2, and related administrative information in Module 1.
30 Apr 2013	Submission of Module 5, associated sections of Module 2, and related administrative information in Module 1.
19 Jun 2013	Submission of QTc study report for 14T-IE-JVBK (IMCL CP12-0712) and submission of associated QT datasets, waveforms, and associated documents.
29 Jul 2013	This submission contained a response based on an email sent by the Agency dated 22 Jul 2013. In this submission, Lily provided documents related to an anti-ramucirumab antibody assay, a ligand binding neutralizing assay, and measurements of both antibodies and neutralizing antibodies in human serum samples.
21 Aug 2013	Lilly provided a response to an information request regarding clinical pharmacology information submitted in the BLA.
23 Aug 2013	Submission of the final portion of the BLA containing Module 3, associated Sections of Module 2, and related administrative information in Module 1.
13 Sep 2013	Clarification regarding the specific baseline blood pressure measurements identified in the vital signs analysis dataset for study CP12-0715.
27 Sep 2013	Submission of bioanalytical study reports as required by the Agency.
30 Oct 2013	This submission provided top-line summary data regarding the JBVE trial and datasets (demographic and survival) to enable FDA to replicate Lilly's analyses. To ensure transparency, Lilly also provided copies of the JVBE protocol, protocol amendments, and final statistical analysis plan.
4 Nov 2013	This submission contained Lilly's responses to information requests identified by FDA in a Filing Communication document and provided additional CMC information to the BLA.
6 Nov 2013	Lilly informed FDA that the JVBD clinical trial documentation was being moved from New Jersey (ImClone site) to Indianapolis (Lilly Corporate Center).
14 Nov 2013	Lilly submitted their voluntary Risk Management Plan based on an OSE request submitted by email by DOP2 on 13 Nov 2013. Lilly stated that this plan was submitted to the EMA on 23 Aug 2013 as part of the European marketing authorization request.
15 Nov 2013	Submission of a written response in regards to an 8 Nov 2013 information request based on quality microbiology sections of the BLA.
19 Nov 2013	Submission of a written response in regards to a 31 Oct 2013 information request based on CMC Sections of the BLA.
21 Nov 2013	Submission that provided locations of data in datasets in order to allow the FDA statistical reviewer to create a Table (pertaining to an analysis of prior therapies) in her review.
9 Dec 2013	This submission contained an information response to provide the studies used to support the (b) (4) for monitoring maintenance of product temperature during shipment.
11 Dec 2012	Lilly submitted the 120 day safety update.

Date of Submission	Purpose of Submission
13 Dec 2013	This submission contained responses to an FDA information request dated 26 Nov 2013 in reference to quality microbiology sections of the BLA.
13 Dec 2013	This second amendment dated 13 Dec 2013 contained method protocols and validation reports for specific analytical methods. The amendment also described requested drug substance and drug product release specifications.
23 Dec 2013	This submission contained responses to an FDA information request in an 18 Dec 2013 email regarding CMC sections of the BLA. This submission also notified FDA that Lilly removed the [redacted] (b) (4)) site from the drug product manufacturing section of the BLA. Lilly provided a replacement Section 3.2.P.3.1 in the BLA.
30 Dec 2013	This submission contained method protocols/SOPs for nine (quality related) methods that FDA requested on 21 Dec 2013.
9 Jan 2014	This submission contained information (in response to a 31 Dec 2013 information request by FDA) pertaining to anti-drug assays, anti-drug antibody screening assay, the neutralizing anti-drug antibody assay, and the reference standard.
15 Jan 2014	Lilly submitted information requested by FDA that included additional process parameters and control limits for the parameters for DP and DS manufacturing processes. Lilly also provided information regarding [redacted] (b) (4)
17 Jan 2014	Lilly provided requested [redacted] (b) (4) and chromatograms for supportive DS and DP stability lots that were listed in the BLA.
20 Jan 2014	In response to a 16 Jan 2014 email, Lilly provided replacement Sections for certain manufacturing portions of the BLA in Module 3. Lilly also provided Section 3.2.R.2.6 Method Transfer Reports for Non-Compendial Analytical Methods to supplement Section 3.2.R.2 in Module 3.
21 Jan 2014	Lilly submitted population pharmacokinetic information from JVBD in response to an 8 Jan 2014 query from FDA regarding potential differences in PK profiles observed between Japanese and non-Japanese patients in two trials (JVBN and JVBI) reviewed by the Office of Clinical Pharmacology.
22 Jan 2014	In response to a 21 Jan 2014 email from FDA, Lilly provided replacement Sections 3.2.S.2.5 and 3.2.P.3.3 with updated protocols in the BLA.
23 Jan 2014	Lilly provided information regarding bleeding in patients who received non-steroidal anti-inflammatory drugs (NSAIDS) during the time they received ramucirumab.
24 Jan 2014	Lilly provided clarification regarding plans for conducting discriminating physico-chemical identity test(s) for ramucirumab vials following packaging and labeling.
29 Jan 2014	Lilly responded to an FDA Quality Microbiology information request dated 23 Jan 2014.
31 Jan 2014	Lilly provided MedWatch reports for cases of reversible posterior leukoencephalopathy syndrome. At the time of the submission, the cases remained blinded.
7 Feb 2014	This submission contained a relevant replacement section in Module 3. Module 3 was also revised [redacted] (b) (4) in order to ensure consistency with the updated manufacturing protocol. Lilly provided revised carton and container labeling.
27 Feb 2014	Lilly provided a response regarding PMC and PMR agreements.

Date of Submission	Purpose of Submission
4 Mar 2014	Lilly provided revised draft labeling.
12 Mar 2014	Lilly provided amended carton labeling as requested by FDA.
12 Mar 2014	Lilly submitted finalized PMCs and PMRs.

3. CMC

Dr.'s Dougherty and Kennett from the Division of Monoclonal Antibodies (DMA) reviewed the product quality sections of the BLA and recommended approval of the BLA (as amended to remove the (b) (4) manufacturing site). Dr. Dougherty concluded that the manufacture of ramucirumab is well controlled and that ramucirumab is pure and potent. Dr. Dougherty also concluded that ramucirumab is free of endogenous and adventitious infectious agents sufficient to meet parameters recommended by FDA. DMA recommended an expiration dating period of (b) (4) for ramucirumab drug substance (DS) when stored at (b) (4) and an expiration dating period of 36 months for ramucirumab drug product (DP) when stored at 2-8 degrees Celsius.

DMA recommended multiple post-marketing commitments and requirements during the course of the review. These commitments included re-evaluation of both DS and DP lot release and stability specifications after manufacture of (b) (4) lots; confirmation of stability (b) (4) and performance of a shipping study to confirm validation of commercial ramucirumab DP shipping conditions. DMA recommended post-marketing requirements (PMRs) for Lilly to develop valid, sensitive, and accurate assays for the detection of binding and neutralizing antibodies to ramucirumab. Regarding these PMRs, DMA found that ramucirumab immunogenicity and neutralizing antibody assays were not characterized by sufficient drug tolerance. *Comment: Refer to Section 11.5 of this review for pertinent discussion with Lilly regarding these PMRs that occurred following the completion of the DMA reviews.*

3.1 Drug substance

Ramucirumab is a human monoclonal antibody against the vascular endothelial growth factor 2 receptor that contains two heavy gamma-1 chains and two light kappa chains. The gamma chains each contain 446 amino acid residues and the light chains each contain 214 amino acid residues. The predicted molecular weight of ramucirumab is (b) (4) . The DMA review stated that the ImClone Systems LLC site in Branchburg NJ manufactures DS in accordance with current Good Manufacturing Practices (GMP).

Lilly manufactures ramucirumab (b) (4) (b) (4)

3.2 Drug product

Dr. Dougherty stated that the major component of the DP was ramucirumab DS, 10 mg/mL, in a histidine (b) (4), including sodium chloride and glycine (b) (4) and polysorbate 80 (b) (4) . Lilly supplies DP in either 10 mL or 50 mL Type I glass vials stoppered with (b) (4) stoppers and sealed (b) (4) . During the clinical development of ramucirumab, commercial manufacturing was transferred multiple times. DP will be manufactured by Lilly in Indianapolis, Indiana.

Ramucirumab DP is a sterile, preservative-free solution at pH 6.0. Lilly supplies ramucirumab DP as a clear to slightly opalescent, colorless to slightly yellow solution that is free from visible particles.

3.3 Quality microbiology

Dr. Suvarna and Dr. Hughes recommended approval of ramucirumab from a product (drug substance) quality perspective. FDA inspected the drug substance manufacturing site (ImClone Systems Branchburg, NJ) from 4 Nov 2013 to 13 Nov 2013 and classified the site as NAI (no action indicated). Dr. Suvarna found the microbial control of the drug substance manufacturing process to be acceptable.

Dr. Gomez Broughton and Dr. Hughes recommended approval of the amended BLA from a product quality (drug product) microbiology perspective. Among other analyses, ramucirumab met acceptance criteria regarding the microbial quality of the drug product. The DP Quality Microbiology review described ramucirumab as a sterile, preservative-free, 10 mg/mL solution for intravenous infusion.

4. Nonclinical Pharmacology/Toxicology

Dr. Khasar, the primary nonclinical reviewer, concluded that the nonclinical studies were sufficient to support the use of ramucirumab in the proposed patient population and that there were no outstanding nonclinical pharmacology/toxicology issues preventing the approval of ramucirumab.

4.1 Nonclinical pharmacology

The nonclinical overview in the BLA stated that a surrogate antibody for ramucirumab (DC101) was used for initial nonclinical pharmacology testing because ramucirumab is not cross-reactive in mice. The applicant stated that DC101 exhibited anti-tumor and anti-angiogenic activity in a broad range of mouse xenograft models; however, cross-species extrapolation regarding exposure (to observe anti-tumor activity) was limited based on the lower affinity of DC101 for the murine receptor and differences in the route of exposure (intraperitoneal) with resultant differences in pharmacokinetics. Lilly stated in the report that 18 micrograms/mL was the targeted serum concentration in the first-in-humans study based on the estimated minimum circulating plasma concentration of DC101 required to significantly inhibit the growth of tumors in a pancreatic cancer xenograft model (BxPC-3).

Other *in vitro* and *in vivo* studies characterized ramucirumab as a monoclonal antibody that binds to human vascular endothelial growth factor receptor 2 (VEGFR2) and that ramucirumab

can displace the VEGFR2 ligands including VEGF-A, VEGF-C, and VEGF-D. Ramucirumab demonstrated antiangiogenic effects in a mouse model using mice subcutaneously implanted with a mix of human endothelial progenitor cells and adipose-derived stem cells.

4.2 Nonclinical toxicology

Nonclinical toxicology testing was conducted in monkeys because ramucirumab only binds to human and non-human primate VEGF2. Lilly submitted the results of 5-week (dose levels tested up to 40 mg/kg administered on days 1, 15, 22, and 29) and 39-week (doses levels tested up to 50 mg/kg every week) GLP compliant toxicity studies conducted in cynomolgus monkeys in support of the BLA.

In both the 5- and 39-week studies, high levels of creatine phosphokinase (CPK) were detected which were not dose-related. The non-clinical reviewer described evidence of correlated histopathologic findings in skeletal muscle in the 5- but not in the 39-week study. The non-clinical review also stated that there were findings of mineralization and inflammation of gray matter as well as lymphocytic cuffing in the meninges and choroid plexus in animals from all ramucirumab dose groups.

The applicant reported renal toxicity in the 39 week study including moderate to severe glomerulonephritis at doses ≥ 16 mg/kg. The non-clinical reviewer stated that these effects may be delayed and that these effects were not observed at the mid-term sacrifice on Day 85 of the study. *Anti-VEGF antibodies (or anti-VEGFR antibodies) appear to cause proteinuria and nephrotic syndrome as a class effect.*

Ramucirumab did not impair wound healing in monkeys on Day 8 following a single dose of up to 50 mg/kg ramucirumab; however, Lilly stated that this risk cannot be discounted based on the importance of VEGF/VEFR-2 in wound healing.

Ramucirumab caused bone growth plate changes in immature monkeys after 39 weeks of weekly intravenous infusions at 5 mg/kg. Lilly stated that this was an anticipated finding; however this would not be expected to affect older adults in the indicated population (previously treated patients with gastric cancer).

In accordance with ICH S6, Lilly did not submit genotoxicity data in the BLA for this biotherapeutic protein not expected to interact with DNA or other chromosomal material. Lilly also did not submit a carcinogenicity study in accordance with ICH S9. In lieu of a dedicated reproductive toxicology study, Lilly submitted a literature-based assessment of the potential effects of inhibition of VEGF2 signaling during pregnancy (performed in accordance with principles cited in the ICH S9 document). FDA review staff agreed that the scientific literature supports a critical role for VEGR2 signaling in the maintenance of pregnancy and in embryonic vasculogenesis. The non-clinical review staff stated that ramucirumab should not be used during pregnancy unless the benefits to the mother outweigh the risk to the fetus.

5. Clinical Pharmacology

5.1 General clinical pharmacology considerations

The clinical pharmacology review team (Dr. Zhang as primary reviewer) concluded that this BLA is acceptable from a clinical pharmacology perspective. The applicant submitted limited pharmacokinetic data from Trial JVBD (primary randomized trial submitted in support of the application) from 58 patients. The applicant discussed these limitations (for the conduct of population PK analyses) with FDA prior to submission of the BLA. Nevertheless, these limitations precluded substantive analyses of exposure-response in Trial JVBD and analyses of PKs in different patient subgroups.

OCP (Office of Clinical Pharmacology) recommended a post-marketing requirement to evaluate immunogenicity with an improved assay because the assays used in the detection of anti-ramucirumab antibodies and neutralizing antibodies were interfered (based on data reviewed in the application) by the presence of ramucirumab in the patients' serum samples. *Comment: Refer to Section 11.5 of this review for pertinent discussion with Lilly regarding these PMRs that occurred following the completion of the OCP reviews.*

5.1.1 Dose selection

The applicant submitted results of two dose finding trials: Study JVBM evaluated the safety of weekly doses of ramucirumab from 2 to 16 mg/kg and Study JVBN evaluated the safety of ramucirumab administered either every two weeks (6 to 10 mg/kg) or every three weeks (15 to 20 mg/kg). A maximum tolerated dose was not identified in either group in Study JVBN.

In determining a dose to evaluate in Trial JVBD, the applicant targeted a serum concentration associated with inhibition of tumor growth in a preclinical xenograft model (C_{min} > 18 μg/mL). Additionally, the applicant stated that the PK profile of ramucirumab appeared linear at doses of 8 mg/kg and above, suggesting saturation of the target-mediated clearance pathway.

Dr. Zhang stated in her review that approximately 95% of the 58 patients in the PK subgroup of Trial JVBD (primary randomized gastric cancer trial) achieved a ramucirumab C_{min} > 18 μg/mL.

5.1.2 Pharmacokinetics

The applicant submitted results of Study JVBW characterizing the pharmacokinetics of ramucirumab in 6 Japanese patients with gastric cancer who received ramucirumab 8 mg/kg every other week in combination with paclitaxel (80 mg/m^2 intravenously on days 1, 8, and 15 of 28 day cycles). The OCP review summarized data from 6 patients following the first dose of ramucirumab and 4 patients following the third dose of ramucirumab. The geometric half-life was approximately seven and a half days following the first dose of ramucirumab; however, data (for this analysis) were obtained from only four patients and the terminal elimination half-life may not have been completely captured (as PK data were collected up to 14 days following the first dose).

In addition to the limitations described above, the OCP reviewer stated that cross-study PK profiles from two studies evaluating ramucirumab in patients with solid tumors (JVBI and the

previously described JVBN) suggested that Japanese patients may have higher exposure than non-Japanese patients. Accordingly, OCP recommended removal of PK findings from the Japanese study in the U.S. product label.

OCP recommended summarizing PK data in the label from the JVBD gastric cancer trial stating that the geometric mean of the serum ramucirumab minimum concentration (C_{min}) was 50 μg/mL after the third dose and 74 μg/mL after the sixth dose.

5.2 Drug-drug interactions

Ramucirumab is not expected to have an effect on CYP enzymes or be metabolized by CYP enzymes and therefore unlikely to have clinically relevant drug-drug interactions.

5.3 Demographic interactions/special populations

OCP recommended that the label contain no statements describing how intrinsic factors influence PKs based on the limited PK data collected in Trial JVBD. Body weight showed a possible effect on PKs; however, lower weight patients maintained target concentrations greater than 18 μg/mL.

5.4 Thorough QT study or other QT assessment

Ramucirumab is a therapeutic monoclonal antibody and as such is not expected to inhibit hERG function or other ion channels involved in cardiac repolarization. Nevertheless, the applicant submitted the results of one study that evaluated the effects of ramucirumab on QT intervals. This study (JVBK) was a multicenter, open-label, single-arm trial evaluating ramucirumab 10 mg/kg as a single agent administered every three weeks for a minimum of 9 weeks to patients with advanced solid tumors. The OCP review stated that no clinically relevant changes in the mean QTc were detected.

6. Clinical Microbiology

This section is not applicable to this review.

7. Clinical/Statistical-Efficacy

The clinical reviewer (Dr. Sandra Casak) recommended approval of this application based on the improvement in overall survival demonstrated in the JVBD clinical trial that was supported by data received in the application from the JVBE clinical trial. Both clinical trials enrolled patients with previously treated metastatic gastric cancer (or GEJ cancer). The statistical reviewer (Dr. Hui Zhang) concluded that based on the data and analyses from JVBD, ramucirumab plus best supportive care demonstrated a statistically significant improvement in OS and PFS.

This section of the CDTL review will focus on the demonstration of safety and efficacy in adequate and well controlled trials (predominantly JVBD with supportive efficacy findings from JVBE) and thus will not focus on trials in other indications (e.g., that provided safety data) or on trials that supported the dose of ramucirumab (refer to Clinical Pharmacology Section above).

7.1 Background of clinical program

The initial protocol for the pivotal trial [JVBD (I4T-IE-JVBD) also known as REGARD and previously listed as IMCL CP12-0715)] was dated 5 Mar 2008 and contained the following title: A Phase 3, Randomized, Double-Blinded Study of IMC-1121B and Best Supportive Care (BSC) Versus Placebo and BSC in the Treatment of Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy.

During the review of the application, Lilly informed FDA of the results of a second randomized trial evaluating the use of ramucirumab in patients with gastric cancer who were previously treated with platinum and a fluoropyrimidine. This trial was listed as JVBE (I4T-IE-JVBE) and previously listed as IMCL CP12-0922 (also known as RAINBOW) and contained the following title: 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.

7.2 Design of JVBD

7.2.1 Primary endpoint (JVBD)

The primary endpoint of JVBD was overall survival (OS), defined as the time from randomization to the date of death from any cause. *Comment: As stated in the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf; accessed on 03 Oct 2013), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.*

7.2.2 Secondary endpoints (JVBD)

Secondary endpoints defined by the original protocol included progression free survival (PFS), 16-week PFS, overall response rate, and duration of response. The protocol stated that the overall significance level for PFS was 0.05; significance levels were not described for the other endpoints.

The protocol defined progression free survival as the time from the date of randomization until the date of objectively determined progressive disease or death due to any cause. The protocol included a provision to censor patients who died (in the PFS analysis) without evidence of tumor progression at the time of the last tumor analysis if the patient died after missing two or more tumor assessments.

The use of investigator assessments for progression (and response) was acceptable because the primary endpoint was overall survival (i.e., the PFS and ORR endpoints are considered supportive of the overall survival results). Additionally, this trial was blinded which allows for increased confidence in the overall PFS results.

The protocol defined 16-week PFS as the proportion of the ITT population alive and progression-free 16 weeks after randomization, as extracted from the Kaplan-Meier curves. *Comment: This reviewer recommends against the inclusion of results from this endpoint in product labeling because this landmark analysis does not provide an informative estimate of the overall treatment effect on progression free survival (e.g., as opposed to estimates based on the hazard ratio).*

The protocol defined overall tumor response as the proportion of all patients with a confirmed partial response (PR) or complete response (CR) according to RECIST criteria from the start of treatment until disease progression or recurrence. Confirmation required a repeat assessment no less than four weeks following documentation of the initial response. The protocol defined duration of response from the time that a patient first met criteria for CR/PR until the first date that criteria for progressive disease were met or death was documented. Patients without progression were censored on the day of their last tumor assessment.

7.2.3 Eligibility criteria (JVBD)

Patients with histologically or cytologically confirmed and measurable metastatic gastric or gastroesophageal junction adenocarcinoma were eligible for enrollment in the clinical trial. The protocol also allowed for enrollment of patients with locally-recurrent, unresectable, refractory disease if the patient had lymph node metastases. The protocol required previous treatment with combination chemotherapy that included a platinum or a fluoropyrimidine 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 listed the following additional eligibility criteria (*for brevity, only select criteria are listed*): age ≥ 18 years, ECOG 0-1; total bilirubin ≤ 1.5 mg/dL; urinary protein ≤ 1+ on dipstick or < 1,000 mg of protein in a 24 hour urine collection if 2+ on dipstick; New York Heart Association Class I function or better if a patient was previously exposed to an anthracycline.

The protocol excluded patients with the following (*for brevity, only select criteria are listed*): ≥ Grade 3 bleeding within 3 months, arterial thrombotic event within 6 months; symptomatic heart failure; unstable angina pectoris; uncontrolled thrombotic disorder; uncontrolled hemorrhagic disorder; uncontrolled or poorly controlled hypertension; serious or non-healing wound, ulcer, or bone fracture; major surgery within 28 days; venous access device placement within seven days; and receipt of chronic anti-platelet therapy other than once daily aspirin (≤ 325 mg/day). *Comment: the protocol restricted anti-platelet therapy during the course of the study; however, anticoagulant therapy was permitted if the patient did not have a pathological condition that would subject the patient to high risk of bleeding (for example, tumor involving major blood vessels).*

7.2.4 General study design/treatment plan (JVBD)

- The trial was a double-blinded, randomized (2:1), multi-center, international trial. Randomization occurred via an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS). The protocol instructed investigators to

initiate ramucirumab or placebo within 7 days of randomization. The protocol allowed for unblinding only for emergency purposes.

- JVBD randomized patients to receive either placebo or ramucirumab every two weeks at a dose of 8 mg/kg. Patients in both arms received best supportive care.
- The protocol contained recommendations for the management of infusion reactions including the requirement for permanent discontinuation of ramucirumab or placebo for Grade 3 or 4 infusion reactions.
- The protocol contained instructions for the management of hypertension. If a patient required interruption of study therapy more than once for hypertension, the protocol recommended dose reduction to 6 mg/kg every other week. A second dose reduction to 5 mg/kg was permitted if study related therapy required interruption a third time. The protocol required permanent discontinuation of ramucirumab or placebo for Grade 4 hypertension or poorly controlled hypertension (> 160 mm Hg systolic or > 100 mmHg diastolic for > 4 weeks despite oral antihypertensive therapy).
- The protocol required interruption of ramucirumab or placebo if proteinuria developed that was ≥ 2 grams in 24 hours. If proteinuria decreased to less than 2 grams (in 24 hours) within 2 weeks, treatment could be reinitiated at a reduced dose (6 mg/kg).
- The protocol allowed up to two dose reductions (to 6 mg/kg and 5 mg/kg) for non-life threatening Grade 3 or 4 adverse events (e.g., fatigue, anorexia, and fever) according to NCI-CTCAE Version 3.0 (dose interruption alone was permitted following the first occurrence of such an event).
- Patients continued either blinded placebo or ramucirumab until progressive disease, unacceptable toxicity, decline of ECOG PS of ≥ 2 points, or withdrawal of consent.
- Patients underwent assessments for tumor size every 8 weeks. To assess for response and progression (via RECIST guidelines), the protocol recommended CT scans of the chest and abdomen with contrast (unless contrast was contraindicated). For patients with contraindications to contrast, the protocol recommended CT of the chest without contrast and MRI of the abdomen. Additional imaging (e.g., bone scans) was permitted if clinically indicated.
- Following discontinuation of placebo or ramucirumab, the protocol stipulated follow-up of surviving patients every three months for a minimum of 18 months and a maximum of 40 months to obtain survival information and information regarding subsequent anticancer therapy.
- While patients received placebo or ramucirumab, the protocol required bi-weekly evaluations of vital signs, performance status, adverse events (severity assessed using NCI-CTCAE Version 3.0), and chemistry and hematology labs. Investigators also collected a blood sample for anti-product antibodies at baseline, prior to Cycle 5, prior to Cycle 9, and during the 30 day follow-up visit following the end of study-related treatment.
- The protocol established an Independent Data Monitoring Committee (IDMC) with meetings at least twice a year, when 50 and 150 patients received at least two cycles of

study drug (or died or discontinued prior to two cycles), and for interim analyses of futility and efficacy.

7.2.5 Statistical design and analysis issues (JVBD)

Randomization/Stratification Factors
The original protocol specified the following two stratification factors: weight loss (≥ 10% over the prior 3 months versus < 10%) and geographic region (North America, Australia, and New Zealand versus South and Central America versus Asia).

Determination of Sample Size
The protocol stated that 651 patients were to be randomized (2:1) to each arm. A total of 531 events (deaths) were required for 90% power to identify an improvement in OS at a HR of 1.33 (estimated OS of 5 months in the placebo arm and 6.65 months in the ramucirumab arm) at a 0.05 two-sided significance level. This sample size accounted for one interim analysis to be conducted after 75% of events occurred. Alpha would be adjusted using methods described by Lan and DeMets. The protocol also specified three interim futility analyses.

Analyses
The protocol stated that the primary efficacy analysis for overall survival would be tested using a stratified log-rank test. The protocol specified that the primary analysis would be conducted using the intent-to-treat population consisting of all patients randomized. The protocol stated that the overall significance level for the secondary endpoint of PFS was 0.05 (overall alpha maintained using a hierarchical testing procedure).

7.2.6 Protocol amendments (JVBD)

Version 2.0 (dated 22 Jul 2008)
The following list describes major changes contained in Version 2.0 of the protocol:

- Modified eligibility guidelines to require a hemoglobin concentration of ≥ 9 gm/dL (versus 8 gm/dL).
- Clarified that patients are eligible if they have either metastatic disease or locally-recurrent, unresectable, refractory disease with measurable lymph node metastases.
- Added location of primary tumor as a stratification factor (gastric versus GEJ site) at randomization and a stratification factor in the analyses described in the statistical analysis section.
- Allowed for premedication prior to administration of ramucirumab or placebo based on investigator discretion. Recommendations for Grade 1 and 2 infusion reactions were also updated.
- Required more frequent monitoring for bleeding if the hemoglobin concentration fell below 9 g/dL and there were signs or symptoms of bleeding.

Version 3.0 (dated 24 November 2008)

No patient was enrolled prior to this amendment. The following list describes major changes contained in Version 3.0 of the protocol [Version 3.1, dated 23 Dec 2008 was submitted to update the EudraCT (European Union Drug Regulating Authorities Clinical Trial) number]:

- Changed a secondary endpoint from 16 week PFS to 12 week PFS (*this reviewer's comment above regarding 16 week PFS also applies to this endpoint*).
- Removed the requirement for "refractory" disease in patients with locally-recurrent unresectable disease and clarified that at least one measurable lymph node metastasis was required.
- Eligibility criteria modified to allow patients with evaluable disease (e.g., measurable disease not required) *(this criteria appeared to conflict with the prior criterion for patients with locally recurrent, unresectable disease).*
- Required assessments for tumor size every six weeks rather than every 8 weeks.
- Changed the timing for IDMC assessments of safety data.
- Changed censoring criteria for PFS to censor data on the date of the last objective tumor assessment for patients who began a new anticancer therapy.

Version 4.0 (dated 1 Jul 2009)

The following list describes major changes contained in Version 4.0 of the protocol:

- Removed language mandating the (b) (4) maximum follow-up duration for survival.
- Updated the protocol to use NCI-CTCAE Version 4.0 (rather than Version 3.0) to assess the severity of adverse events.
- Amended geographic region strata as follows: North America, Europe, Australia, and New Zealand versus South and Central America, India, Egypt, South Africa, Jordan, Lebanon, and Saudi Arabia versus Asia *(this change added African countries, Middle Eastern countries, and India to the South and Central America stratum, rather than the Asian stratum).*
- Revised the primary eligibility criteria to state "The patient has metastatic disease or locally recurrent, unresectable disease." Three bullets followed this statement: (1) Patients with non-regional lymph node metastases are eligible; lymph node metastases must be measured as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.0; (2) Patients with locally-recurrent, unresectable disease are eligible; (3) For patients who have received prior radiotherapy, 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. *This reviewer interpreted this statement to indicate that patients with locally recurrent, unresectable disease were eligible irrespective of the presence of a lymph node metastasis (although this was not clear based on the first and second bullets).*
- Clarified that no increase in the dose of ramucirumab was permitted following dose reduction due to an adverse event.

Version 5.0 (dated 8 Feb 2010)

The following describes major changes contained in Version 5.0 of the protocol (Version 5.1, dated 20 April 2010 added a section to detail the handling of small target lesions and to amend instructions for the management of hypertension).

- Clarified that imaging was required every six weeks until documentation of progression or initiation of new anticancer therapy unless the investigator deemed such an evaluation as clinically not feasible.
- Updated the protocol to use NCI-CTCAE Version 4.02 (rather than Version 4.0) to assess the severity of adverse events.

Version 6.0 (dated 23 Nov 2010)

The following list describes major changes contained in Version 6.0 of the protocol.

- This amendment reduced the planned sample size from 615 patients to 315 patients and the number of events for the final analysis from 344 events to 256 events. Assumptions regarding the sample size reduction were changed including decreasing the power to (b) (4) and increasing the effect size that the study was powered to detect (HR of 1.45 with a median 5 months survival in the placebo arm versus 7.25 months in the ramucirumab arm). The amendment also eliminated the provision allowing for the interim analysis of efficacy.

  Comment: Of the 355 patients in the final OS analysis, only 39 (11%) signed informed consent prior to 23 Nov 2010. Furthermore, < 4% of events (deaths) occurred prior to this date. Thus, it is unlikely that this reduction in sample size compromised the integrity of the clinical trial.

- Removed language permitting the sponsor to provide waivers regarding the eligibility criteria.
- Required imaging assessments for PFS every six weeks until documented progression for patients who discontinued study therapy for any reason other than progressive disease.

Version 7.0 (approved 31 Oct 2011)

The following list describes major changes contained in Version 7.0 of the protocol.

- Increased the sample size from 315 to 348 patients and the number of events from 256 events to 268 events. This version allowed for a single interim *futility* analysis after (b) (4) of the total number of planned events. The protocol stated that the change in the sample size was based on adjustments to the accrual rate.
- Stipulated follow-up for survival every two months rather than every three months to reduce the delay in capturing deaths and allow more accurate survival times for patients alive at data cut-off.

  Comment: The planned futility analysis occurred during an IDMC meeting on 12 Dec 2011 (after the promulgation of this amendment).

7.3 Design of JVBE

As stated above, JVBE was a second large, international, randomized clinical trial evaluating ramucirumab in patients with previously treated gastric (or GEJ) adenocarcinoma.

7.3.1 Primary endpoint (JVBE)

The primary endpoint of JVBE was overall survival (OS), defined as the time from randomization to the date of death from any cause.

7.3.2 Secondary endpoints (JVBE)

Planned secondary endpoints included progression free survival (PFS), time to progression (TTP), and best overall response (BOR).

PFS was defined as the time from randomization until the first radiographic documentation of progression as defined by RECIST (Version 1.1) or death due to any cause. The protocol contained a provision to censor data on the date of a patient's last tumor assessment for patients lost to follow-up, after two or more consecutive missing radiographic visits, or if the patient was alive and without progression on the data cut-off date. If no baseline or post-baseline radiographic assessment was available, data was censored at the date of randomization (for the PFS analysis).

TTP was defined from the time of randomization until the date of radiographic progression according to RECIST guidelines. Best overall response was determined using RECIST criteria (Version 1.1).

7.3.3 Eligibility criteria (JVBE)

Patients with histologically or cytologically confirmed, unresectable or metastatic gastric or gastroesophageal adenocarcinoma were eligible for the trial. The protocol required previous treatment with a platinum and fluoropyrimidine in the first-line setting for unresectable or metastatic gastric (or GEJ) cancer. Patients in JVBE must have progressed during first-line therapy or within four months after the last dose of first-line therapy.

The protocol listed the following additional eligibility criteria (*for brevity, only major select criteria are listed*): age ≥ 18 years; ECOG 0-1; total bilirubin ≤ ULN; urinary protein ≤ 1+ on dipstick or < 1,000 mg of protein in a 24 hour urine collection if 2+ on dipstick; and an INR ≤ 1.5.

The protocol excluded patients with the following (*for brevity, only select criteria are listed*): major surgery within 28 days; previous anti-VEGF therapy; history of DVT, PE, or thromboembolism within previous three months; receiving therapeutic anticoagulation with warfarin, heparins, or similar agents; chronic NSAID or aspirin use (aspirin up to 325 mg/day was permitted); significant bleeding disorders; gastrointestinal perforation or fistula within the prior 6 months; symptomatic heart failure; any arterial thrombotic event within 6 months; uncontrolled hypertension (≥ 150/90 mmHg despite standard medical management); serious or non-healing wound or ulcer; history of bowel obstruction; or history of other serious medical illness or condition.

7.3.4 General study design/treatment plan (JVBE)

- The trial was a double-blinded, randomized (1:1), multi-center, international trial. Randomization occurred via an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS).

- The protocol instructed investigators to initiate paclitaxel in combination with either ramucirumab or placebo within 7 days of randomization. The protocol allowed for unblinding only for emergency purposes.
- JVBE randomized patients to receive paclitaxel 80 mg/m^2 on days 1, 8, and 15 of every four week cycle in combination with either placebo or ramucirumab 8 mg/kg on days 1 and 15 of each four week cycle. The protocol instructed investigators to administer paclitaxel intravenously at least one hour after the ramucirumab infusion for the first two cycles. The protocol stated that the one hour observation period could be omitted if no infusion-related reactions occurred during the first two cycles.
- The protocol allowed for the discontinuation of one of the agents (paclitaxel or ramucirumab / placebo) if the toxicity was recognized as being caused by the agent (e.g., hypertension with ramucirumab).
- For paclitaxel, no dose modification was permitted within a cycle (paclitaxel was to be withheld for specified reasons including severe neutropenia, renal insufficiency, and liver toxicity). The protocol permitted paclitaxel dose reductions (by 10 mg/m^2) during the following cycle for Grade 4 hematological toxicity or Grade 3 non-hematological toxicity. The protocol required permanent discontinuation of paclitaxel if 60 mg/m^2 was not tolerated or following paclitaxel-related life-threatening adverse events.
- The protocol contained recommendations for the management of infusion reactions including the requirement for permanent discontinuation of ramucirumab or placebo for Grade 3 or 4 infusion reactions.
- The protocol contained instructions for the management of hypertension. If a patient required interruption of study therapy more than once for hypertension, the protocol recommended dose reduction to 6 mg/kg every other week. A second dose reduction to 5 mg/kg every other week was also permitted if a patient required interruption a third time. The protocol required permanent discontinuation of ramucirumab or placebo for Grade 4 hypertension or poorly controlled hypertension (> 160 mmHg systolic or > 100 mmHg diastolic for > 4 weeks) despite oral antihypertensive therapy.
- The protocol required interruption of ramucirumab or placebo if proteinuria developed that was ≥ 2 grams in 24 hours. If proteinuria decreased to less than 2 grams (in 24 hours) within 2 weeks, treatment could be reinitiated at a reduced dose (6 mg/kg).
- The protocol allowed up to two dose reductions of ramucirumab or placebo (to 6 mg/kg and 5 mg/kg) for non-life threatening Grade 3 or 4 adverse events (e.g., fatigue, anorexia, and fever) according to NCI-CTCAE Version 3.0 (dose interruption alone was also permitted following the first occurrence of such an event).
- In general, patients continued either blinded placebo or ramucirumab until progressive disease (radiographic or *symptomatic*), unacceptable toxicity, or withdrawal of consent.
- Patients underwent assessments for tumor size every 6 weeks. To assess for response and progression (via RECIST guidelines), the protocol required CT scans of the thorax, abdomen, and pelvis (MRI was a complimentary method to assess the abdomen and pelvis).

- The protocol instructed investigators to contact patients every two months to obtain information regarding survival status and information regarding subsequent systemic anticancer therapy or disease progression.
- The protocol required a hematology profile and liver profile within 24 hours of administering paclitaxel on days 1, 8, and 15 of each cycle. Investigators obtained a full chemistry profile on day 1 of each treatment cycle. Vital signs were obtained before and at the completion of each ramucirumab (or placebo) dose and after the completion of chemotherapy. A urinalysis was also obtained biweekly while either ramucirumab or placebo was administered.
- The protocol established an Independent Data Monitoring Committee (IDMC) with meetings at least twice a year, until all patients were randomized and received two 4-week cycles of study-related treatment (or discontinued the study or died).

7.3.5 Statistical design and analysis issues (JVBE)

Randomization/Stratification Factors

The initial protocol specified the following stratification factors: disease measurability (measurable versus non-measurable); geographic region [Europe (including Israel) / North America / Australia versus Asia versus rest of the world (including South America)]; and time to progression on first-line therapy (< 6 months versus ≥ 6 months). The protocol used stratified permuted block randomization to assign patients into treatment arms.

Determination of Sample Size

The initial protocol stated that 663 patients were to be randomized (1:1) to each arm. A total of 510 events (deaths) were required for (b) (4) power to identify an improvement in OS at a HR of 0.75 (estimated OS of 7 months in the paclitaxel plus placebo arm and 9.33 months in the paclitaxel plus ramucirumab arm) at a 0.025 one-sided significance level. The protocol specified one interim analysis for futility after (b) (4) of the projected events occurred (the futility boundary was specified in the protocol).

Analyses

The protocol stated that the primary efficacy analysis for overall survival would be tested using a stratified log-rank test. The protocol specified that the primary analysis would be conducted using the intent-to-treat population consisting of all patients randomized. The protocol stated that the overall significance level for PFS was 2.5% (one-sided) and that the other endpoints would be analyzed in a "non-confirmatory sense."

7.3.6 Protocol amendments (JVBE)

Version 2.0 (dated 06 Dec 2010)

The following describes major changes contained in Version 2.0 of the protocol:

- Clarified that patients were eligible with a diagnosis of gastric or gastroesophageal junction adenocarcinoma (rather than gastroesophageal adenocarcinoma).
- Changed the frequency of tumor assessments (from every 6 weeks) to every 6 weeks for the first 6 months following the first dose followed by every 9 weeks thereafter.

Version 3.0 (dated 08 Oct 2012)

The following list describes major changes contained in Version 3.0 of the protocol:

- Allowed for more frequent collection of survival information.
- Incorporated extension language to permit the continuation of study treatment in patients who were receiving clinical benefit following the completion of the study.
- Amended the dose modification section for ramucirumab / placebo to permit continued dosing in the setting of certain non-life threatening and reversible Grade 3 to 4 adverse events (e.g., Grade 4 fever or certain laboratory abnormalities).

7.4 Efficacy results (JVBD)

The first patient was enrolled into JVBD (monotherapy study) on 6 Oct 2009 and the last patient was enrolled on 10 Jan 2012. A total of 459 patients were screened, and 104 patients were not randomized (with the majority related to ineligibility for one or more of the exclusion criteria). The study data cut-off date was 25 Jul 2012, and 290 patients died on or prior to the date of data cut-off.

7.4.1 Demographics (JVBD)

Median age of patients randomized to the ramucirumab arm was 60 years (range 31 to 86) versus 61 years (range 24 to 88) in the placebo arm. The majority of patients in both arms (73%) had the primary tumor present at trial entry. Table 3 (data from Dr. Casak's review) shows that the gender and ethnic background of patients enrolled into JVBD were similar between arms.

Table 3 Demographics, JVBD

	Ramucirumab N=238 (%)	Placebo N=117 (%)
Age		
≥ 65 years	34	39
Female		
Yes	29	32
Race		
White	76	78
Black	2	2
Asian	16	15
Other	6	6
Geographic Region		
Region 1	69	69
Region 2	23	25
Region 3	8	7

Region 1 = North America, Europe, Australia, New Zealand
Region 2 = South and Central America, India, South Africa, Jordan, Egypt, Saudi Arabia, Lebanon
Region 3 = Other Asian countries

In general, demographic characteristics of patients were balanced in the two arms. Patients in the placebo arm had a modestly higher incidence of intestinal histology; however, the more

aggressive diffuse histology was balanced in the two arms. Patients in the placebo arm also had modestly increased incidence of peritoneal metastases.

Table 4 Disease characteristics at baseline, JVBD

	Ramucirumab N=238 (%)	Placebo N=117 (%)
ECOG PS		
0	28	26
1	72	73
2	0	1
Weight loss ≥ 10%		
Yes	17	17
Primary site of disease		
Gastric	75	74
GEJ	25	26
Histology		
Intestinal	22	30
Diffuse	40	38
Other/not-available	38	32
Metastases		
≥ 3 Sites	33	39
Peritoneal	27	38
Liver	44	48

7.4.2 Disposition (JVBD)

The cut-off date for the data-analysis was 25 Jul 2012. A total of 236 out of 238 patients in the ramucirumab arm and 115 of 117 patients in the placebo arm received study-directed investigational drugs. Table 5 (data from Dr. Casak's review) shows the reasons for discontinuation of ramucirumab or placebo during the trial. Most patients in both arms discontinued due to progressive disease; however, a higher proportion of patients discontinued due to progressive disease or death in the placebo arm. More patients who received ramucirumab discontinued due to an adverse event.

Table 5 Patient disposition, JVBD

	Ramucirumab N=238 (%)	Placebo N=117 (%)
Progressive disease	53	62
Symptomatic deterioration	17	14
Death	8	11
Withdrawal of consent	3	2
Adverse event	11	6
Other reasons	1	3

The investigators (and applicant) appeared to adequately follow patients for survival. Six patients were lost to follow-up and six additional patients withdrew consent for OS follow-up (constituting less than 5% of the randomized population).

7.4.3 OS analyses (JVBD)

Table 6, data obtained from the statistical review, shows the OS results determined at the time of data-cut off (25 Jul 2012). Seventy-eight percent of patients died (across both arms) by the time of data-cut off, constituting a mature analysis of survival. The pre-specified analysis of OS was statistically significant at the two-sided 0.05 level. The applicant conducted sensitivity analyses that supported the pre-specified findings [including analyses based on strata using CRF data (rather than entered in the IVRS), unstratified analyses, and the analysis at exactly 268 events]. The p value for each of these analyses was less than 0.05. More importantly, however, the results from a second trial (JVBE, see below) confirmed the results observed in Trial JVBD.

Although the magnitude of the effect was clinically modest, i.e., a median difference of 1.4 months with a hazard ratio of 0.78, the effect was observed with a manageable toxicity profile, especially when compared to drugs commonly administered to patients with cancer.

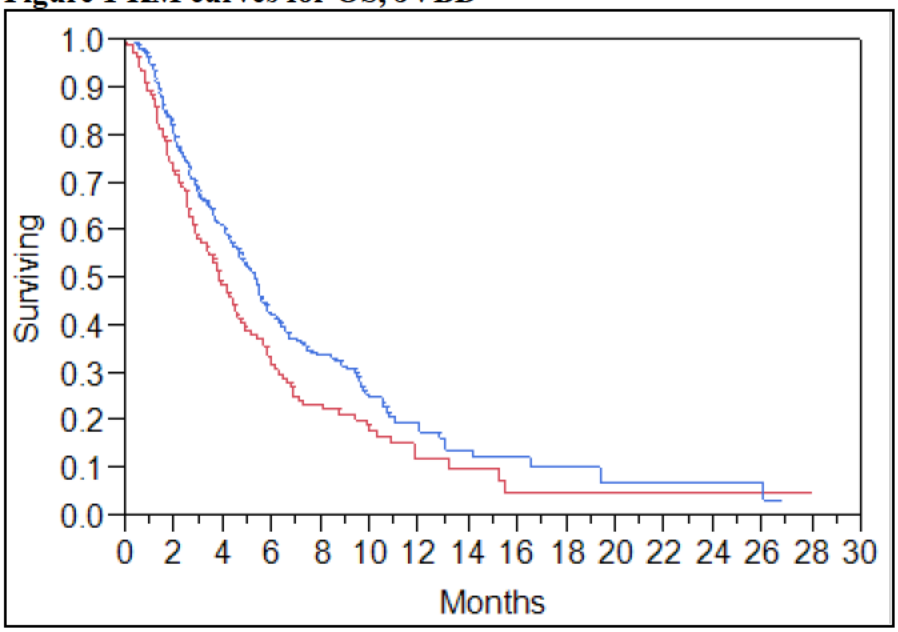
Table 6 OS analyses (ITT), JVBD

	Ramucirumab N=238	**Placebo N=117**
Number of deaths, n (%)	179 (75%)	99 (85%)
Median overall survival (months)	5.2	3.8
95% CI	(4.4, 5.7)	(2.8, 4.7)
HR (95% CI)	0.776 (0.603, 0.998)	
Stratified log-rank test p-value[a]	0.0473	

[a] Stratified by planned stratification factors (see above)

Figure 1, copied from the clinical review, shows the proportion of patients alive at each time point during the trial. The curves presented in the applicant's clinical study report and statistical review were similar to the KM curves presented in the clinical review (the statistical review shows the number of patients at risk at various time-points). Separation of the KM curves remained constant throughout the duration of the trial until the tails of the curves were reached. Because few patients were assessable after 9 months, no conclusions can be made regarding the tails of these curves.

Figure 1 KM curves for OS, JVBD



*blue (top) line is ramucirumab, red (bottom) line is placebo

Table 7 (data copied from the statistical review) shows that for almost all subgroups tested, that the HR (point estimate) was less than one. The 95% CIs crossed one for many of the analyses; however, the sample size in these subgroups was smaller (than the overall patient population) and thus these subgroups were not adequately powered to demonstrate a (nominally) statistically significant effect on OS.

Table 7 Subgroup analyses for OS, JVBD

Subgroup	N*	HR (95% CI)
Race		
White	181/91	0.78 (0.59, 1.04)
Asian	39/17	0.64 (0.31, 1.32)
Gender		
Women	69/38	1.43 (0.85, 2.41)
Men	169/79	0.68 (0.50, 0.92)
Age in years		
< 65	156/71	0.85 (0.61, 1.17)
≥ 65	82/46	0.72 (0.47, 1.11)
Region (see Table 3 above)		
1	165/80	0.94 (0.70, 1.26)
2	55/29	0.46 (0.27, 0.79)
3	18/8	0.63 (0.24, 1.63)
Prior Therapy		
Adjuvant or neoadjuvant	39/14	0.78 (0.37, 1.65)
Metastatic	199/103	0.79 (0.61, 1.04)
Histology		

Subgroup	N*	HR (95% CI)
Diffuse	96/44	0.56 (0.37, 0.86)
Intestinal	52/35	1.01 (0.58, 1.75)
Unknown	90/38	0.91 (0.58, 1.42)
Location of primary tumor		
Gastric	178/87	0.78 (0.58, 1.04)
GEJ	60/30	0.69 (0.43, 1.08)
ECOG PS		
0	67/31	1.08 (0.64, 1.81)
≥ 1	171/86	0.68 (0.51, 0.92)

*ramucirumab/placebo

The survival results from two subgroups (women and Region 1) from Trial JVBD were problematic at the time of the initial BLA submission in regards to whether the Agency should approve ramucirumab based on the results a single trial. The HR (point estimate) for OS in women was 1.43 suggesting worse overall survival in women receiving ramucirumab. While this reviewer agrees that there were potential explanations for this finding [including a higher proportion of women with diffuse histology receiving ramucirumab versus women receiving placebo (see clinical review)], this reviewer would expect to see additional data in this population in order to confirm or refute this finding (especially given the p value close to 0.05 in the ITT population and modest overall survival effect in the ITT population).

Additionally, the point estimate for OS in Region 1 that included North America, Europe, Australia, and New Zealand was close to 1.0 suggesting less of an effect in this region that is likely to be the most representative of the U.S. population. Although this reviewer agrees that such subgroup analyses should be interpreted with caution, and are likely related to chance effects in non-random populations, they can be problematic when data from only one study are available for review.

Ultimately, Lilly addressed these issues by submitting results from a second trial (JVBE) where the OS effects in women and in Region 1 appeared favorable in comparison with the overall ITT population (see analyses of Trial JVBE below). Furthermore, more women were enrolled in JVBE and based on the totality of the evidence, the ramucirumab treatment effect in women (and in U.S./North American patients) is likely best described by the ramucirumab treatment effect in the ITT population (rather than the specific effects observed in the subgroup analyses).

7.4.4 Secondary endpoints (JVBD)

Overall, the applicant reported few responses in each arm (less than 4%) so this review will not discuss this endpoint further. The primary secondary endpoint was progression free survival.

Table 8 (data copied from the statistical review) shows that ramucirumab increased progression free survival compared to control. The effect at the median was modest (less than one month); however, the separation in the curves (see clinical and statistical reviews) increased after the medians such that the hazard ratio may be a better indicator of the treatment

effect. *Comment: the lack of separation of the KM curves prior to (approximately) two months was likely influenced by the imaging schedule with the first CT scan obtained at week 8.*

Table 8 PFS analyses (ITT), JVBD

	Ramucirumab N=238	Placebo N=117
Number of events, n (%)	199 (84%)	108 (92%)
Median PFS (months)	2.1	1.3
95% CI	(1.5, 2.7)	(1.3, 1.4)
HR (95% CI)	0.483 (0.376, 0.620)	
Stratified log-rank test p-value[a]	< 0.0001	

[a] Stratified by planned stratification factors (see above)

Comment: Ultimately, the clinical benefit of ramucirumab is based on the effect on overall survival rather than any modest effect on PFS.

7.5 Efficacy results (JVBE)

As previously described, JVBE (the study that confirmed the results of JVBD) was a multinational, multicenter, randomized, double-blind study that evaluated ramucirumab in combination with paclitaxel in the treatment of patients with metastatic gastric cancer or GEJ adenocarcinoma following first-line platinum and fluoropyrimidine-containing chemotherapy regimens. Patients were randomized (1:1) to receive paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 of every 28-day cycle plus either placebo or ramucirumab (8 mg/kg every other week). The data cut-off date for Lilly's analysis was 12 July 2013, and patients were enrolled in the trial from 23 Dec 2010 to 23 Sep, 2012. A total of 665 patients comprised the intention-to-treat population with 330 patients in the ramucirumab arm and 335 patients in the placebo arm. A total of 516 patients died by the data cut-off date.

7.4.1 Demographics (JVBE)

Table 9 shows the major demographic characteristics to be balanced between the treatment arms. Compared to JVBD, JVBE enrolled a higher proportion of patients from Asia. Median age of patients enrolled in JVBE was 61 years in both arms.

Table 9 Demographics, JVBE

	Ramucirumab / paclitaxel N=330 (%)	Placebo / paclitaxel N=335 (%)
Age		
≥ 65 years	38	37
Female		
Yes	31	27
Race		
White	63	59
Asian	33	36
Other	4	5

	Ramucirumab / paclitaxel N=330 (%)	Placebo / paclitaxel N=335 (%)
Geographic Region		
Region 1	60	60
Region 2	7	6
Region 3	33	34

Region 1 = North America, Europe, Australia,
Region 2 = Argentina, Brazil, Chile, Mexico
Region 3 = Hong Kong, Japan, Korea, Singapore, Taiwan

Table 10 summarizes the major disease characteristics of patients across arms which appeared balanced. A slightly higher proportion of patients in the ramucirumab arm were ECOG PS 1 compared to the placebo arm. Eighty-one percent of patients in both arms had measurable disease and time to progression on first-line therapy was less than six months in 76% of patients across both arms. The majority of patients in both arms had documented metastases (98% for ramucirumab versus 97% for ramucirumab).

Table 10 Disease characteristics at baseline, JVBE

	Ramucirumab / paclitaxel N=330 (%)	Placebo / paclitaxel N=335 (%)
ECOG PS		
0	35	43
1	65	57
Weight loss ≥ 10%		
Yes	16	14
Primary site of disease		
Gastric	80	79
GEJ	20	21
Histology		
Intestinal	44	40
Diffuse	35	40
Mixed	6	4
Unknown	15	16

7.4.2 Disposition (JVBE)

Few patients enrolled in JVBE received treatment at the time of data cut-off: 4% in the ramucirumab arm and 2% in the placebo arm. Four patients in the ramucirumab arm and 5 in the placebo arm never received treatment. Disease progression constituted the most common reason for treatment discontinuation across both arms. Loss to follow-up (or withdrawal of consent with loss to follow-up occurred infrequently in both arms (Refer to Table 11 below for reasons for treatment discontinuation in JVBE).

Table 11 Patient disposition (reasons for treatment discontinuation), JVBE

	Ramucirumab / paclitaxel N=330 (%)	Placebo / paclitaxel N=335 (%)
Progressive disease	72	76
Death	4	4
Withdrawal of consent follow-up continued	6	2
Withdrawal of consent (no follow-up)	1	2
Loss to follow-up	0	< 1
Adverse event	12	11
Other reasons	1	1

7.4.3 OS analyses (JVBE)

As described above, Lilly amended their BLA to submit datasets from Study JVBE after submitting the BLA based on Study JVBD. Table 12, data obtained from the clinical review, shows the OS results determined at the time of data-cut off. Seventy-eight percent of patients died (across both arms) at the time of data-cut off, constituting a mature analysis of survival. The pre-specified analysis of OS was statistically significant at the two-sided 0.05 level. These results provided confirmation of the effects observed in Study JVBD.

The magnitude of effect when ramucirumab was added to paclitaxel was similar in terms of the observed hazard ratio; however, the difference in median survival between arms was slightly longer in JVBE (2.3 months) compared to the duration in JVBD (1.4 months).

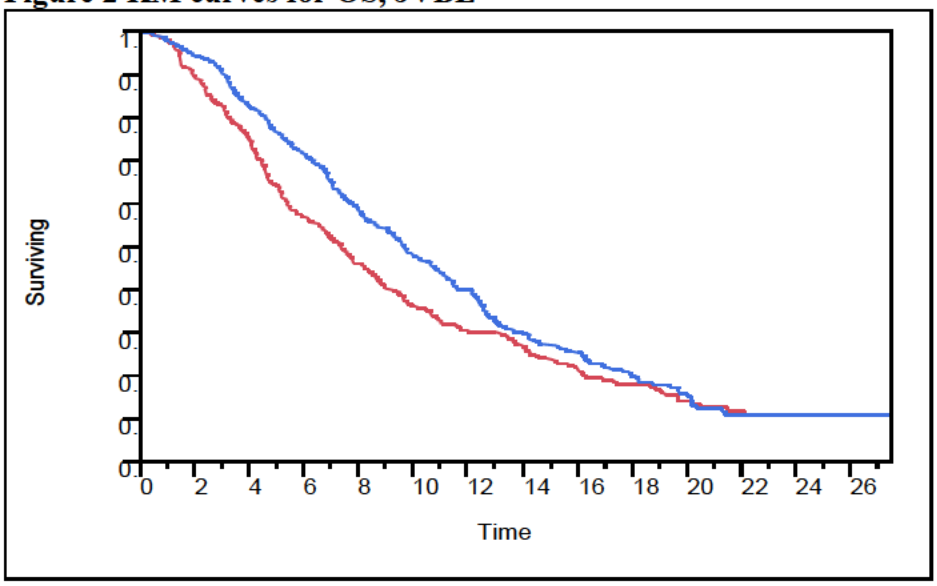
Table 12 OS analyses (ITT), JVBE

	Ramucirumab / Paclitaxel N=330	Placebo / paclitaxel N=335
Number of deaths, n (%)	256 (78%)	260 (78%)
Median overall survival (months)	9.63	7.36
95% CI	(8.48, 10.81)	(6.31, 8.38)
HR (95% CI)	0.807 (0.678, 0.962)	
Stratified log-rank test p-value[a]	0.0169	

[a] Stratified by planned stratification factors (see above)

Figure 2, copied from the clinical review, shows the proportion of patients alive at each time point during the trial. Separation in the KM curves remained constant throughout the duration of the curves until the tails of the curves were reached.

Figure 2 KM curves for OS, JVBE



*blue (top) line is ramucirumab plus paclitaxel, red (bottom) line is placebo plus paclitaxel

In order to further assess the efficacy results related to this application (specifically the request to approve ramucirumab as a monotherapy for patients with previously treated gastric cancer), the clinical reviewer focused on the subgroups of concern from the monotherapy study (JVBD).

In Study JVBD, the point estimate for the hazard ratio in Region 1 (including the United States) was 0.94 raising the potential concern of a smaller effect in U.S. patients (or more accurately, patients who received similar standards of care to that in the United States). In Study JVBE, 398 patients were randomized from Region 1 (constituting a randomization stratum) and the point estimate for the hazard ratio for OS was 0.73 (95% CI: 0.58, 0.91). This estimate provided supportive evidence that the effect observed in JVBD was a chance finding in an underpowered subgroup and that the ITT point estimate is better descriptor of the overall treatment effect among all patients (including those enrolled in Region 1).

More concerning than the regional treatment effect was the potential for a detrimental treatment effect among women. In JVBD, the point estimate for the hazard ratio for OS was 1.43 (95% CI: 0.85, 2.41) in the female subgroup of patients. As described above and in the clinical review, imbalances in baseline prognostic factors existed that could *potentially* explain this finding. Nevertheless, review of a second study was important in order to either confirm or refute this explanation. A total of 193 women were randomized in JVBE (a larger number than in JVBD) and the point estimate for the hazard ratio for OS among women was 0.672 (95% CI: 0.483, 0.935). This point estimate was lower than the point estimate in the ITT population. This estimate provided supportive evidence that the effect observed in women in JVBD was a chance finding and that the ITT point estimate is a better descriptor of the overall treatment effect among all patients (including women).

7.4.4 Secondary endpoints (JVBE)

Table 13, data copied from the clinical review, shows that ramucirumab plus paclitaxel modestly increased PFS compared to paclitaxel alone.

Table 13 PFS analyses (ITT), JVBE

	Ramucirumab / Paclitaxel N=330	Placebo / paclitaxel N=335
Number of events, n (%)	279 (85%)	296 (88%)
Median PFS (months)	4.40	2.86
95% CI	(4.24, 5.32)	(2.78, 3.02)
HR (95% CI)	0.635 (0.536, 0.572)	
Stratified log-rank test p-value[a]	< 0.0001	

[a] Stratified by planned stratification factors (see above)

8. Safety

8.1 Adequacy of database

Based on the treatment effect (overall survival improvement) observed in JVBD that was confirmed in JVBE, the clinical reviewer found the safety database to be adequate. Lilly submitted datasets in CDISC (STDM and ADaM) format which facilitated the FDA clinical reviewer to complete the review in a timely manner.

The clinical review primarily focused on data from Trial JVBD as this was the large controlled trial intended to support approval of ramucirumab for the indicated patient population. Lilly stated during the review that (b) (4) will provide safety data from Trial JVBE. Lilly notified the Agency of an imbalance of Grade 3 hemorrhage in the JVBE trial and proposed including this information in the ramucirumab product labeling. Importantly, the safety of ramucirumab administered to patients with gastric cancer receiving NSAIDS (who may be at increased risk for bleeding based on the location of the tumor) was not systematically studied during Trials JVBD and JVBE. Although, Lilly submitted data from patients who took or received NSAIDS, data regarding duration of use was limited.

The placebo control allowed for the clinical reviewer to conduct an analysis of safety against background adverse events that commonly occur in patients with advanced cancer. The safety population of JVBD included 236 patients with advanced gastric cancer who received ramucirumab and 115 who received placebo plus best supportive care. Two patients in each arm dropped out prior to receiving ramucirumab or placebo (one patient died and three had new clinical findings that precluded further participation in the trial). The clinical reviewer also considered data from other dose escalation trials and activity estimating trials in her evaluation of the safety profile of ramucirumab [data from an additional 334 patients in the original BLA submission (30 Apr 2013 clinical module)].

In JVBD, patients received ramucirumab for a median duration of 8 weeks compared to a median duration of 6 weeks in the placebo arm. *Comment: The short duration of therapy in both arms reflected the poor prognosis of patients with previously treated metastatic gastric*

cancer. Based on the short duration of exposure, comparisons of safety to other anti-VEGF monoclonal antibodies would not be appropriate. Nevertheless, this reviewer agrees that it is appropriate to take action on this application despite the lack of long-term safety data based on the modest improvement in overall survival and the short life expectancy of patients with previously treated gastric cancer. Despite the brief exposure of most patients, dose reductions were few (three in the ramucirumab arm and one in the placebo arm). Investigators held or omitted doses (for any reasons) in more patients in the ramucirumab arm (20.3%) compared to the placebo arm (10.4%).

8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

8.2.1 Deaths

The clinical reviewer found that the majority of deaths in JVBD occurred due to progression of the underlying gastric malignancy. The KM curves of OS in Section 7 of this review summarize the overall occurrence of deaths in JVBD. These curves provided some assurance of the relative safety of ramucirumab.

A total of 78 deaths occurred while on treatment or within 30 days of the last dose of ramucirumab or placebo. In her assessment of *possible* adverse-event related deaths, the clinical reviewer did not consider deaths due to disease progression, gastric cancer, or neoplasm and recorded 26 patients (11%) in the ramucirumab arm and 12 (10%) in the placebo arm who experienced an adverse event (irrespective of attribution) with a fatal outcome. Although some deaths were caused by events classically associated with VEGF inhibition (e.g., hemorrhage and large intestinal perforation), such events also occurred in the placebo arm. Overall, the incidence rate of adverse-event associated deaths in JVBD was similar in both arms and did not show any consistent patterns of ramucirumab-*related* fatal events.

8.2.2 SAEs

Lilly's clinical study report defined (*non-verbatim definition*) a serious adverse event (SAE) as any untoward medical occurrence that resulted in death; was life-threatening; required inpatient hospitalization or caused prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect; required intervention to prevent permanent impairment or damage; or was an important medical event that could jeopardize the patient or require intervention to prevent one of the other serious outcomes listed above.

The clinical reviewer's analysis differed from that of the applicant's by omitting fatal events (which were described in the analysis of deaths by the clinical reviewer). In general, the clinical reviewer found the incidence rate of most nonfatal serious adverse events occurring in JVBD to be similar between arms. Table 14, shows SAEs at the MedDRA preferred term level (including deaths) that occurred in at least 2% of patients in the ramucirumab arm. Lilly stated that medication errors were reported as SAEs according to the protocol; however, these were not associated with adverse health consequences.

Table 14 SAEs, JVBD

	Ramucirumab N=236 (%)	Placebo N=115 (%)
Any SAE	44.9	44.3
Abdominal pain	4.2	2.6
Anemia	3.8	1.7
Medication error	3.0	0.9
Ascities	2.5	2.6
Vomiting	2.5	4.3
Multi-organ failure	2.5	0.9
Intestinal obstruction	2.1	0
Dysphagia	2.1	2.6

8.2.3 Drop-outs and discontinuations due to adverse events

According to the applicant, 10.5% of patients in the ramucirumab arm versus 6% in the placebo arm discontinued study treatment due to an AE. Two of the cases in the ramucirumab arm were considered non-treatment emergent including one patient who experienced inguinal hernia more than one month after the last dose.

An *additional* 10 patients (9 in the ramucirumab arm and one in the placebo arm) experienced a treatment emergent adverse event with an outcome of treatment discontinuation. Most of the patients in this later group discontinued due to disease progression (6), death (2), or who experienced a gastrointestinal AE with progression of disease recorded as the reason for end of treatment.

The clinical review described the specific reasons provided for treatment discontinuation. Two patients in the ramucirumab arm discontinued due to proteinuria. No other clear patterns emerged regarding reasons for treatment discontinuation; one patient in the ramucirumab arm experienced a cerebrovascular accident. Patients in both arms discontinued study therapy due to upper gastrointestinal hemorrhage.

8.2.4 Common adverse events

Table 15, shows the analysis of adverse events (rounded to the nearest integer and occurring with a per-patient incidence rate of ≥ 10% in the ramucirumab arm). In general, ramucirumab was well tolerated with many adverse events reported at the same rate in both arms. *Although some adverse events occurred at a higher incidence rate in the placebo arm, this reviewer recommends against allowing labeling claims based on safety (i.e., that ramucirumab is less toxic than placebo) because the study was not designed to show that ramucirumab causes fewer adverse events than placebo (Lilly did not request such claims in their proposed product label).*

Table 15 Common AEs, JVBD

	Ramucirumab (N=236)		Placebo (N=115)	
	All Grades (%)	≥ Grade 3 (%)	All Grades (%)	≥ Grade 3 (%)
Fatigue	25	4	24	4
Decreased appetite	24	3	23	4
Vomiting	20	3	25	4
Abdominal pain	19	5	25	3
Nausea	19	1	26	0
Constipation	15	0	23	3
Hypertension	15	7	8	3
Anemia	15	6	15	8
Diarrhea	14	1	9	2
Asthenia	12	2	17	7
Upper abdominal pain	11	1	4	0
Decreased weight	11	1	10	1
Dysphagia	11	2	10	4

Although there appeared to be a difference in the upper abdominal pain preferred term, this difference largely disappeared in the composite high level term (HLT) analysis (30% incidence of gastrointestinal and abdominal pains in ramucirumab-treated patients versus 29% in the placebo arm).

In summary, the most common adverse reactions (i.e., with a higher incidence in the ramucirumab arm) were hypertension and diarrhea. Few patients experienced severe diarrhea.

8.2.5 Laboratory tests

The clinical reviewer found that ramucirumab did not result in clinically significant myelotoxicity when administered as a single-agent. Likewise, anemia, a manifestation of either myelotoxicity or bleeding occurred at a similar incidence rate in both arms.

Ramucirumab did not appear to cause clinically significant increases in liver enzymes in Trial JVBD. A similar proportion of patients in both arms met *laboratory criteria* for Hy's law; however, these patients (in both arms) appeared to have disease progression as the cause of the liver enzyme findings. Although hepatotoxicity was not observed in Trial JVBD, the clinical reviewer documented a potential safety concern in patients who received ramucirumab in Trial JVBF (an investigation of ramucirumab in patients with hepatocellular cancer). In Trial JVBF, ramucirumab appeared to exacerbate the sequelae of cirrhosis (rather than directly cause liver injury). Serious adverse events reported in JVBF included encephalopathy, exacerbation of ascities, and possibly hepatorenal syndrome. Based on these events, Trial JVBF was modified to exclude patients with Child-Pugh B cirrhosis, history of hepatic encephalopathy, or clinically meaningful ascities. A warning describing these risks in patients with cirrhosis was proposed in product labeling.

Ramucirumab did not appear to cause clinically significant renal toxicity in Trial JVBD. There was a slight imbalance in hyponatremia in the ramucirumab arm in the adverse event analysis. However the shift tables did not indicate a large difference in patients who "shifted" from mild hyponatremia to severe hyponatremia. Based on the shift tables in the BLA, 25 out of 216 (12%) patients in the ramucirumab arm with baseline Grade 1 or 2 hyponatremia progressed to Grade 3 (< 130 to 120 mmol/L) or Grade 4 (< 120 mmol/L) hyponatremia during the trial. In the placebo arm, 11 out of 102 (11%) patients with baseline Grade 0 or 1 hyponatremia progressed to Grade 3 or 4 during the trial.

Assessments for the total incidence of proteinuria were complicated by differences in units/measurements contained in the datasets. The clinical reviewer found that 8% of patients in the ramucirumab arm and 3% in the placebo arm had proteinuria (including dipstick positivity). These values differed from the analysis of *adverse events* described as proteinuria (3% for ramucirumab versus 2.6% for placebo). Two patients discontinued ramucirumab because of proteinuria. *Based on these inconsistencies in measurements, use of ramucirumab as monotherapy, and short duration of exposure, comparisons of the rate of proteinuria to other anti-VEGF antibodies should not be made.*

8.3 Special safety concerns

8.3.1 Drug-demographic interactions

The clinical reviewer conducted analyses of adverse events by age range (≥ 65 years versus less than 65 years), gender, geographic area, and tumor location. In general, adverse events occurred at similar rates in the various groups. Meaningful conclusions of differences in adverse events were difficult to make because these were non-randomized subgroups, and in some cases, the numbers of patients in certain groups was small. Refer to Section 7.5.3 of the clinical review for adverse events that differed in proportion between subgroups. Refer to Section 8.2.5 of this review regarding the potential risks related to ramucirumab in patients with cirrhosis.

8.3.2 Additional in-depth analyses of specific events

Based on prior knowledge of adverse reactions related to other anti-VEGF antibodies and adverse events occurring in ramucirumab clinical trials, the clinical reviewer performed additional in-depth analyses of the following adverse events: hypertension, infusion-related reactions, proteinuria, arterial thrombotic events, venous thrombotic events, bleeding / hemorrhagic events, gastrointestinal perforation, liver injury / failure, congestive heart failure, and posterior reversible encephalopathy syndrome.

Differences in the incidence rate of adverse events would be expected in comparison to other anti-VEGF antibodies based on the following: ramucirumab was studied as a monotherapy (bevacizumab is only approved as monotherapy for patients with glioblastoma multiforme); exposure (exposure in second-line gastric cancer is of shorter duration compared to the exposure in patients with metastatic colorectal cancer); and knowledge based on prior experience of drugs in the class (e.g., aggressive treatment of hypertension; exclusion of patients at high risk of bleeding; exclusion of patients with recent surgery or with severe wounds).

As expected, and as shown in Table 15 (above), hypertension occurred more frequently among ramucirumab-treated patients. Severe hypertension (e.g., Grade 3 hypertension) occurred in 7% of patients. Although, in general, hypertension was manageable, the overall incidence of hypertension may have been underestimated (see Section 7.4.3 of the clinical review) based purely on the adverse event reporting (rather than blood pressure measurements) and that (in an exploratory analysis) the systolic blood pressure appeared to be increased by approximately 5-10 mmHg in ramucirumab-treated patients compared to patients who received placebo (analysis of median blood pressure effects in the populations in each arm in each cycle).

Refer to the clinical review for further analyses of other anti-VEGF toxicities described above.

Finally, in Trial JVBE (ramucirumab in combination with paclitaxel trial), Lilly stated that arterial thrombotic events occurred at a similar rate in both arms and there were no events of impaired wound healing, fistula, or posterior reversible encephalopathy syndrome (PRES). Although investigators reported more hematological toxicity when ramucirumab was administered with paclitaxel, such toxicity is not expected when administered in the absence of chemotherapy. The summary report stated that in JVBE, four patients experienced gastrointestinal perforation in the ramucirumab arm versus none in patients who received placebo. Proteinuria also occurred more frequently in the ramucirumab arm [17% (1% Grade 3) versus 6% in the placebo arm].

8.4 Discussion of primary reviewer's findings and conclusions

The clinical reviewer concluded that patients receiving ramucirumab experienced an increased incidence of anti-VEGF axis toxicities (compared to patients receiving placebo); however, most patients tolerated ramucirumab without requiring dose reductions or permanent discontinuation.

The clinical reviewer determined the safety database to be adequate for the intended indication given the overall survival effect observed in Trial JVBD (and subsequently confirmed in Trial JVBE); a total of 236 patients received ramucirumab in trial JVBD, and approximately 570 patients received ramucirumab as a single agent across multiple clinical trials. Based on the poor prognosis of patients with previously treated gastric cancer and the modest effect of ramucirumab, treatment duration was limited in Trial JVBD; patients received ramucirumab for a median treatment duration of 8 weeks compared to a median duration of 6 weeks in the placebo arm.

The most important adverse reactions caused by ramucirumab (as monotherapy) included adverse reactions typically understood in the setting of anti-VEGF axis treatment. Such adverse reactions included hemorrhage, arterial thrombotic events, hypertension, proteinuria, and gastrointestinal perforation. Infusion-related reactions can also occur following treatment with ramucirumab.

Although ramucirumab can cause serious (and potentially life-threatening) toxicities, the overall risk benefit profile was considered favorable based on the demonstrated improvement in overall survival in a patient population with terminal cancer. Most of the toxicities are

familiar to trained oncologists, and it is standard practice to monitor for these adverse reactions, institute treatment as necessary, and to dose modify therapy or discontinue therapy if necessary. Additionally, in general, most patients tolerated monotherapy with ramucirumab and few patients permanently discontinued ramucirumab due to adverse events. The incidence rate of many adverse events was similar to that observed in the placebo arm.

Comment: This reviewer agreed with the major conclusions in the clinical review. The incidence of adverse events in the clinical review was, in general, similar to (or the same as) those of the applicant. Small differences in the incidence rates of certain adverse events were not clinically significant.

9. Advisory Committee Meeting

Although FDA planned for an advisory committee meeting upon submission of the application (based solely on the results of Trial JVBD), the review team determined that an ODAC meeting was not necessary following the submission of data from Trial JVBE that confirmed the OS results observed in Trial JVBD. FDA review staff considered the effects on OS to be (statistically) robust based on the results observed in two trials, and trained oncologists are familiar with the types of toxicities caused by ramucirumab.

10. Pediatrics

This BLA is exempt from the requirement to assess the safety and effectiveness of this product for the claimed indication in all pediatric age groups because FDA granted orphan-drug designation to the ramucirumab active moiety for the treatment of patients with gastric cancer on 16 Feb 2012.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

The BLA contained a statement signed by the Senior Director of Global Regulatory Affairs (U.S.) from Eli Lilly that certified that Eli Lilly did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11.2 Financial disclosures

The majority of investigators reported that they did not enter into any financial arrangements whereby the value of compensation to the investigator would be expected to affect the outcome of the study as defined in 21 CFR 54.2(a). The applicant certified that the listed investigators referenced on Form 3454 did not disclose financial interests as defined in 21 CFR 54.2(b) or significant payments as described in 21 CFR 54.2(f). Lilly also reported that the six members of the IDMC were in compliance with the requirement for financial clarification and disclosure information (21 CFR, Part 54).

Eli Lilly reported obtaining financial disclosure forms from all but two investigators / sub-investigators. Lilly reported contacting the sub-investigators (one in New Zealand and one in Spain) multiple times via electronic mail and telephone and also attempted to contact the

primary investigators at these sites. Despite these attempts, Lilly could not obtain the financial information prior to departure from their respective institutions. Lilly subsequently conducted an internal record of payments and did not identify a record of disclosable payments to these individuals.

Two sub-investigators disclosed reportable financial interests. Lilly stated that these interests did not, in any way, influence the outcome of the clinical trial. One sub-investigator reported receiving $27,725 in honorariums. The site (of this sub-investigator) randomized (b) (6) to the placebo arm whose overall survival was longer that the median OS among patients receiving placebo (and thus did not appear to bias the study towards a favorable result for the ramucirumab arm).

A second sub-investigator (b) (6) reported receiving honorariums of $34,100. This site randomized (b) (6) to each arm. There were (b) (4) potential outliers at this site who lived longer than 24 months; (b) (4) Additionally the overall mean and median survival between the (b) (4) patients in each arm at this site were similar (within one month for each analysis). Based on these findings, and because these constituted a minority of the patients enrolled in Study JVBD (a large multi-center study with the primary endpoint of overall survival), this reviewer agrees that these reported interests did not influence the primary outcome of the clinical trial.

11.3 GCP issues

Lilly provided an audit certificate that stated that 13 investigational sites (from Study JVBD) were audited. Lilly included a statement in the JVBD final study report that the PI or designee promptly submitted the protocol to applicable Ethical Review Boards (ERBs). The ERBs provided written approval of both the protocol and informed consent document. Eli Lilly submitted the name and address of each ERB (or IRB) in an appendix to the clinical study report.

Lilly also included a statement in the JVBD clinical study report that the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and consistent with good clinical practices (GCPs) and applicable laws and regulations.

In general, the numbers of protocol violations were similar between arms. One patient in each arm received the wrong treatment. Although there were entry criteria violations reported in each arm, the types of violations were unlikely to have had a major impact on the overall study results.

11.4 OSI audits

Because ramucirumab is an NME, DOP2 requested OSI inspections of clinical sites. DOP2 and OSI selected three clinical sites based on site-specific efficacy results, protocol violations, or patient enrollment at each site. OSI inspected sites in Brazil, South Korea, and Texas and classified all three (interim classification) as NAI (no action indicated). OSI found no evidence of underreporting of adverse events at the study sites. OSI also inspected the

applicant's records and found clear procedures and records. Lilly received an interim classification of NAI.

11.5 Late-Cycle meeting

Lilly and FDA met on 11 Feb 2014 to discuss outstanding issues related to BLA 125477. Much of the discussion pertained to potential Postmarketing Commitments (PMCs) and Postmarketing Requirements (PMRs). The Agency and Lilly initially discussed the PMR that would require Lilly to develop a validated, sensitive, and accurate assay for the detection of binding antibodies to ramucirumab, including procedures for 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. Lilly asked whether additional data could be submitted to support the use of the current assay. Based on Lilly's request, FDA stated that the intent of the PMR could be satisfied *either* by developing a new assay or by providing data showing acceptable drug tolerance of the ADA assay between (b) (4) of ADA. Additionally, if the current assay is sufficient, then Lilly will not need to re-test 300 patient samples using the new assay.

In regards to the neutralizing assay PMR, Lilly stated that it may be difficult to improve the drug tolerance of the current assay. Lilly provided summary validation data stating that the sensitivity of the assay exceeds the 2009 FDA guidance for sensitivity of the neutralizing ADA. FDA (OCP) stated that the Agency would further discuss the PMRs regarding neutralizing assays internally and determine whether they were necessary.

During the meeting, Lilly agreed to provide timelines regarding Postmarketing Commitments (PMCs) pertaining to drug substance and drug product release and stability specifications, product stability (b) (4), and to perform a shipping study.

11.6 Other discipline consults

11.6.1 DRISK

DRISK concurred with DOP2 that a REMS is not necessary for ramucirumab.

11.6.2 OPDP

DOP2 did not agree with the OPDP labeling recommendation to remove the following statement: As with all therapeutic proteins, there is the potential for immunogenicity. This is a standard statement included in labeling of monoclonal antibodies. DOP2 also did not agree with the provision to include all warnings in the patient counselling information section because this section should focus on major risks of the drug and how the patient may mitigate or manage them. For example, mitigation of infusion reactions is the responsibility of the treating physician and not the patient (e.g., through the administration of intravenous antihistamines or corticosteroids).

11.6.3 Drug name review (DMEPA)

During the review of this application, DMEPA sent a letter on 25 Oct 2013 informing Lilly that the proposed trade name of Cyramza was (conditionally) acceptable. The DMEPA review considered the name from a promotional perspective in consultation with DOP2 and OPDP.

DMEPA also considered the name Cyramza from a safety perspective (i.e., performed assessments for look-alike and sound-alike drugs) and found the name acceptable.

12. Labeling

FDA sent draft labeling recommendations to Lilly on 25 Feb 2014 prior to the date stipulated by the 21st Century Review Process (24 Mar 2014). Labeling recommendations described below should not be considered final as labeling negotiations are ongoing.

In general, DOP2 revised all sections of the label for brevity and clarity (*this reviewer acknowledges that Lilly facilitated FDA's review process by submitting their initial label following the spirit of PLR*). The remainder of this section of the review will only focus on high-level issues regarding the label submitted by Lilly. Numbering below is consistent with the applicable sections in product labeling. This review will not comment on all sections of the label (for example, if only minor edits were made to a section). This reviewer agreed with the recommendations made by the review teams that are described below.

1. Indication and Usage: FDA recommended revising the indication to specify the prior chemotherapy regimen for patients with gastric cancer.

2. Dosage and Administration: FDA review staff, including DMEPA, recommended re-ordering sections under Dosage and Administration. DMEPA also recommended revising the dose modification section to ensure consistency with other labels.

5. Warnings and Precautions: FDA recommended inclusion of a boxed warning for hemorrhage. However, the incidence of gastrointestinal perforation and compromised wound healing *as monotherapy* did not support the inclusion of a boxed warning for these two adverse reactions (which are described in Section 5 of the label).

The clinical reviewer recommended the addition of a warning for Reversible Posterior Leukoencephalopathy Syndrome (RPLS) based on reports in a ramucirumab trial along with evidence of RPLS occurring following the use of other anti-VEGF therapies. *Comment: During the Late-Cycle meeting, held after the completion of the clinical review, FDA was informed by Lilly that the reported cases were from a clinical trial that remains blinded as to the treatment assignment. Therefore, as of the completion of this review, it is uncertain whether this adverse event should be included as a separate warning in product labeling.*

FDA recommended describing the incidence rate of adverse reactions in the Warnings section of the label.

FDA recommended including information regarding the lack of data regarding concomitant ramucirumab and NSAID use (in the hemorrhage warning).

6. Adverse Reactions: FDA recommended describing certain exclusion criteria of Trial JVBD in order to contextualize the safety information contained in the label. FDA also added exposure information and information regarding the most common

serious adverse reactions and adverse reactions resulting in treatment discontinuation. FDA also recommended removal of statements regarding (b) (4) from the label and revised the Immunogenicity section to provide information regarding the assay used to test ADAs.

8.1. Pregnancy: FDA recommended inclusion of a statement that ramucirumab may cause fetal harm based on animal models linking inhibition of VEGF to critical aspects of female reproduction, embryofetal development, and postnatal development.

8.4. Pediatric Use: FDA recommended inclusion of animal data pertaining to pediatric use (specifically effects on epiphyseal growth plates).

8.5. Geriatric use: FDA revised this section because insufficient numbers of patients were enrolled in Trial JVBD to determine whether differences in safety or efficacy existed in this subpopulation of patients.

8.8. Females and Males of Reproductive Potential: FDA added this section and included information regarding fertility and contraception.

11. Description: DMA recommended deleting information regarding mechanism of action because this information is described in Section 12.1 of the label.

(b) (4)

14. Clinical Studies: FDA recommended removal of information regarding (b) (4) FDA added number of deaths in the efficacy results table to provide information regarding the maturity of the analysis.

FDA recommended removal of the PFS Kaplan-Meier curves from the label. Although (for brevity) the Division recommended removal of the Kaplan-Meier curves, the Division does not object to the use of the curves (proposed in the label) in promotional materials (as otherwise permitted in the United States under current law) and recognizes that the PFS effect was statistically significant (i.e., substantial evidence was submitted in the application to support the presentation of the PFS curves).

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

This reviewer recommends regular approval of BLA 125477 based on substantial evidence from two adequate and well controlled trials (JBVD and JVBE) establishing that ramucirumab can prolong the overall survival of patients with previously treated, locally advanced,

unresectable or metastatic gastric cancer. This approval recommendation is contingent upon reaching agreement on labeling, PMCs, and PMRs.

The submission of data from confirmatory Study JVBE during the review addressed two major deficiencies in the application: reliance on data from a single study (JVBD) with a p value just under 0.05 and the possibility that ramucirumab could harm women. In the confirmatory trial, JVBE, the point estimate for the OS HR in women was lower than the point estimate for OS in men. The female subgroup in JVBE was also larger (n=193) than the female subgroup in JVBD (n=107). Thus, the most likely explanation for the gender effect observed in JVBD was chance (e.g., due to imbalances in demographic variables).

Given the effects observed on overall survival, this reviewer agrees that regulatory discretion can be exercised in approving ramucirumab (as a single agent) prior to the receipt of the full clinical study report for JBVE. FDA previously exercised such discretion when the Agency approved ipilimumab for the treatment of patients with metastatic melanoma on 25 Mar 2011 (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125377Orig1s000SumR.pdf, accessed on 24 Dec 2013). In an amendment to BLA 125477, Lilly provided demographic and survival datasets from Trial JBVE to confirm the summary survival analyses. Lilly also provided the protocol, protocol amendments, and statistical analysis plan in the amended BLA.

13.2 Risk-benefit assessment

The recommendation for approval of this application is based on a statistically significant (but clinically modest) improvement on OS observed in two trials, JVBD and JVBE. According to the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf; accessed on 23 Dec 2013), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.

Because metastatic (or locally advanced, unresectable) gastric cancer is an incurable disease, the goals of treatment are to prolong life or improve quality of life. In JVBD, patients who received ramucirumab in combination with best supportive care lived a median 1.4 months longer than patients who received placebo in combination with best supportive care [HR = 0.776 (0.603, 0.998), p = 0.047]. This treatment effect on overall survival was confirmed in Trial JVBE where patients lived a median 2.3 months longer than patients in the placebo arm [HR = 0.807 (0.678, 0.962), p = 0.017)].

The effects on OS were supported by a statistically significant effect on progression free survival in Trial JVBD [HR 0.483 (0.376, 620), p < 0.0001]. The estimated difference in median PFS was 0.8 months; however, the timing of scans in Trial JBVD likely affected the estimates and the curves appeared to further separate after the medians. Nevertheless, the effects on PFS should be considered supportive of the OS results rather than as evidence of direct clinical benefit.

Adverse events observed in the JVBD trial were generally considered in-line with toxicities observed following the administration of other anti-VEGF monoclonal antibodies. Nevertheless, multiple factors may have contributed to differences in adverse event rates between ramucirumab and other approved monoclonal antibodies that target the VEGF pathway. In addition to specific product-related factors (e.g., differences in targets), other factors included brief duration (median of 8 weeks) of ramucirumab exposure in JVBD; monotherapy indication for ramucirumab (as opposed to use in combination with chemotherapy with other products); and accumulated knowledge regarding the use of other anti-VEGF inhibitors (e.g., resulting in more proactive management of toxicities including hypertension). The eligibility criteria in JVBD may have also mitigated some of the serious toxicities related to ramucirumab (e.g., exclusion of patients receiving NSAIDS).

Importantly, the risk-benefit profile in Trial JVBD was studied in a patient population with ECOG PS 0 and 1. This reviewer cannot extrapolate the survival benefit (observed in JVBD) to patients with ECOG PS 2 or greater. The hazard for death is sufficiently high in these patients that the risk-benefit profile may differ compared to patients with less co-morbidity. As such, this reviewer recommends that Section 14 of the label describe the population studied in JVBD (i.e., ECOG PS 0-1).

This reviewer acknowledges that the 1.4 month improvement in median overall survival represents a modest effect and that based on this modest effect, a reasonable person may decide whether or not to receive ramucirumab (e.g., versus no treatment, alternative treatment, or enrollment into a clinical trial). However, because an effect on OS was observed in two trials, this reviewer believes that there is substantial evidence to support the claim that ramucirumab *does* (modestly) improve overall survival. Although, this FDA reviewer recommends approving this application (and has recommended approval of other applications that demonstrated a 1.4 month median improvement in overall survival in patients with advanced cancer), this reviewer hopes that, in the future, sponsors target drug development to products intended to demonstrate larger treatment effects.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

The review teams did not identify any REMS as necessary prior to a marketing authorization for ramucirumab. Ramucirumab will be prescribed by oncologists who are trained how to monitor, diagnose, and manage serious toxicities caused by anti-neoplastic drugs including VEGF-targeted therapies. Standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

13.4 Recommendation for other postmarketing requirements and commitments

All PMCs and PMRs were recommended by the Division of Monoclonal Antibodies or the Office of Clinical Pharmacology. These PMCs and PMRs are described elsewhere in this review (e.g., Section 11.5).

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/s/

STEVEN J LEMERY
04/21/2014

Cross-Discipline Team Leader Review

Date	14 Mar 2014
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
BLA #	125477
Applicant	Eli Lilly and Company
Date of Submission	23 Aug 2013 (complete application with final Module of rolling submission)
PDUFA Goal Date	23 Apr 2013
Proprietary Name / Established Name	Cyramza / ramucirumab
Dosing Regimen	8 mg/kg intravenously every two weeks
Proposed Indication(s)	Treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy
Recommended:	*Approval contingent upon reaching agreement on labeling, PMRs, and PMCs*

Table of Contents

Table of Figures

Table of Tables

1. Introduction

FDA received Biologics License Application (BLA) 125477 from Eli Lilly (Lilly) on 23 Apr 2013 requesting marketing authorization (regular approval) for ramucirumab (proposed trade-name Cyramza) for the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy.

Disclaimer: Any data or information described below that Lilly does not own (for example, summary data from other drugs used to treat patients with metastatic gastric cancer or other cancers) is included for descriptive purposes only. This information was not relied upon or necessary to make a decision regarding this application.

The primary issue considered during the *initial* review of Module 5 of this BLA (clinical module as submitted on 30 Apr 2013) was whether the results of a single adequate and well controlled clinical trial (JVBD) provided substantial evidence of effectiveness to support the approval of ramucirumab.

FDA Guidance (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998) states that reliance on a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome and confirmation of the results in a second trial would be practically or ethically impossible.

JVBD was a randomized (2:1), multicenter, multinational, double-blind, placebo-controlled trial where patients with (previously treated unresectable and locally advanced or previously treated metastatic) gastric cancer or gastroesophageal junction cancer received ramucirumab (8 mg/kg every two weeks) plus best supportive care or placebo plus best supportive care (generally until disease progression or unacceptable toxicity). Table 1 (data obtained from the statistical review) summarizes the efficacy results from JVBD. The results demonstrated a statistically significant improvement in overall survival (OS). Nevertheless, the improvement was of a modest magnitude (median improvement in survival of 1.4 months) and the p value was just under 0.05.

Table 1 Summary of OS efficacy results (JVBD)

	Ramucirumab N = 238	**Placebo N = 117**
# of events	179	99
Median (in mos.)	5.2	3.8
Stratified HR (95% CI)	0.776 (0.603, 0.998)	
p-value (two-sided)	0.0473	

In addition to the modest effect on OS, JVBD showed potential imbalances in treatment effects by geographic region and gender. Most concerning regarding approval consideration was the point estimate for the treatment effect among women [HR = 1.43 (0.85, 2.41)]. Although there were potential reasons to explain this subgroup effect (e.g., there was a larger proportion of

women with diffuse histology who received ramucirumab compared to placebo), this reviewer would have reservations whether to approve ramucirumab (a new molecular entity) based on a single trial demonstrating a modest six week improvement in overall survival, with a p value of 0.047, and the potential for detrimental survival among women.

Based on the modest effects observed in JVBD, one could argue that a second trial of ramucirumab could ethically be conducted, especially to further evaluate the effects of ramucirumab in women. Additionally, the second study could further evaluate the treatment effects of ramucirumab in the North American subgroup (the point estimate for the hazard ratio in this subgroup was closer to one than the ITT point estimate).

Ultimately, during the clinical review, on 30 Oct 2013, Lilly was able to strengthen the application by submitting survival data (including datasets) from a second study, JVBE. JVBE was a randomized (1:1) multicenter, multinational, double-blind, placebo-controlled trial that evaluated ramucirumab (same dose and schedule as JVBD) in combination with paclitaxel versus placebo in combination with paclitaxel as a treatment for patients (n = 665) with previously treated metastatic or unresectable, locally advanced gastric cancer. After 516 events (deaths) were observed in JVBE, patients in the ramucirumab arm lived a median 2.3 months longer than patients in the placebo arm [HR = 0.807 (0.678, 0.962), p = 0.017)]. The results were supported by a modest effect on progression free survival [HR 0.635 (0.536, 0.752), p < 0.0001]. *Comment: Lilly submitted the datasets in standardized [SDTM (CDISC) / ADaM] formats which facilitated FDA's ability to rapidly review clinical data during the review cycle.*

Importantly, JVBE provided results showing that ramucirumab appears effective in women [HR point estimate for OS was 0.67 (0.48, 0.94)] and in patients enrolled in the region that included the United States.

Based on the results of study JVBE, this reviewer agrees that this application contained substantial evidence from adequate and well controlled *trials* that ramucirumab can (modestly) prolong survival when administered to patients with previously treated, metastatic gastric cancer.

2. Background

2.1 Disease and therapy related issues

Lilly requested marketing authorization for ramucirumab for the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy. In general, because metastatic gastric cancer is an incurable disease, the goal of treatment for these patients is to prolong life and/or improve quality of life.

Oncologists treat patients with metastatic gastric cancer with cytotoxic chemotherapy and with trastuzumab (for patients with tumors that overexpress HER2). For brevity, this review will not focus on supportive treatment of patients with gastric cancer; however, this reviewer acknowledges that a multidisciplinary approach is necessary to help improve the life-altering

symptoms of such patients (for example, due to gastrointestinal obstruction, thromboembolic events, hemorrhage, pain, weight loss, anorexia, nausea, and depression).

FDA approved trastuzumab for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease on 20 Oct 2010. FDA approved trastuzumab based on an improvement in overall survival when trastuzumab was added to a fluoropyrimidine (capecitabine or 5-fluorouracil) and cisplatin. Trastuzumab improved overall survival by a median 2.5 months [HR = 0.73 (0.60, 0.91), p = 0.0038].

On 22 Mar 2006, FDA approved docetaxel in combination with cisplatin and fluorouracil (CF) for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease. FDA approved docetaxel based on an improvement on time to progression and on overall survival. The hazard ratio described in the product label for overall survival is 0.77 [(0.62, 0.96), p = 0.0201]. The hazard ratio appeared to be a better estimate of overall survival compared to the median difference of 0.6 months, because the KM curves appeared to converge at the median and then separate.

In addition to trastuzumab and docetaxel which are both approved in the first-line setting, older (FDA) approvals for metastatic gastric cancer include fluorouracil, doxorubicin, and mitomycin C. In general, patients with previously treated metastatic disease receive single-agent therapy [for example, with irinotecan or a taxane (both off-label)] or best supportive care. Many such patients cannot receive cytotoxic therapy due to underlying performance status.

2.2 U.S. regulatory history

The following summarizes the pertinent regulatory history and meetings held in relation to this BLA. (b) (4)

20 May 2008 (Type B meeting between FDA and ImClone): FDA and ImClone held this meeting to discuss manufacturing issues, an immunogenicity assay, and issues related to the design of a drug-drug interaction study. ImClone requested FDA advice regarding plans to support comparability of two different manufacturing processes [Process B (b) (4) ; and Process C (b) (4) and plans to support the use of drug substance (DS) from Process C in randomized (phase 3) clinical trials. FDA agreed with the design of a proposed monkey study to assess the pharmacokinetics (PKs) of material manufactured using the different processes; however, FDA stated that that the Agency would review the results of the monkey PK study prior to determining whether human PK data would be necessary.

FDA provided advice regarding stability studies including adding a potency bioassay as a stability test, reporting percentages of aggregates and fragments in HPLC acceptance criteria, and testing for sub-visible particulates.

During the meeting, FDA agreed with a proposed DDI study plan to determine the relative effect of docetaxel on the pharmacokinetics of ramucirumab and provided advice regarding the immunogenicity assay which would be reviewed in full after submission of a BLA.

28 May 2008 (Type B meeting between FDA and ImClone): ImClone requested this meeting to reach agreement on the design of a proposed trial, CP12-0715, entitled "A Phase 3, Randomized, Double-Blinded Study of IMC1121B 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 Combination Therapy." During the meeting, FDA agreed that ImClone could enroll patients with GEJ tumors and that use of a placebo was acceptable provided that patients received adequate informed consent regarding (alternative) standard treatments. FDA also agreed with ImClone's approach regarding the conduct of futility assessments (at 25%, 50%, and 75% of OS events) and that the IDMC charter was acceptable. FDA agreed with ImClone's approach to conduct a single interim analysis following the observance of 75% of the planned events.

During the meeting, FDA recommended stratification of the trial based on an additional variable (i.e., gastroesophageal junction tumor versus other); however, ImClone provided a report (from the REAL-2 study) suggesting that the site of tumor was not a strong prognostic factor for overall survival in previously treated patients. FDA agreed to review the REAL-2 study results prior to making a decision regarding whether the approach was acceptable.

FDA also communicated to ImClone that for a single pivotal study to support licensure, the results should show a highly statistically significant effect (a p value of less than 0.01 was suggested during the meeting) on survival that is internally consistent across relevant subgroups and that the results of the single pivotal trial must be sufficiently robust and so compelling that it would be unethical to repeat the study. FDA stated that the acceptability of study CP12-0715 as a single trial to support the approval of IMC-1121B as second-line therapy in metastatic or GEJ adenocarcinoma will be contingent upon the magnitude and robustness of the effect. Alternatively, FDA stated that a second trial in gastric cancer (either first- or second- line) could generate sufficient supportive evidence if conducted at the 0.05 significance level.

07 Apr 2009 (letter to ImClone): FDA sent a letter to ImClone based on an amendment to the IND submitted on 4 Feb 2009 regarding a new DS manufacturing site and an additional drug product manufacturing facility. FDA requested information regarding viral clearance steps during production and information regarding the identity (b) (4) of ramucirumab. FDA stated that products manufactured from processes B and C appeared pharmacokinetically comparable.

29 Oct 2009 (letter to ImClone): FDA sent this letter in response to questions posed by ImClone regarding protocol IMCL-CP12-0712: "A Study to Evaluate the Relationship Between Ramucirumab (IMC-1121B) Therapy and Corrected QT (QTc) Interval Changes in Patients with Advanced Cancer." In the letter, FDA recommended revising the study to evaluate the highest therapeutic dose of ramucirumab (i.e., 20 mg/kg every three weeks). FDA

stated that co-administration of moxifloxacin was not required. FDA agreed with the proposed timing, intervals, and analyses of ECGs during the study.

27 May 2010 (Type B meeting between FDA and ImClone): ImClone requested this meeting to reach agreement on the design of a proposed trial, CP12-0922, entitled "A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel With or Without Ramucirumab Drug Product in Patients with Metastatic Gastric Adenocarcinoma, Refractory to or Progressive after First-Line Therapy with Platinum and Fluoropyrimidine." ImClone stated that patients in the trial would receive paclitaxel (80 mg/m^2 on days 1, 8, and 15 of each 28 day cycle) plus either placebo or ramucirumab (8 mg/kg) every other week. The proposed primary endpoint was overall survival. FDA stated that the overall design of the randomized (1:1) study appeared acceptable to support a BLA. However, FDA reiterated advice regarding approval based on one study conferred during the 28 May 2008, Type B meeting.

23 Sep 2010 (letter to ImClone): FDA sent this letter to ImClone in reference to an amendment dated 6 Apr 2019 to protocol IMCL-CP12-0715 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 Combination Therapy." In the letter, FDA recommended changes to the protocol in order to make claims based on progression free survival (i.e., to continue imaging assessments following the initiation of new anticancer therapy).

15 Nov 2011 (Type C meeting between FDA and ImClone): ImClone requested this meeting to discuss a comparability strategy for the proposed ramucirumab (IMC-1121B) commercial manufacturing processes and (b) (4) changes to the drug substance (DS), the primary container changes for the drug product (DP), and the addition of an alternate drug product (DP) manufacturing site. ImClone planned on submitting information from two processes (C1 and C2) in the BLA with process validation to be performed on Process C1. ImClone proposed Process C1 as the initial commercial material; this material differed from Process C0 material used in Phase 2 and Phase 3 clinical trials in that Process C1 included (b) (4) The only proposed change in Process C2 was a change (b) (4) . In general, FDA found ImClone's comparability assessment as acceptable; however, FDA requested that ImClone assess additional parameters as "critical quality attributes" (b) (4) . FDA requested real-time and accelerated stability data in the comparability package.

During the meeting, FDA also provided advice regarding the proposed analytic characterization program; agreed with the proposed stability approach to support Process C1; provided advice regarding data necessary to support Process C2; agreed to the planned approach for viral control and the viral validation program using two challenge viruses

including (b) (4); and provided comments regarding the approach to validation of drug product manufacturing processes.

23 Jan 2012 (Type C meeting between ImClone and FDA): During this meeting, FDA confirmed that ImClone's proposed population PK strategy appeared sufficient to support planned BLAs in gastric (b) (4) cancer. However, FDA did not agree with ImClone's plan for an early PK database "snapshot" at 75% of events because unblinding of the trial could potentially jeopardize the integrity of the trial. ImClone stated that no unblinded safety or efficacy data would be evaluated in the population PK analysis. FDA stated that ImClone would need to provide a summary of steps taken to ensure integrity including evidence that the analysis plans for primary and key secondary endpoints were finalized prior to the conduct of the population PK analysis.

16 Feb 2012 (letter to ImClone): FDA granted orphan-drug designation (#11-3597) for the "treatment of patients with gastric cancer."

29 Jun 2012 (letter to ImClone): FDA responded to an ImClone request for a waiver from conducting a nonclinical reproductive and developmental toxicity study in a pharmacologically responsive species due to scientific and regulatory reasons (including knowledge of the biological pathway and available non-clinical ramucirumab data). FDA stated that the Agency would consider the request following review of data/information submitted to the IND; however, FDA stated that ImClone cannot rely on product-specific published literature describing results of studies from other biological drugs.

18 Sep 2012 (letter to ImClone): FDA sent a letter to ImClone regarding an (b) (4) method and data requested by the Agency during a 15 Nov 2011 CMC meeting. FDA provided advice regarding data and studies necessary to support stability and shelf-life across manufacturing processes.

14 Nov 2012 (Fast Track letter): 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. FDA granted Fast Track designation based on the plan to investigate the effect of ramucirumab on overall survival.

17 Jan 2013 (Type B, pre-BLA meeting between ImClone and FDA): The major issue discussed during this meeting was whether the results from the single JVBD study were sufficient to support the proposed indication. FDA stated that the trial showed a modest effect on overall survival and that the results were not robust as discussed in FDA guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf, accessed 01 Oct 2013). FDA also identified the modest effect observed in the North American subgroup. FDA stated that the Agency may request advisory committee advice regarding whether the Agency should wait for the results of Study JVBE (also in gastric cancer), which if positive, would confirm the results of Study JVBD. FDA encouraged ImClone to submit the results of the JVBE trial; however, FDA stated that the results of the JVBE trial would not be required for filing. FDA agreed to meet with ImClone if the top-line

results from JVBE became available during the review of a BLA (based on data from the JVBD trial) in order to determine which top-line data from JVBE should be submitted in the BLA.

During the meeting, FDA and ImClone agreed that the BLA would contain the following:

- Integrated Summaries of Safety and Effectiveness (ISS and ISE) as described in FDA Guidance Documents (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf, and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf).
- Case report forms only from completed studies.
- Financial disclosure information from Study JVBD (as other studies were not considered a "covered study").

The contents of a complete application were discussed; however, agreement on the contents of a complete application was not reached because the pre-BLA CMC meeting was yet to be held and because additional discussion was required regarding the clinical pharmacology sections of the BLA. FDA and ImClone held a preliminary discussion regarding the need for a REMS and concluded that a REMS did not appear necessary to ensure the safe use of ramucirumab for the proposed indication. FDA also did not anticipate the need for a MedGuide because ramucirumab will be administered in infusion centers and prescribed by oncologists who routinely obtain informed consent prior to administering anti-cancer therapeutics. FDA stated that the Agency would consider the application for priority review; however, FDA stated that priority review designation would be determined when the BLA is received.

During the meeting, FDA stated that the Agency would not object to a proposal to initiate an expanded access program (for ramucirumab) as long as the program did not interfere with recruitment in the ongoing JVBE trial.

23 Jan 2013 (Type B, CMC pre-BLA meeting between ImClone and FDA): ImClone requested this meeting to seek agreement regarding the structure and contents of Modules 2.3 and 3 (Quality) of their BLA. A subsequent telephone conference was held on 25 Jan 2013; the minutes from both conferences were contained in a single document.

In addition to discussing the structure of the application, ImClone and FDA discussed requirements for the preparation of a new working cell bank, validation approach to (b) (4) during drug substance manufacturing, drug substance and drug product release specifications, approach to (b) (4) method in release and stability testing with an (b) (4) method (b) (4), testing methods for endotoxin, and the proposed stability package. FDA stated that ImClone should be prepared to submit a simple stability update if requested during the review of the BLA.

During the meeting, FDA requested that ImClone provide gels and chromatograms generated during stability studies in sections 3.2.S.7 and 3.2.P.9 of the application. FDA also requested

that ImClone submit a batch record from one lot from each site where drug product is manufactured. Finally, FDA stated that based on the information provided in the pre-BLA briefing package, no deficiencies were identified that would result in a refuse-to-file action.

15 Mar 2013 (letter to ImClone): FDA (DMEPA) sent a letter stating that the proposed proprietary name of Cyramza was conditionally acceptable.

26 Mar 2013 (letter to ImClone): FDA sent a letter to ImClone that granted a rolling review of the proposed BLA based on agreements on the contents of a complete application reached during meetings held on 17 Jan 2013 and on 23 Jan 2013 and in an email dated 21 Feb 2013 regarding the proposed clinical pharmacology sections of the BLA.

10 Oct 2013 (telephone conference with Lilly in reference to high-level results of Study JVBE): During this meeting Lilly provided high level results of Study JVBE, a second randomized clinical trial that confirmed the results observed in Study JVBD. FDA informed Lilly that these top-line results would strengthen the application and FDA previously agreed to review this information during the pre-BLA meeting held on 17 Jan 2013. FDA requested that Lilly provide the following in the BLA:

- Overall survival and demographic datasets to allow the Agency to replicate Lilly's findings of overall survival in the intent-to-treat population and in relevant subgroups.
- Copies of meeting minutes between ImClone and FDA in reference to the JVBE trial.
- Copies of the protocol, all amendments, and statistical analysis plan for the JVBE trial.
- Brief report describing the major efficacy findings.
- Safety information only if the safety information would strengthen the Warnings and Precautions Section of the label and/or would change the risk/benefit assessment of ramucirumab for use in the current application.

During the meeting, Lilly informed FDA that they will plan on submitting a BLA based on the results of JVBE in 2014.

19 Dec 2013 (Mid-Cycle communication meeting with Lilly): FDA advised Lilly that the Agency issued a warning letter to the (b) (4) manufacturing site on (b) (4). In response, Lilly proposed revising Section 3.2.P.3.1 of the BLA, withdrawing the (b) (4) manufacturing site and listing the Lilly manufacturing site as the sole DP manufacturing site. Lilly stated that the Lilly manufacturing site will be able to supply the U.S. market if ramucirumab is approved. FDA agreed during the meeting that this revision to the BLA would not constitute a major amendment.

During the meeting, FDA requested that Lilly provide information, if available, regarding the incidence of bleeding in patients who received ramucirumab while taking NSAIDS (as NSAID use was an exclusion criterion in Trial JVBD).

11 Feb 2014 (Late-Cycle meeting with Lilly): See Section 11.5 of this review for a summary of items discussed during the Late-Cycle Meeting.

2.3 Application history

The following table summarizes the contents of amendments submitted to the BLA.

Table 2 Amendments to BLA 125477 (as of the date of the completion of this review)

Date of Submission	Purpose of Submission
26 Mar 2013	Original BLA submission. This submission contained Modules 4, associated sections of Module 2, and related administrative information in Module 1.
30 Apr 2013	Submission of Module 5, associated sections of Module 2, and related administrative information in Module 1.
19 Jun 2013	Submission of QTc study report for 14T-IE-JVBK (IMCL CP12-0712) and submission of associated QT datasets, waveforms, and associated documents.
29 Jul 2013	This submission contained a response based on an email sent by the Agency dated 22 Jul 2013. In this submission, Lily provided documents related to an anti-ramucirumab antibody assay, a ligand binding neutralizing assay, and measurements of both antibodies and neutralizing antibodies in human serum samples.
21 Aug 2013	Lilly provided a response to an information request regarding clinical pharmacology information submitted in the BLA.
23 Aug 2013	Submission of the final portion of the BLA containing Module 3, associated Sections of Module 2, and related administrative information in Module 1.
13 Sep 2013	Clarification regarding the specific baseline blood pressure measurements identified in the vital signs analysis dataset for study CP12-0715.
27 Sep 2013	Submission of bioanalytical study reports as required by the Agency.
30 Oct 2013	This submission provided top-line summary data regarding the JBVE trial and datasets (demographic and survival) to enable FDA to replicate Lilly's analyses. To ensure transparency, Lilly also provided copies of the JVBE protocol, protocol amendments, and final statistical analysis plan.
4 Nov 2013	This submission contained Lilly's responses to information requests identified by FDA in a Filing Communication document and provided additional CMC information to the BLA.
6 Nov 2013	Lilly informed FDA that the JVBD clinical trial documentation was being moved from New Jersey (ImClone site) to Indianapolis (Lilly Corporate Center).
14 Nov 2013	Lilly submitted their voluntary Risk Management Plan based on an OSE request submitted by email by DOP2 on 13 Nov 2013. Lilly stated that this plan was submitted to the EMA on 23 Aug 2013 as part of the European marketing authorization request.
15 Nov 2013	Submission of a written response in regards to an 8 Nov 2013 information request based on quality microbiology sections of the BLA.
19 Nov 2013	Submission of a written response in regards to a 31 Oct 2013 information request based on CMC Sections of the BLA.
21 Nov 2013	Submission that provided locations of data in datasets in order to allow the FDA statistical reviewer to create a Table (pertaining to an analysis of prior therapies) in her review.
9 Dec 2013	This submission contained an information response to provide the studies used to support the (b) (4) for monitoring maintenance of product temperature during shipment.
11 Dec 2012	Lilly submitted the 120 day safety update.

Date of Submission	Purpose of Submission
13 Dec 2013	This submission contained responses to an FDA information request dated 26 Nov 2013 in reference to quality microbiology sections of the BLA.
13 Dec 2013	This second amendment dated 13 Dec 2013 contained method protocols and validation reports for specific analytical methods. The amendment also described requested drug substance and drug product release specifications.
23 Dec 2013	This submission contained responses to an FDA information request in an 18 Dec 2013 email regarding CMC sections of the BLA. This submission also notified FDA that Lilly removed the (b) (4) site from the drug product manufacturing section of the BLA. Lilly provided a replacement Section 3.2.P.3.1 in the BLA.
30 Dec 2013	This submission contained method protocols/SOPs for nine (quality related) methods that FDA requested on 21 Dec 2013.
9 Jan 2014	This submission contained information (in response to a 31 Dec 2013 information request by FDA) pertaining to anti-drug assays, anti-drug antibody screening assay, the neutralizing anti-drug antibody assay, and the reference standard.
15 Jan 2014	Lilly submitted information requested by FDA that included additional process parameters and control limits for the parameters for DP and DS manufacturing processes. Lilly also provided information regarding the (b) (4)
17 Jan 2014	Lilly provided requested gels and chromatograms for supportive DS and DP stability lots that were listed in the BLA.
20 Jan 2014	In response to a 16 Jan 2014 email, Lilly provided replacement Sections for certain manufacturing portions of the BLA in Module 3. Lilly also provided Section 3.2.R.2.6 Method Transfer Reports for Non-Compendial Analytical Methods to supplement Section 3.2.R.2 in Module 3.
21 Jan 2014	Lilly submitted population pharmacokinetic information from JVBD in response to an 8 Jan 2014 query from FDA regarding potential differences in PK profiles observed between Japanese and non-Japanese patients in two trials (JVBN and JVBI) reviewed by the Office of Clinical Pharmacology.
22 Jan 2014	In response to a 21 Jan 2014 email from FDA, Lilly provided replacement Sections 3.2.S.2.5 and 3.2.P.3.3 with updated protocols in the BLA.
23 Jan 2014	Lilly provided information regarding bleeding in patients who received non-steroidal anti-inflammatory drugs (NSAIDS) during the time they received ramucirumab.
24 Jan 2014	Lilly provided clarification regarding plans for conducting discriminating physico-chemical identity test(s) for ramucirumab vials following packaging and labeling.
29 Jan 2014	Lilly responded to an FDA Quality Microbiology information request dated 23 Jan 2014.
31 Jan 2014	Lilly provided MedWatch reports for cases of reversible posterior leukoencephalopathy syndrome. At the time of the submission, the cases remained blinded.
7 Feb 2014	This submission contained a relevant replacement section in Module 3. Module 3 was also revised (b) (4) in order to ensure consistency with the updated manufacturing protocol. Lilly provided revised carton and container labeling.
27 Feb 2014	Lilly provided a response regarding PMC and PMR agreements.

Date of Submission	Purpose of Submission
4 Mar 2014	Lilly provided revised draft labeling.
12 Mar 2014	Lilly provided amended carton labeling as requested by FDA.
12 Mar 2014	Lilly submitted finalized PMCs and PMRs.

3. CMC

Dr.'s Dougherty and Kennett from the Division of Monoclonal Antibodies (DMA) reviewed the product quality sections of the BLA and recommended approval of the BLA (as amended to remove the (b) (4) manufacturing site). Dr. Dougherty concluded that the manufacture of ramucirumab is well controlled and that ramucirumab is pure and potent. Dr. Dougherty also concluded that ramucirumab is free of endogenous and adventitious infectious agents sufficient to meet parameters recommended by FDA. DMA recommended an expiration dating period of (b) (4) for ramucirumab drug substance (DS) when stored at (b) (4) and an expiration dating period of 36 months for ramucirumab drug product (DP) when stored at 2-8 degrees Celsius.

DMA recommended multiple post-marketing commitments and requirements during the course of the review. These commitments included re-evaluation of both DS and DP lot release and stability specifications after manufacture of (b) (4) lots; confirmation of stability (b) (4) and performance of a shipping study to confirm validation of commercial ramucirumab DP shipping conditions. DMA recommended post-marketing requirements (PMRs) for Lilly to develop valid, sensitive, and accurate assays for the detection of binding and neutralizing antibodies to ramucirumab. Regarding these PMRs, DMA found that ramucirumab immunogenicity and neutralizing antibody assays were not characterized by sufficient drug tolerance. *Comment: Refer to Section 11.5 of this review for pertinent discussion with Lilly regarding these PMRs that occurred following the completion of the DMA reviews.*

3.1 Drug substance

Ramucirumab is a human monoclonal antibody against the vascular endothelial growth factor 2 receptor that contains two heavy gamma-1 chains and two light kappa chains. The gamma chains each contain 446 amino acid residues and the light chains each contain 214 amino acid residues. The predicted molecular weight of ramucirumab is (b) (4) . The DMA review stated that the ImClone Systems LLC site in Branchburg NJ manufactures DS in accordance with current Good Manufacturing Practices (GMP).

Lilly manufactures ramucirumab (b) (4) (b) (4)

3.2 Drug product

Dr. Dougherty stated that the major component of the DP was ramucirumab DS, 10 mg/mL, in a histidine (b) (4), including sodium chloride and glycine (b) (4) and polysorbate 80 (b) (4) Lilly supplies DP in either 10 mL or 50 mL Type I glass vials stoppered with (b) (4) stoppers and sealed (b) (4) (b) (4). During the clinical development of ramucirumab, commercial manufacturing was transferred multiple times. DP will be manufactured by Lilly in Indianapolis, Indiana.

Ramucirumab DP is a sterile, preservative-free solution at pH 6.0. Lilly supplies ramucirumab DP as a clear to slightly opalescent, colorless to slightly yellow solution that is free from visible particles.

3.3 Quality microbiology

Dr. Suvarna and Dr. Hughes recommended approval of ramucirumab from a product (drug substance) quality perspective. FDA inspected the drug substance manufacturing site (ImClone Systems Branchburg, NJ) from 4 Nov 2013 to 13 Nov 2013 and classified the site as NAI (no action indicated). Dr. Suvarna found the microbial control of the drug substance manufacturing process to be acceptable.

Dr. Gomez Broughton and Dr. Hughes recommended approval of the amended BLA from a product quality (drug product) microbiology perspective. Among other analyses, ramucirumab met acceptance criteria regarding the microbial quality of the drug product. The DP Quality Microbiology review described ramucirumab as a sterile, preservative-free, 10 mg/mL solution for intravenous infusion.

4. Nonclinical Pharmacology/Toxicology

Dr. Khasar, the primary nonclinical reviewer, concluded that the nonclinical studies were sufficient to support the use of ramucirumab in the proposed patient population and that there were no outstanding nonclinical pharmacology/toxicology issues preventing the approval of ramucirumab.

4.1 Nonclinical pharmacology

The nonclinical overview in the BLA stated that a surrogate antibody for ramucirumab (DC101) was used for initial nonclinical pharmacology testing because ramucirumab is not cross-reactive in mice. The applicant stated that DC101 exhibited anti-tumor and anti-angiogenic activity in a broad range of mouse xenograft models; however, cross-species extrapolation regarding exposure (to observe anti-tumor activity) was limited based on the lower affinity of DC101 for the murine receptor and differences in the route of exposure (intraperitoneal) with resultant differences in pharmacokinetics. Lilly stated in the report that 18 micrograms/mL was the targeted serum concentration in the first-in-humans study based on the estimated minimum circulating plasma concentration of DC101 required to significantly inhibit the growth of tumors in a pancreatic cancer xenograft model (BxPC-3).

Other *in vitro* and *in vivo* studies characterized ramucirumab as a monoclonal antibody that binds to human vascular endothelial growth factor receptor 2 (VEGFR2) and that ramucirumab

can displace the VEGFR2 ligands including VEGF-A, VEGF-C, and VEGF-D. Ramucirumab demonstrated antiangiogenic effects in a mouse model using mice subcutaneously implanted with a mix of human endothelial progenitor cells and adipose-derived stem cells.

4.2 Nonclinical toxicology

Nonclinical toxicology testing was conducted in monkeys because ramucirumab only binds to human and non-human primate VEGF2. Lilly submitted the results of 5-week (dose levels tested up to 40 mg/kg administered on days 1, 15, 22, and 29) and 39-week (doses levels tested up to 50 mg/kg every week) GLP compliant toxicity studies conducted in cynomolgus monkeys in support of the BLA.

In both the 5- and 39-week studies, high levels of creatine phosphokinase (CPK) were detected which were not dose-related. The non-clinical reviewer described evidence of correlated histopathologic findings in skeletal muscle in the 5- but not in the 39-week study. The non-clinical review also stated that there were findings of mineralization and inflammation of gray matter as well as lymphocytic cuffing in the meninges and choroid plexus in animals from all ramucirumab dose groups.

The applicant reported renal toxicity in the 39 week study including moderate to severe glomerulonephritis at doses ≥ 16 mg/kg. The non-clinical reviewer stated that these effects may be delayed and that these effects were not observed at the mid-term sacrifice on Day 85 of the study. *Anti-VEGF antibodies (or anti-VEGFR antibodies) appear to cause proteinuria and nephrotic syndrome as a class effect.*

Ramucirumab did not impair wound healing in monkeys on Day 8 following a single dose of up to 50 mg/kg ramucirumab; however, Lilly stated that this risk cannot be discounted based on the importance of VEGF/VEFR-2 in wound healing.

Ramucirumab caused bone growth plate changes in immature monkeys after 39 weeks of weekly intravenous infusions at 5 mg/kg. Lilly stated that this was an anticipated finding; however this would not be expected to affect older adults in the indicated population (previously treated patients with gastric cancer).

In accordance with ICH S6, Lilly did not submit genotoxicity data in the BLA for this biotherapeutic protein not expected to interact with DNA or other chromosomal material. Lilly also did not submit a carcinogenicity study in accordance with ICH S9. In lieu of a dedicated reproductive toxicology study, Lilly submitted a literature-based assessment of the potential effects of inhibition of VEGF2 signaling during pregnancy (performed in accordance with principles cited in the ICH S9 document). FDA review staff agreed that the scientific literature supports a critical role for VEGR2 signaling in the maintenance of pregnancy and in embryonic vasculogenesis. The non-clinical review staff stated that ramucirumab should not be used during pregnancy unless the benefits to the mother outweigh the risk to the fetus.

5. Clinical Pharmacology

5.1 General clinical pharmacology considerations

The clinical pharmacology review team (Dr. Zhang as primary reviewer) concluded that this BLA is acceptable from a clinical pharmacology perspective. The applicant submitted limited pharmacokinetic data from Trial JVBD (primary randomized trial submitted in support of the application) from 58 patients. The applicant discussed these limitations (for the conduct of population PK analyses) with FDA prior to submission of the BLA. Nevertheless, these limitations precluded substantive analyses of exposure-response in Trial JVBD and analyses of PKs in different patient subgroups.

OCP (Office of Clinical Pharmacology) recommended a post-marketing requirement to evaluate immunogenicity with an improved assay because the assays used in the detection of anti-ramucirumab antibodies and neutralizing antibodies were interfered (based on data reviewed in the application) by the presence of ramucirumab in the patients' serum samples. *Comment: Refer to Section 11.5 of this review for pertinent discussion with Lilly regarding these PMRs that occurred following the completion of the OCP reviews.*

5.1.1 Dose selection

The applicant submitted results of two dose finding trials: Study JVBM evaluated the safety of weekly doses of ramucirumab from 2 to 16 mg/kg and Study JVBN evaluated the safety of ramucirumab administered either every two weeks (6 to 10 mg/kg) or every three weeks (15 to 20 mg/kg). A maximum tolerated dose was not identified in either group in Study JVBN.

In determining a dose to evaluate in Trial JVBD, the applicant targeted a serum concentration associated with inhibition of tumor growth in a preclinical xenograft model (C_{min} > 18 μg/mL). Additionally, the applicant stated that the PK profile of ramucirumab appeared linear at doses of 8 mg/kg and above, suggesting saturation of the target-mediated clearance pathway.

Dr. Zhang stated in her review that approximately 95% of the 58 patients in the PK subgroup of Trial JVBD (primary randomized gastric cancer trial) achieved a ramucirumab C_{min} > 18 μg/mL.

5.1.2 Pharmacokinetics

The applicant submitted results of Study JVBW characterizing the pharmacokinetics of ramucirumab in 6 Japanese patients with gastric cancer who received ramucirumab 8 mg/kg every other week in combination with paclitaxel (80 mg/m^2 intravenously on days 1, 8, and 15 of 28 day cycles). The OCP review summarized data from 6 patients following the first dose of ramucirumab and 4 patients following the third dose of ramucirumab. The geometric half-life was approximately seven and a half days following the first dose of ramucirumab; however, data (for this analysis) were obtained from only four patients and the terminal elimination half-life may not have been completely captured (as PK data were collected up to 14 days following the first dose).

In addition to the limitations described above, the OCP reviewer stated that cross-study PK profiles from two studies evaluating ramucirumab in patients with solid tumors (JVBI and the

previously described JVBN) suggested that Japanese patients may have higher exposure than non-Japanese patients. Accordingly, OCP recommended removal of PK findings from the Japanese study in the U.S. product label.

OCP recommended summarizing PK data in the label from the JVBD gastric cancer trial stating that the geometric mean of the serum ramucirumab minimum concentration (C_{min}) was 50 μg/mL after the third dose and 74 μg/mL after the sixth dose.

5.2 Drug-drug interactions

Ramucirumab is not expected to have an effect on CYP enzymes or be metabolized by CYP enzymes and therefore unlikely to have clinically relevant drug-drug interactions.

5.3 Demographic interactions/special populations

OCP recommended that the label contain no statements describing how intrinsic factors influence PKs based on the limited PK data collected in Trial JVBD. Body weight showed a possible effect on PKs; however, lower weight patients maintained target concentrations greater than 18 μg/mL.

5.4 Thorough QT study or other QT assessment

Ramucirumab is a therapeutic monoclonal antibody and as such is not expected to inhibit hERG function or other ion channels involved in cardiac repolarization. Nevertheless, the applicant submitted the results of one study that evaluated the effects of ramucirumab on QT intervals. This study (JVBK) was a multicenter, open-label, single-arm trial evaluating ramucirumab 10 mg/kg as a single agent administered every three weeks for a minimum of 9 weeks to patients with advanced solid tumors. The OCP review stated that no clinically relevant changes in the mean QTc were detected.

6. Clinical Microbiology

This section is not applicable to this review.

7. Clinical/Statistical-Efficacy

The clinical reviewer (Dr. Sandra Casak) recommended approval of this application based on the improvement in overall survival demonstrated in the JVBD clinical trial that was supported by data received in the application from the JVBE clinical trial. Both clinical trials enrolled patients with previously treated metastatic gastric cancer (or GEJ cancer). The statistical reviewer (Dr. Hui Zhang) concluded that based on the data and analyses from JVBD, ramucirumab plus best supportive care demonstrated a statistically significant improvement in OS and PFS.

This section of the CDTL review will focus on the demonstration of safety and efficacy in adequate and well controlled trials (predominantly JVBD with supportive efficacy findings from JVBE) and thus will not focus on trials in other indications (e.g., that provided safety data) or on trials that supported the dose of ramucirumab (refer to Clinical Pharmacology Section above).

7.1 Background of clinical program

The initial protocol for the pivotal trial [JVBD (14T-IE-JVBD) also known as REGARD and previously listed as IMCL CP12-0715)] was dated 5 Mar 2008 and contained the following title: A Phase 3, Randomized, Double-Blinded Study of IMC-1121B and Best Supportive Care (BSC) Versus Placebo and BSC in the Treatment of Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy.

During the review of the application, Lilly informed FDA of the results of a second randomized trial evaluating the use of ramucirumab in patients with gastric cancer who were previously treated with platinum and a fluoropyrimidine. This trial was listed as JVBE (14T-IE-JVBE) and previously listed as IMCL CP12-0922 (also known as RAINBOW) and contained the following title: 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.

7.2 Design of JVBD

7.2.1 Primary endpoint (JVBD)

The primary endpoint of JVBD was overall survival (OS), defined as the time from randomization to the date of death from any cause. *Comment: As stated in the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf; accessed on 03 Oct 2013), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.*

7.2.2 Secondary endpoints (JVBD)

Secondary endpoints defined by the original protocol included progression free survival (PFS), 16-week PFS, overall response rate, and duration of response. The protocol stated that the overall significance level for PFS was 0.05; significance levels were not described for the other endpoints.

The protocol defined progression free survival as the time from the date of randomization until the date of objectively determined progressive disease or death due to any cause. The protocol included a provision to censor patients who died (in the PFS analysis) without evidence of tumor progression at the time of the last tumor analysis if the patient died after missing two or more tumor assessments.

The use of investigator assessments for progression (and response) was acceptable because the primary endpoint was overall survival (i.e., the PFS and ORR endpoints are considered supportive of the overall survival results). Additionally, this trial was blinded which allows for increased confidence in the overall PFS results.

The protocol defined 16-week PFS as the proportion of the ITT population alive and progression-free 16 weeks after randomization, as extracted from the Kaplan-Meier curves. *Comment: This reviewer recommends against the inclusion of results from this endpoint in product labeling because this landmark analysis does not provide an informative estimate of the overall treatment effect on progression free survival (e.g., as opposed to estimates based on the hazard ratio).*

The protocol defined overall tumor response as the proportion of all patients with a confirmed partial response (PR) or complete response (CR) according to RECIST criteria from the start of treatment until disease progression or recurrence. Confirmation required a repeat assessment no less than four weeks following documentation of the initial response. The protocol defined duration of response from the time that a patient first met criteria for CR/PR until the first date that criteria for progressive disease were met or death was documented. Patients without progression were censored on the day of their last tumor assessment.

7.2.3 Eligibility criteria (JVBD)

Patients with histologically or cytologically confirmed and measurable metastatic gastric or gastroesophageal junction adenocarcinoma were eligible for enrollment in the clinical trial. The protocol also allowed for enrollment of patients with locally-recurrent, unresectable, refractory disease if the patient had lymph node metastases. The protocol required previous treatment with combination chemotherapy that included a platinum or a fluoropyrimidine 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 listed the following additional eligibility criteria (*for brevity, only select criteria are listed*): age ≥ 18 years, ECOG 0-1; total bilirubin ≤ 1.5 mg/dL; urinary protein ≤ 1+ on dipstick or < 1,000 mg of protein in a 24 hour urine collection if 2+ on dipstick; New York Heart Association Class I function or better if a patient was previously exposed to an anthracycline.

The protocol excluded patients with the following (*for brevity, only select criteria are listed*): ≥ Grade 3 bleeding within 3 months, arterial thrombotic event within 6 months; symptomatic heart failure; unstable angina pectoris; uncontrolled thrombotic disorder; uncontrolled hemorrhagic disorder; uncontrolled or poorly controlled hypertension; serious or non-healing wound, ulcer, or bone fracture; major surgery within 28 days; venous access device placement within seven days; and receipt of chronic anti-platelet therapy other than once daily aspirin (≤ 325 mg/day). *Comment: the protocol restricted anti-platelet therapy during the course of the study; however, anticoagulant therapy was permitted if the patient did not have a pathological condition that would subject the patient to high risk of bleeding (for example, tumor involving major blood vessels).*

7.2.4 General study design/treatment plan (JVBD)

- The trial was a double-blinded, randomized (2:1), multi-center, international trial. Randomization occurred via an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS). The protocol instructed investigators to

initiate ramucirumab or placebo within 7 days of randomization. The protocol allowed for unblinding only for emergency purposes.

- JVBD randomized patients to receive either placebo or ramucirumab every two weeks at a dose of 8 mg/kg. Patients in both arms received best supportive care.
- The protocol contained recommendations for the management of infusion reactions including the requirement for permanent discontinuation of ramucirumab or placebo for Grade 3 or 4 infusion reactions.
- The protocol contained instructions for the management of hypertension. If a patient required interruption of study therapy more than once for hypertension, the protocol recommended dose reduction to 6 mg/kg every other week. A second dose reduction to 5 mg/kg was permitted if study related therapy required interruption a third time. The protocol required permanent discontinuation of ramucirumab or placebo for Grade 4 hypertension or poorly controlled hypertension (> 160 mm Hg systolic or > 100 mmHg diastolic for > 4 weeks despite oral antihypertensive therapy).
- The protocol required interruption of ramucirumab or placebo if proteinuria developed that was ≥ 2 grams in 24 hours. If proteinuria decreased to less than 2 grams (in 24 hours) within 2 weeks, treatment could be reinitiated at a reduced dose (6 mg/kg).
- The protocol allowed up to two dose reductions (to 6 mg/kg and 5 mg/kg) for non-life threatening Grade 3 or 4 adverse events (e.g., fatigue, anorexia, and fever) according to NCI-CTCAE Version 3.0 (dose interruption alone was permitted following the first occurrence of such an event).
- Patients continued either blinded placebo or ramucirumab until progressive disease, unacceptable toxicity, decline of ECOG PS of ≥ 2 points, or withdrawal of consent.
- Patients underwent assessments for tumor size every 8 weeks. To assess for response and progression (via RECIST guidelines), the protocol recommended CT scans of the chest and abdomen with contrast (unless contrast was contraindicated). For patients with contraindications to contrast, the protocol recommended CT of the chest without contrast and MRI of the abdomen. Additional imaging (e.g., bone scans) was permitted if clinically indicated.
- Following discontinuation of placebo or ramucirumab, the protocol stipulated follow-up of surviving patients every three months for a minimum of 18 months and a maximum of 40 months to obtain survival information and information regarding subsequent anticancer therapy.
- While patients received placebo or ramucirumab, the protocol required bi-weekly evaluations of vital signs, performance status, adverse events (severity assessed using NCI-CTCAE Version 3.0), and chemistry and hematology labs. Investigators also collected a blood sample for anti-product antibodies at baseline, prior to Cycle 5, prior to Cycle 9, and during the 30 day follow-up visit following the end of study-related treatment.
- The protocol established an Independent Data Monitoring Committee (IDMC) with meetings at least twice a year, when 50 and 150 patients received at least two cycles of

study drug (or died or discontinued prior to two cycles), and for interim analyses of futility and efficacy.

7.2.5 Statistical design and analysis issues (JVBD)

Randomization/Stratification Factors
The original protocol specified the following two stratification factors: weight loss (≥ 10% over the prior 3 months versus < 10%) and geographic region (North America, Australia, and New Zealand versus South and Central America versus Asia).

Determination of Sample Size
The protocol stated that 651 patients were to be randomized (2:1) to each arm. A total of 531 events (deaths) were required for 90% power to identify an improvement in OS at a HR of 1.33 (estimated OS of 5 months in the placebo arm and 6.65 months in the ramucirumab arm) at a 0.05 two-sided significance level. This sample size accounted for one interim analysis to be conducted after 75% of events occurred. Alpha would be adjusted using methods described by Lan and DeMets. The protocol also specified three interim futility analyses.

Analyses
The protocol stated that the primary efficacy analysis for overall survival would be tested using a stratified log-rank test. The protocol specified that the primary analysis would be conducted using the intent-to-treat population consisting of all patients randomized. The protocol stated that the overall significance level for the secondary endpoint of PFS was 0.05 (overall alpha maintained using a hierarchical testing procedure).

7.2.6 Protocol amendments (JVBD)

Version 2.0 (dated 22 Jul 2008)
The following list describes major changes contained in Version 2.0 of the protocol:

- Modified eligibility guidelines to require a hemoglobin concentration of ≥ 9 gm/dL (versus 8 gm/dL).
- Clarified that patients are eligible if they have either metastatic disease or locally-recurrent, unresectable, refractory disease with measurable lymph node metastases.
- Added location of primary tumor as a stratification factor (gastric versus GEJ site) at randomization and a stratification factor in the analyses described in the statistical analysis section.
- Allowed for premedication prior to administration of ramucirumab or placebo based on investigator discretion. Recommendations for Grade 1 and 2 infusion reactions were also updated.
- Required more frequent monitoring for bleeding if the hemoglobin concentration fell below 9 g/dL and there were signs or symptoms of bleeding.

Version 3.0 (dated 24 November 2008)

No patient was enrolled prior to this amendment. The following list describes major changes contained in Version 3.0 of the protocol [Version 3.1, dated 23 Dec 2008 was submitted to update the EudraCT (European Union Drug Regulating Authorities Clinical Trial) number]:

- Changed a secondary endpoint from 16 week PFS to 12 week PFS (*this reviewer's comment above regarding 16 week PFS also applies to this endpoint*).
- Removed the requirement for "refractory" disease in patients with locally-recurrent unresectable disease and clarified that at least one measurable lymph node metastasis was required.
- Eligibility criteria modified to allow patients with evaluable disease (e.g., measurable disease not required) *(this criteria appeared to conflict with the prior criterion for patients with locally recurrent, unresectable disease).*
- Required assessments for tumor size every six weeks rather than every 8 weeks.
- Changed the timing for IDMC assessments of safety data.
- Changed censoring criteria for PFS to censor data on the date of the last objective tumor assessment for patients who began a new anticancer therapy.

Version 4.0 (dated 1 Jul 2009)

The following list describes major changes contained in Version 4.0 of the protocol:

- Removed language mandating the (b) (4) maximum follow-up duration for survival.
- Updated the protocol to use NCI-CTCAE Version 4.0 (rather than Version 3.0) to assess the severity of adverse events.
- Amended geographic region strata as follows: North America, Europe, Australia, and New Zealand versus South and Central America, India, Egypt, South Africa, Jordan, Lebanon, and Saudi Arabia versus Asia *(this change added African countries, Middle Eastern countries, and India to the South and Central America stratum, rather than the Asian stratum).*
- Revised the primary eligibility criteria to state "The patient has metastatic disease or locally recurrent, unresectable disease." Three bullets followed this statement: (1) Patients with non-regional lymph node metastases are eligible; lymph node metastases must be measured as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.0; (2) Patients with locally-recurrent, unresectable disease are eligible; (3) For patients who have received prior radiotherapy, 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. *This reviewer interpreted this statement to indicate that patients with locally recurrent, unresectable disease were eligible irrespective of the presence of a lymph node metastasis (although this was not clear based on the first and second bullets).*
- Clarified that no increase in the dose of ramucirumab was permitted following dose reduction due to an adverse event.

Version 5.0 (dated 8 Feb 2010)

The following describes major changes contained in Version 5.0 of the protocol (Version 5.1, dated 20 April 2010 added a section to detail the handling of small target lesions and to amend instructions for the management of hypertension).

- Clarified that imaging was required every six weeks until documentation of progression or initiation of new anticancer therapy unless the investigator deemed such an evaluation as clinically not feasible.
- Updated the protocol to use NCI-CTCAE Version 4.02 (rather than Version 4.0) to assess the severity of adverse events.

Version 6.0 (dated 23 Nov 2010)

The following list describes major changes contained in Version 6.0 of the protocol.

- This amendment reduced the planned sample size from 615 patients to 315 patients and the number of events for the final analysis from 344 events to 256 events. Assumptions regarding the sample size reduction were changed including decreasing the power to (b) (4) and increasing the effect size that the study was powered to detect (HR of 1.45 with a median 5 months survival in the placebo arm versus 7.25 months in the ramucirumab arm). The amendment also eliminated the provision allowing for the interim analysis of efficacy.

  Comment: Of the 355 patients in the final OS analysis, only 39 (11%) signed informed consent prior to 23 Nov 2010. Furthermore, < 4% of events (deaths) occurred prior to this date. Thus, it is unlikely that this reduction in sample size compromised the integrity of the clinical trial.

- Removed language permitting the sponsor to provide waivers regarding the eligibility criteria.
- Required imaging assessments for PFS every six weeks until documented progression for patients who discontinued study therapy for any reason other than progressive disease.

Version 7.0 (approved 31 Oct 2011)

The following list describes major changes contained in Version 7.0 of the protocol.

- Increased the sample size from 315 to 348 patients and the number of events from 256 events to 268 events. This version allowed for a single interim *futility* analysis after (b) (4) of the total number of planned events. The protocol stated that the change in the sample size was based on adjustments to the accrual rate.
- Stipulated follow-up for survival every two months rather than every three months to reduce the delay in capturing deaths and allow more accurate survival times for patients alive at data cut-off.

  Comment: The planned futility analysis occurred during an IDMC meeting on 12 Dec 2011 (after the promulgation of this amendment).

7.3 Design of JVBE

As stated above, JVBE was a second large, international, randomized clinical trial evaluating ramucirumab in patients with previously treated gastric (or GEJ) adenocarcinoma.

7.3.1 Primary endpoint (JVBE)

The primary endpoint of JVBE was overall survival (OS), defined as the time from randomization to the date of death from any cause.

7.3.2 Secondary endpoints (JVBE)

Planned secondary endpoints included progression free survival (PFS), time to progression (TTP), and best overall response (BOR).

PFS was defined as the time from randomization until the first radiographic documentation of progression as defined by RECIST (Version 1.1) or death due to any cause. The protocol contained a provision to censor data on the date of a patient's last tumor assessment for patients lost to follow-up, after two or more consecutive missing radiographic visits, or if the patient was alive and without progression on the data cut-off date. If no baseline or post-baseline radiographic assessment was available, data was censored at the date of randomization (for the PFS analysis).

TTP was defined from the time of randomization until the date of radiographic progression according to RECIST guidelines. Best overall response was determined using RECIST criteria (Version 1.1).

7.3.3 Eligibility criteria (JVBE)

Patients with histologically or cytologically confirmed, unresectable or metastatic gastric or gastroesophageal adenocarcinoma were eligible for the trial. The protocol required previous treatment with a platinum and fluoropyrimidine in the first-line setting for unresectable or metastatic gastric (or GEJ) cancer. Patients in JVBE must have progressed during first-line therapy or within four months after the last dose of first-line therapy.

The protocol listed the following additional eligibility criteria (*for brevity, only major select criteria are listed*): age ≥ 18 years; ECOG 0-1; total bilirubin ≤ ULN; urinary protein ≤ 1+ on dipstick or < 1,000 mg of protein in a 24 hour urine collection if 2+ on dipstick; and an INR ≤ 1.5.

The protocol excluded patients with the following (*for brevity, only select criteria are listed*): major surgery within 28 days; previous anti-VEGF therapy; history of DVT, PE, or thromboembolism within previous three months; receiving therapeutic anticoagulation with warfarin, heparins, or similar agents; chronic NSAID or aspirin use (aspirin up to 325 mg/day was permitted); significant bleeding disorders; gastrointestinal perforation or fistula within the prior 6 months; symptomatic heart failure; any arterial thrombotic event within 6 months; uncontrolled hypertension (≥ 150/90 mmHg despite standard medical management); serious or non-healing wound or ulcer; history of bowel obstruction; or history of other serious medical illness or condition.

7.3.4 General study design/treatment plan (JVBE)

- The trial was a double-blinded, randomized (1:1), multi-center, international trial. Randomization occurred via an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS).

- The protocol instructed investigators to initiate paclitaxel in combination with either ramucirumab or placebo within 7 days of randomization. The protocol allowed for unblinding only for emergency purposes.
- JVBE randomized patients to receive paclitaxel 80 mg/m^2 on days 1, 8, and 15 of every four week cycle in combination with either placebo or ramucirumab 8 mg/kg on days 1 and 15 of each four week cycle. The protocol instructed investigators to administer paclitaxel intravenously at least one hour after the ramucirumab infusion for the first two cycles. The protocol stated that the one hour observation period could be omitted if no infusion-related reactions occurred during the first two cycles.
- The protocol allowed for the discontinuation of one of the agents (paclitaxel or ramucirumab / placebo) if the toxicity was recognized as being caused by the agent (e.g., hypertension with ramucirumab).
- For paclitaxel, no dose modification was permitted within a cycle (paclitaxel was to be withheld for specified reasons including severe neutropenia, renal insufficiency, and liver toxicity). The protocol permitted paclitaxel dose reductions (by 10 mg/m^2) during the following cycle for Grade 4 hematological toxicity or Grade 3 non-hematological toxicity. The protocol required permanent discontinuation of paclitaxel if 60 mg/m^2 was not tolerated or following paclitaxel-related life-threatening adverse events.
- The protocol contained recommendations for the management of infusion reactions including the requirement for permanent discontinuation of ramucirumab or placebo for Grade 3 or 4 infusion reactions.
- The protocol contained instructions for the management of hypertension. If a patient required interruption of study therapy more than once for hypertension, the protocol recommended dose reduction to 6 mg/kg every other week. A second dose reduction to 5 mg/kg every other week was also permitted if a patient required interruption a third time. The protocol required permanent discontinuation of ramucirumab or placebo for Grade 4 hypertension or poorly controlled hypertension (> 160 mmHg systolic or > 100 mmHg diastolic for > 4 weeks) despite oral antihypertensive therapy.
- The protocol required interruption of ramucirumab or placebo if proteinuria developed that was ≥ 2 grams in 24 hours. If proteinuria decreased to less than 2 grams (in 24 hours) within 2 weeks, treatment could be reinitiated at a reduced dose (6 mg/kg).
- The protocol allowed up to two dose reductions of ramucirumab or placebo (to 6 mg/kg and 5 mg/kg) for non-life threatening Grade 3 or 4 adverse events (e.g., fatigue, anorexia, and fever) according to NCI-CTCAE Version 3.0 (dose interruption alone was also permitted following the first occurrence of such an event).
- In general, patients continued either blinded placebo or ramucirumab until progressive disease (radiographic or *symptomatic*), unacceptable toxicity, or withdrawal of consent.
- Patients underwent assessments for tumor size every 6 weeks. To assess for response and progression (via RECIST guidelines), the protocol required CT scans of the thorax, abdomen, and pelvis (MRI was a complimentary method to assess the abdomen and pelvis).

- The protocol instructed investigators to contact patients every two months to obtain information regarding survival status and information regarding subsequent systemic anticancer therapy or disease progression.
- The protocol required a hematology profile and liver profile within 24 hours of administering paclitaxel on days 1, 8, and 15 of each cycle. Investigators obtained a full chemistry profile on day 1 of each treatment cycle. Vital signs were obtained before and at the completion of each ramucirumab (or placebo) dose and after the completion of chemotherapy. A urinalysis was also obtained biweekly while either ramucirumab or placebo was administered.
- The protocol established an Independent Data Monitoring Committee (IDMC) with meetings at least twice a year, until all patients were randomized and received two 4-week cycles of study-related treatment (or discontinued the study or died).

7.3.5 Statistical design and analysis issues (JVBE)

Randomization/Stratification Factors

The initial protocol specified the following stratification factors: disease measurability (measurable versus non-measurable); geographic region [Europe (including Israel) / North America / Australia versus Asia versus rest of the world (including South America)]; and time to progression on first-line therapy (< 6 months versus ≥ 6 months). The protocol used stratified permuted block randomization to assign patients into treatment arms.

Determination of Sample Size

The initial protocol stated that 663 patients were to be randomized (1:1) to each arm. A total of 510 events (deaths) were required for (b) (4) power to identify an improvement in OS at a HR of 0.75 (estimated OS of 7 months in the paclitaxel plus placebo arm and 9.33 months in the paclitaxel plus ramucirumab arm) at a 0.025 one-sided significance level. The protocol specified one interim analysis for futility after (b) (4) of the projected events occurred (the futility boundary was specified in the protocol).

Analyses

The protocol stated that the primary efficacy analysis for overall survival would be tested using a stratified log-rank test. The protocol specified that the primary analysis would be conducted using the intent-to-treat population consisting of all patients randomized. The protocol stated that the overall significance level for PFS was 2.5% (one-sided) and that the other endpoints would be analyzed in a "non-confirmatory sense."

7.3.6 Protocol amendments (JVBE)

Version 2.0 (dated 06 Dec 2010)

The following describes major changes contained in Version 2.0 of the protocol:

- Clarified that patients were eligible with a diagnosis of gastric or gastroesophageal junction adenocarcinoma (rather than gastroesophageal adenocarcinoma).
- Changed the frequency of tumor assessments (from every 6 weeks) to every 6 weeks for the first 6 months following the first dose followed by every 9 weeks thereafter.

Version 3.0 (dated 08 Oct 2012)

The following list describes major changes contained in Version 3.0 of the protocol:

- Allowed for more frequent collection of survival information.
- Incorporated extension language to permit the continuation of study treatment in patients who were receiving clinical benefit following the completion of the study.
- Amended the dose modification section for ramucirumab / placebo to permit continued dosing in the setting of certain non-life threatening and reversible Grade 3 to 4 adverse events (e.g., Grade 4 fever or certain laboratory abnormalities).

7.4 Efficacy results (JVBD)

The first patient was enrolled into JVBD (monotherapy study) on 6 Oct 2009 and the last patient was enrolled on 10 Jan 2012. A total of 459 patients were screened, and 104 patients were not randomized (with the majority related to ineligibility for one or more of the exclusion criteria). The study data cut-off date was 25 Jul 2012, and 290 patients died on or prior to the date of data cut-off.

7.4.1 Demographics (JVBD)

Median age of patients randomized to the ramucirumab arm was 60 years (range 31 to 86) versus 61 years (range 24 to 88) in the placebo arm. The majority of patients in both arms (73%) had the primary tumor present at trial entry. Table 3 (data from Dr. Casak's review) shows that the gender and ethnic background of patients enrolled into JVBD were similar between arms.

Table 3 Demographics, JVBD

	Ramucirumab N=238 (%)	Placebo N=117 (%)
Age		
≥ 65 years	34	39
Female		
Yes	29	32
Race		
White	76	78
Black	2	2
Asian	16	15
Other	6	6
Geographic Region		
Region 1	69	69
Region 2	23	25
Region 3	8	7

Region 1 = North America, Europe, Australia, New Zealand
Region 2 = South and Central America, India, South Africa, Jordan, Egypt, Saudi Arabia, Lebanon
Region 3 = Other Asian countries

In general, demographic characteristics of patients were balanced in the two arms. Patients in the placebo arm had a modestly higher incidence of intestinal histology; however, the more

aggressive diffuse histology was balanced in the two arms. Patients in the placebo arm also had modestly increased incidence of peritoneal metastases.

Table 4 Disease characteristics at baseline, JVBD

	Ramucirumab N=238 (%)	Placebo N=117 (%)
ECOG PS		
0	28	26
1	72	73
2	0	1
Weight loss ≥ 10%		
Yes	17	17
Primary site of disease		
Gastric	75	74
GEJ	25	26
Histology		
Intestinal	22	30
Diffuse	40	38
Other/not-available	38	32
Metastases		
≥ 3 Sites	33	39
Peritoneal	27	38
Liver	44	48

7.4.2 Disposition (JVBD)

The cut-off date for the data-analysis was 25 Jul 2012. A total of 236 out of 238 patients in the ramucirumab arm and 115 of 117 patients in the placebo arm received study-directed investigational drugs. Table 5 (data from Dr. Casak's review) shows the reasons for discontinuation of ramucirumab or placebo during the trial. Most patients in both arms discontinued due to progressive disease; however, a higher proportion of patients discontinued due to progressive disease or death in the placebo arm. More patients who received ramucirumab discontinued due to an adverse event.

Table 5 Patient disposition, JVBD

	Ramucirumab N=238 (%)	Placebo N=117 (%)
Progressive disease	53	62
Symptomatic deterioration	17	14
Death	8	11
Withdrawal of consent	3	2
Adverse event	11	6
Other reasons	1	3

The investigators (and applicant) appeared to adequately follow patients for survival. Six patients were lost to follow-up and six additional patients withdrew consent for OS follow-up (constituting less than 5% of the randomized population).

7.4.3 OS analyses (JVBD)

Table 6, data obtained from the statistical review, shows the OS results determined at the time of data-cut off (25 Jul 2012). Seventy-eight percent of patients died (across both arms) by the time of data-cut off, constituting a mature analysis of survival. The pre-specified analysis of OS was statistically significant at the two-sided 0.05 level. The applicant conducted sensitivity analyses that supported the pre-specified findings [including analyses based on strata using CRF data (rather than entered in the IVRS), unstratified analyses, and the analysis at exactly 268 events]. The p value for each of these analyses was less than 0.05. More importantly, however, the results from a second trial (JVBE, see below) confirmed the results observed in Trial JVBD.

Although the magnitude of the effect was clinically modest, i.e., a median difference of 1.4 months with a hazard ratio of 0.78, the effect was observed with a manageable toxicity profile, especially when compared to drugs commonly administered to patients with cancer.

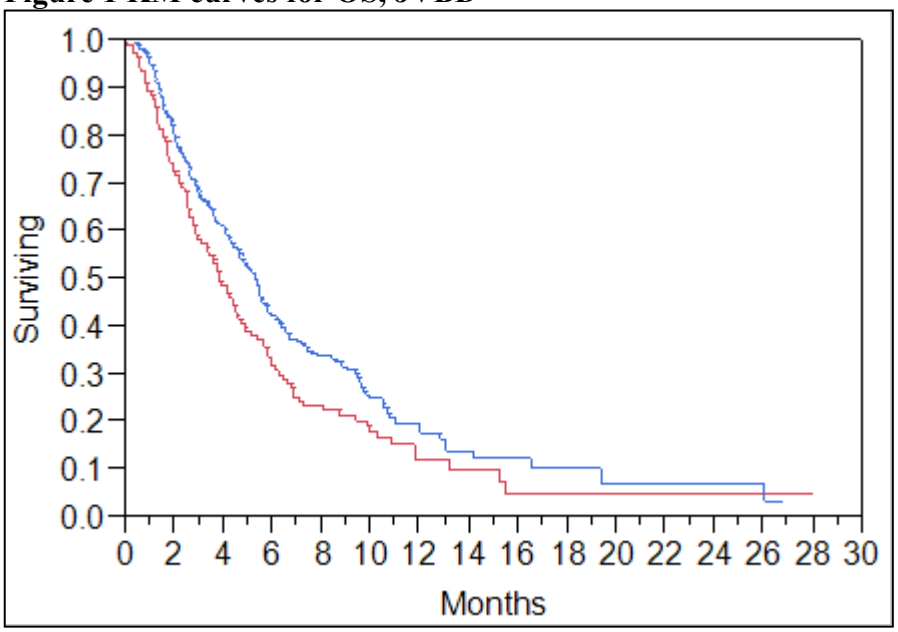
Table 6 OS analyses (ITT), JVBD

	Ramucirumab N=238	**Placebo N=117**
Number of deaths, n (%)	179 (75%)	99 (85%)
Median overall survival (months)	5.2	3.8
95% CI	(4.4, 5.7)	(2.8, 4.7)
HR (95% CI)	0.776 (0.603, 0.998)	
Stratified log-rank test p-value[a]	0.0473	

[a] Stratified by planned stratification factors (see above)

Figure 1, copied from the clinical review, shows the proportion of patients alive at each time point during the trial. The curves presented in the applicant's clinical study report and statistical review were similar to the KM curves presented in the clinical review (the statistical review shows the number of patients at risk at various time-points). Separation of the KM curves remained constant throughout the duration of the trial until the tails of the curves were reached. Because few patients were assessable after 9 months, no conclusions can be made regarding the tails of these curves.

Figure 1 KM curves for OS, JVBD



*blue (top) line is ramucirumab, red (bottom) line is placebo

Table 7 (data copied from the statistical review) shows that for almost all subgroups tested, that the HR (point estimate) was less than one. The 95% CIs crossed one for many of the analyses; however, the sample size in these subgroups was smaller (than the overall patient population) and thus these subgroups were not adequately powered to demonstrate a (nominally) statistically significant effect on OS.

Table 7 Subgroup analyses for OS, JVBD

Subgroup	N*	HR (95% CI)
Race		
White	181/91	0.78 (0.59, 1.04)
Asian	39/17	0.64 (0.31, 1.32)
Gender		
Women	69/38	1.43 (0.85, 2.41)
Men	169/79	0.68 (0.50, 0.92)
Age in years		
< 65	156/71	0.85 (0.61, 1.17)
≥ 65	82/46	0.72 (0.47, 1.11)
Region (see Table 3 above)		
1	165/80	0.94 (0.70, 1.26)
2	55/29	0.46 (0.27, 0.79)
3	18/8	0.63 (0.24, 1.63)
Prior Therapy		
Adjuvant or neoadjuvant	39/14	0.78 (0.37, 1.65)
Metastatic	199/103	0.79 (0.61, 1.04)
Histology		

Subgroup	N*	HR (95% CI)
Diffuse	96/44	0.56 (0.37, 0.86)
Intestinal	52/35	1.01 (0.58, 1.75)
Unknown	90/38	0.91 (0.58, 1.42)
Location of primary tumor		
Gastric	178/87	0.78 (0.58, 1.04)
GEJ	60/30	0.69 (0.43, 1.08)
ECOG PS		
0	67/31	1.08 (0.64, 1.81)
≥ 1	171/86	0.68 (0.51, 0.92)

*ramucirumab/placebo

The survival results from two subgroups (women and Region 1) from Trial JVBD were problematic at the time of the initial BLA submission in regards to whether the Agency should approve ramucirumab based on the results a single trial. The HR (point estimate) for OS in women was 1.43 suggesting worse overall survival in women receiving ramucirumab. While this reviewer agrees that there were potential explanations for this finding [including a higher proportion of women with diffuse histology receiving ramucirumab versus women receiving placebo (see clinical review)], this reviewer would expect to see additional data in this population in order to confirm or refute this finding (especially given the p value close to 0.05 in the ITT population and modest overall survival effect in the ITT population).

Additionally, the point estimate for OS in Region 1 that included North America, Europe, Australia, and New Zealand was close to 1.0 suggesting less of an effect in this region that is likely to be the most representative of the U.S. population. Although this reviewer agrees that such subgroup analyses should be interpreted with caution, and are likely related to chance effects in non-random populations, they can be problematic when data from only one study are available for review.

Ultimately, Lilly addressed these issues by submitting results from a second trial (JVBE) where the OS effects in women and in Region 1 appeared favorable in comparison with the overall ITT population (see analyses of Trial JVBE below). Furthermore, more women were enrolled in JVBE and based on the totality of the evidence, the ramucirumab treatment effect in women (and in U.S./North American patients) is likely best described by the ramucirumab treatment effect in the ITT population (rather than the specific effects observed in the subgroup analyses).

7.4.4 Secondary endpoints (JVBD)

Overall, the applicant reported few responses in each arm (less than 4%) so this review will not discuss this endpoint further. The primary secondary endpoint was progression free survival.

Table 8 (data copied from the statistical review) shows that ramucirumab increased progression free survival compared to control. The effect at the median was modest (less than one month); however, the separation in the curves (see clinical and statistical reviews) increased after the medians such that the hazard ratio may be a better indicator of the treatment

effect. *Comment: the lack of separation of the KM curves prior to (approximately) two months was likely influenced by the imaging schedule with the first CT scan obtained at week 8.*

Table 8 PFS analyses (ITT), JVBD

	Ramucirumab N=238	Placebo N=117
Number of events, n (%)	199 (84%)	108 (92%)
Median PFS (months)	2.1	1.3
95% CI	(1.5, 2.7)	(1.3, 1.4)
HR (95% CI)	0.483 (0.376, 0.620)	
Stratified log-rank test p-value[a]	< 0.0001	

[a] Stratified by planned stratification factors (see above)

Comment: Ultimately, the clinical benefit of ramucirumab is based on the effect on overall survival rather than any modest effect on PFS.

7.5 Efficacy results (JVBE)

As previously described, JVBE (the study that confirmed the results of JVBD) was a multinational, multicenter, randomized, double-blind study that evaluated ramucirumab in combination with paclitaxel in the treatment of patients with metastatic gastric cancer or GEJ adenocarcinoma following first-line platinum and fluoropyrimidine-containing chemotherapy regimens. Patients were randomized (1:1) to receive paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 of every 28-day cycle plus either placebo or ramucirumab (8 mg/kg every other week). The data cut-off date for Lilly's analysis was 12 July 2013, and patients were enrolled in the trial from 23 Dec 2010 to 23 Sep, 2012. A total of 665 patients comprised the intention-to-treat population with 330 patients in the ramucirumab arm and 335 patients in the placebo arm. A total of 516 patients died by the data cut-off date.

7.4.1 Demographics (JVBE)

Table 9 shows the major demographic characteristics to be balanced between the treatment arms. Compared to JVBD, JVBE enrolled a higher proportion of patients from Asia. Median age of patients enrolled in JVBE was 61 years in both arms.

Table 9 Demographics, JVBE

	Ramucirumab / paclitaxel N=330 (%)	Placebo / paclitaxel N=335 (%)
Age		
≥ 65 years	38	37
Female		
Yes	31	27
Race		
White	63	59
Asian	33	36
Other	4	5

	Ramucirumab / paclitaxel N=330 (%)	Placebo / paclitaxel N=335 (%)
Geographic Region		
Region 1	60	60
Region 2	7	6
Region 3	33	34

Region 1 = North America, Europe, Australia,
Region 2 = Argentina, Brazil, Chile, Mexico
Region 3 = Hong Kong, Japan, Korea, Singapore, Taiwan

Table 10 summarizes the major disease characteristics of patients across arms which appeared balanced. A slightly higher proportion of patients in the ramucirumab arm were ECOG PS 1 compared to the placebo arm. Eighty-one percent of patients in both arms had measurable disease and time to progression on first-line therapy was less than six months in 76% of patients across both arms. The majority of patients in both arms had documented metastases (98% for ramucirumab versus 97% for ramucirumab).

Table 10 Disease characteristics at baseline, JVBE

	Ramucirumab / paclitaxel N=330 (%)	Placebo / paclitaxel N=335 (%)
ECOG PS		
0	35	43
1	65	57
Weight loss ≥ 10%		
Yes	16	14
Primary site of disease		
Gastric	80	79
GEJ	20	21
Histology		
Intestinal	44	40
Diffuse	35	40
Mixed	6	4
Unknown	15	16

7.4.2 Disposition (JVBE)

Few patients enrolled in JVBE received treatment at the time of data cut-off: 4% in the ramucirumab arm and 2% in the placebo arm. Four patients in the ramucirumab arm and 5 in the placebo arm never received treatment. Disease progression constituted the most common reason for treatment discontinuation across both arms. Loss to follow-up (or withdrawal of consent with loss to follow-up occurred infrequently in both arms (Refer to Table 11 below for reasons for treatment discontinuation in JVBE).

Table 11 Patient disposition (reasons for treatment discontinuation), JVBE

	Ramucirumab / paclitaxel N=330 (%)	Placebo / paclitaxel N=335 (%)
Progressive disease	72	76
Death	4	4
Withdrawal of consent follow-up continued	6	2
Withdrawal of consent (no follow-up)	1	2
Loss to follow-up	0	< 1
Adverse event	12	11
Other reasons	1	1

7.4.3 OS analyses (JVBE)

As described above, Lilly amended their BLA to submit datasets from Study JVBE after submitting the BLA based on Study JVBD. Table 12, data obtained from the clinical review, shows the OS results determined at the time of data-cut off. Seventy-eight percent of patients died (across both arms) at the time of data-cut off, constituting a mature analysis of survival. The pre-specified analysis of OS was statistically significant at the two-sided 0.05 level. These results provided confirmation of the effects observed in Study JVBD.

The magnitude of effect when ramucirumab was added to paclitaxel was similar in terms of the observed hazard ratio; however, the difference in median survival between arms was slightly longer in JVBE (2.3 months) compared to the duration in JVBD (1.4 months).

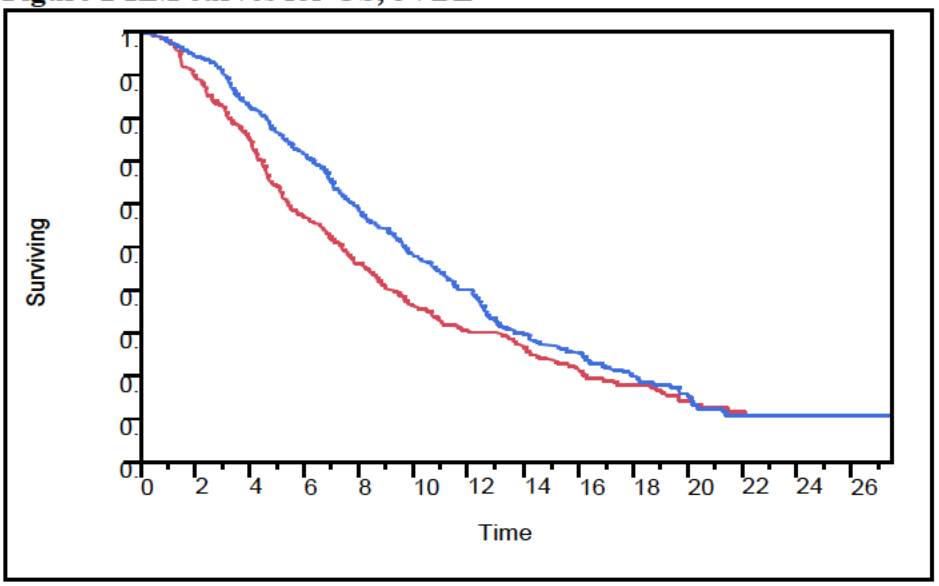
Table 12 OS analyses (ITT), JVBE

	Ramucirumab / Paclitaxel N=330	Placebo / paclitaxel N=335
Number of deaths, n (%)	256 (78%)	260 (78%)
Median overall survival (months)	9.63	7.36
95% CI	(8.48, 10.81)	(6.31, 8.38)
HR (95% CI)	0.807 (0.678, 0.962)	
Stratified log-rank test p-value[a]	0.0169	

[a] Stratified by planned stratification factors (see above)

Figure 2, copied from the clinical review, shows the proportion of patients alive at each time point during the trial. Separation in the KM curves remained constant throughout the duration of the curves until the tails of the curves were reached.

Figure 2 KM curves for OS, JVBE



*blue (top) line is ramucirumab plus paclitaxel, red (bottom) line is placebo plus paclitaxel

In order to further assess the efficacy results related to this application (specifically the request to approve ramucirumab as a monotherapy for patients with previously treated gastric cancer), the clinical reviewer focused on the subgroups of concern from the monotherapy study (JVBD).

In Study JVBD, the point estimate for the hazard ratio in Region 1 (including the United States) was 0.94 raising the potential concern of a smaller effect in U.S. patients (or more accurately, patients who received similar standards of care to that in the United States). In Study JVBE, 398 patients were randomized from Region 1 (constituting a randomization stratum) and the point estimate for the hazard ratio for OS was 0.73 (95% CI: 0.58, 0.91). This estimate provided supportive evidence that the effect observed in JVBD was a chance finding in an underpowered subgroup and that the ITT point estimate is better descriptor of the overall treatment effect among all patients (including those enrolled in Region 1).

More concerning than the regional treatment effect was the potential for a detrimental treatment effect among women. In JVBD, the point estimate for the hazard ratio for OS was 1.43 (95% CI: 0.85, 2.41) in the female subgroup of patients. As described above and in the clinical review, imbalances in baseline prognostic factors existed that could *potentially* explain this finding. Nevertheless, review of a second study was important in order to either confirm or refute this explanation. A total of 193 women were randomized in JVBE (a larger number than in JVBD) and the point estimate for the hazard ratio for OS among women was 0.672 (95% CI: 0.483, 0.935). This point estimate was lower than the point estimate in the ITT population. This estimate provided supportive evidence that the effect observed in women in JVBD was a chance finding and that the ITT point estimate is a better descriptor of the overall treatment effect among all patients (including women).

7.4.4 Secondary endpoints (JVBE)

Table 13, data copied from the clinical review, shows that ramucirumab plus paclitaxel modestly increased PFS compared to paclitaxel alone.

Table 13 PFS analyses (ITT), JVBE

	Ramucirumab / Paclitaxel N=330	**Placebo / paclitaxel N=335**
Number of events, n (%)	279 (85%)	296 (88%)
Median PFS (months)	4.40	2.86
95% CI	(4.24, 5.32)	(2.78, 3.02)
HR (95% CI)	0.635 (0.536, 0.572)	
Stratified log-rank test p-value[a]	< 0.0001	

[a] Stratified by planned stratification factors (see above)

8. Safety

8.1 Adequacy of database

Based on the treatment effect (overall survival improvement) observed in JVBD that was confirmed in JVBE, the clinical reviewer found the safety database to be adequate. Lilly submitted datasets in CDISC (STDM and ADaM) format which facilitated the FDA clinical reviewer to complete the review in a timely manner.

The clinical review primarily focused on data from Trial JVBD as this was the large controlled trial intended to support approval of ramucirumab for the indicated patient population. Lilly stated during the review that (b) (4) will provide safety data from Trial JVBE. Lilly notified the Agency of an imbalance of Grade 3 hemorrhage in the JVBE trial and proposed including this information in the ramucirumab product labeling. Importantly, the safety of ramucirumab administered to patients with gastric cancer receiving NSAIDS (who may be at increased risk for bleeding based on the location of the tumor) was not systematically studied during Trials JVBD and JVBE. Although, Lilly submitted data from patients who took or received NSAIDS, data regarding duration of use was limited.

The placebo control allowed for the clinical reviewer to conduct an analysis of safety against background adverse events that commonly occur in patients with advanced cancer. The safety population of JVBD included 236 patients with advanced gastric cancer who received ramucirumab and 115 who received placebo plus best supportive care. Two patients in each arm dropped out prior to receiving ramucirumab or placebo (one patient died and three had new clinical findings that precluded further participation in the trial). The clinical reviewer also considered data from other dose escalation trials and activity estimating trials in her evaluation of the safety profile of ramucirumab [data from an additional 334 patients in the original BLA submission (30 Apr 2013 clinical module)].

In JVBD, patients received ramucirumab for a median duration of 8 weeks compared to a median duration of 6 weeks in the placebo arm. *Comment: The short duration of therapy in both arms reflected the poor prognosis of patients with previously treated metastatic gastric*

cancer. Based on the short duration of exposure, comparisons of safety to other anti-VEGF monoclonal antibodies would not be appropriate. Nevertheless, this reviewer agrees that it is appropriate to take action on this application despite the lack of long-term safety data based on the modest improvement in overall survival and the short life expectancy of patients with previously treated gastric cancer. Despite the brief exposure of most patients, dose reductions were few (three in the ramucirumab arm and one in the placebo arm). Investigators held or omitted doses (for any reasons) in more patients in the ramucirumab arm (20.3%) compared to the placebo arm (10.4%).

8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

8.2.1 Deaths

The clinical reviewer found that the majority of deaths in JVBD occurred due to progression of the underlying gastric malignancy. The KM curves of OS in Section 7 of this review summarize the overall occurrence of deaths in JVBD. These curves provided some assurance of the relative safety of ramucirumab.

A total of 78 deaths occurred while on treatment or within 30 days of the last dose of ramucirumab or placebo. In her assessment of *possible* adverse-event related deaths, the clinical reviewer did not consider deaths due to disease progression, gastric cancer, or neoplasm and recorded 26 patients (11%) in the ramucirumab arm and 12 (10%) in the placebo arm who experienced an adverse event (irrespective of attribution) with a fatal outcome. Although some deaths were caused by events classically associated with VEGF inhibition (e.g., hemorrhage and large intestinal perforation), such events also occurred in the placebo arm. Overall, the incidence rate of adverse-event associated deaths in JVBD was similar in both arms and did not show any consistent patterns of ramucirumab-*related* fatal events.

8.2.2 SAEs

Lilly's clinical study report defined (*non-verbatim definition*) a serious adverse event (SAE) as any untoward medical occurrence that resulted in death; was life-threatening; required inpatient hospitalization or caused prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect; required intervention to prevent permanent impairment or damage; or was an important medical event that could jeopardize the patient or require intervention to prevent one of the other serious outcomes listed above.

The clinical reviewer's analysis differed from that of the applicant's by omitting fatal events (which were described in the analysis of deaths by the clinical reviewer). In general, the clinical reviewer found the incidence rate of most nonfatal serious adverse events occurring in JVBD to be similar between arms. Table 14, shows SAEs at the MedDRA preferred term level (including deaths) that occurred in at least 2% of patients in the ramucirumab arm. Lilly stated that medication errors were reported as SAEs according to the protocol; however, these were not associated with adverse health consequences.

Table 14 SAEs, JVBD

	Ramucirumab N=236 (%)	Placebo N=115 (%)
Any SAE	44.9	44.3
Abdominal pain	4.2	2.6
Anemia	3.8	1.7
Medication error	3.0	0.9
Ascities	2.5	2.6
Vomiting	2.5	4.3
Multi-organ failure	2.5	0.9
Intestinal obstruction	2.1	0
Dysphagia	2.1	2.6

8.2.3 Drop-outs and discontinuations due to adverse events

According to the applicant, 10.5% of patients in the ramucirumab arm versus 6% in the placebo arm discontinued study treatment due to an AE. Two of the cases in the ramucirumab arm were considered non-treatment emergent including one patient who experienced inguinal hernia more than one month after the last dose.

An *additional* 10 patients (9 in the ramucirumab arm and one in the placebo arm) experienced a treatment emergent adverse event with an outcome of treatment discontinuation. Most of the patients in this later group discontinued due to disease progression (6), death (2), or who experienced a gastrointestinal AE with progression of disease recorded as the reason for end of treatment.

The clinical review described the specific reasons provided for treatment discontinuation. Two patients in the ramucirumab arm discontinued due to proteinuria. No other clear patterns emerged regarding reasons for treatment discontinuation; one patient in the ramucirumab arm experienced a cerebrovascular accident. Patients in both arms discontinued study therapy due to upper gastrointestinal hemorrhage.

8.2.4 Common adverse events

Table 15, shows the analysis of adverse events (rounded to the nearest integer and occurring with a per-patient incidence rate of ≥ 10% in the ramucirumab arm). In general, ramucirumab was well tolerated with many adverse events reported at the same rate in both arms. *Although some adverse events occurred at a higher incidence rate in the placebo arm, this reviewer recommends against allowing labeling claims based on safety (i.e., that ramucirumab is less toxic than placebo) because the study was not designed to show that ramucirumab causes fewer adverse events than placebo (Lilly did not request such claims in their proposed product label).*

Table 15 Common AEs, JVBD

	Ramucirumab (N=236)		Placebo (N=115)	
	All Grades (%)	≥ Grade 3 (%)	All Grades (%)	≥ Grade 3 (%)
Fatigue	25	4	24	4
Decreased appetite	24	3	23	4
Vomiting	20	3	25	4
Abdominal pain	19	5	25	3
Nausea	19	1	26	0
Constipation	15	0	23	3
Hypertension	15	7	8	3
Anemia	15	6	15	8
Diarrhea	14	1	9	2
Asthenia	12	2	17	7
Upper abdominal pain	11	1	4	0
Decreased weight	11	1	10	1
Dysphagia	11	2	10	4

Although there appeared to be a difference in the upper abdominal pain preferred term, this difference largely disappeared in the composite high level term (HLT) analysis (30% incidence of gastrointestinal and abdominal pains in ramucirumab-treated patients versus 29% in the placebo arm).

In summary, the most common adverse reactions (i.e., with a higher incidence in the ramucirumab arm) were hypertension and diarrhea. Few patients experienced severe diarrhea.

8.2.5 Laboratory tests

The clinical reviewer found that ramucirumab did not result in clinically significant myelotoxicity when administered as a single-agent. Likewise, anemia, a manifestation of either myelotoxicity or bleeding occurred at a similar incidence rate in both arms.

Ramucirumab did not appear to cause clinically significant increases in liver enzymes in Trial JVBD. A similar proportion of patients in both arms met *laboratory criteria* for Hy's law; however, these patients (in both arms) appeared to have disease progression as the cause of the liver enzyme findings. Although hepatotoxicity was not observed in Trial JVBD, the clinical reviewer documented a potential safety concern in patients who received ramucirumab in Trial JVBF (an investigation of ramucirumab in patients with hepatocellular cancer). In Trial JVBF, ramucirumab appeared to exacerbate the sequelae of cirrhosis (rather than directly cause liver injury). Serious adverse events reported in JVBF included encephalopathy, exacerbation of ascities, and possibly hepatorenal syndrome. Based on these events, Trial JVBF was modified to exclude patients with Child-Pugh B cirrhosis, history of hepatic encephalopathy, or clinically meaningful ascities. A warning describing these risks in patients with cirrhosis was proposed in product labeling.

Ramucirumab did not appear to cause clinically significant renal toxicity in Trial JVBD. There was a slight imbalance in hyponatremia in the ramucirumab arm in the adverse event analysis. However the shift tables did not indicate a large difference in patients who "shifted" from mild hyponatremia to severe hyponatremia. Based on the shift tables in the BLA, 25 out of 216 (12%) patients in the ramucirumab arm with baseline Grade 1 or 2 hyponatremia progressed to Grade 3 (< 130 to 120 mmol/L) or Grade 4 (< 120 mmol/L) hyponatremia during the trial. In the placebo arm, 11 out of 102 (11%) patients with baseline Grade 0 or 1 hyponatremia progressed to Grade 3 or 4 during the trial.

Assessments for the total incidence of proteinuria were complicated by differences in units/measurements contained in the datasets. The clinical reviewer found that 8% of patients in the ramucirumab arm and 3% in the placebo arm had proteinuria (including dipstick positivity). These values differed from the analysis of *adverse events* described as proteinuria (3% for ramucirumab versus 2.6% for placebo). Two patients discontinued ramucirumab because of proteinuria. *Based on these inconsistencies in measurements, use of ramucirumab as monotherapy, and short duration of exposure, comparisons of the rate of proteinuria to other anti-VEGF antibodies should not be made.*

8.3 Special safety concerns

8.3.1 Drug-demographic interactions

The clinical reviewer conducted analyses of adverse events by age range (≥ 65 years versus less than 65 years), gender, geographic area, and tumor location. In general, adverse events occurred at similar rates in the various groups. Meaningful conclusions of differences in adverse events were difficult to make because these were non-randomized subgroups, and in some cases, the numbers of patients in certain groups was small. Refer to Section 7.5.3 of the clinical review for adverse events that differed in proportion between subgroups. Refer to Section 8.2.5 of this review regarding the potential risks related to ramucirumab in patients with cirrhosis.

8.3.2 Additional in-depth analyses of specific events

Based on prior knowledge of adverse reactions related to other anti-VEGF antibodies and adverse events occurring in ramucirumab clinical trials, the clinical reviewer performed additional in-depth analyses of the following adverse events: hypertension, infusion-related reactions, proteinuria, arterial thrombotic events, venous thrombotic events, bleeding / hemorrhagic events, gastrointestinal perforation, liver injury / failure, congestive heart failure, and posterior reversible encephalopathy syndrome.

Differences in the incidence rate of adverse events would be expected in comparison to other anti-VEGF antibodies based on the following: ramucirumab was studied as a monotherapy (bevacizumab is only approved as monotherapy for patients with glioblastoma multiforme); exposure (exposure in second-line gastric cancer is of shorter duration compared to the exposure in patients with metastatic colorectal cancer); and knowledge based on prior experience of drugs in the class (e.g., aggressive treatment of hypertension; exclusion of patients at high risk of bleeding; exclusion of patients with recent surgery or with severe wounds).

As expected, and as shown in Table 15 (above), hypertension occurred more frequently among ramucirumab-treated patients. Severe hypertension (e.g., Grade 3 hypertension) occurred in 7% of patients. Although, in general, hypertension was manageable, the overall incidence of hypertension may have been underestimated (see Section 7.4.3 of the clinical review) based purely on the adverse event reporting (rather than blood pressure measurements) and that (in an exploratory analysis) the systolic blood pressure appeared to be increased by approximately 5-10 mmHg in ramucirumab-treated patients compared to patients who received placebo (analysis of median blood pressure effects in the populations in each arm in each cycle).

Refer to the clinical review for further analyses of other anti-VEGF toxicities described above.

Finally, in Trial JVBE (ramucirumab in combination with paclitaxel trial), Lilly stated that arterial thrombotic events occurred at a similar rate in both arms and there were no events of impaired wound healing, fistula, or posterior reversible encephalopathy syndrome (PRES). Although investigators reported more hematological toxicity when ramucirumab was administered with paclitaxel, such toxicity is not expected when administered in the absence of chemotherapy. The summary report stated that in JVBE, four patients experienced gastrointestinal perforation in the ramucirumab arm versus none in patients who received placebo. Proteinuria also occurred more frequently in the ramucirumab arm [17% (1% Grade 3) versus 6% in the placebo arm].

8.4 Discussion of primary reviewer's findings and conclusions

The clinical reviewer concluded that patients receiving ramucirumab experienced an increased incidence of anti-VEGF axis toxicities (compared to patients receiving placebo); however, most patients tolerated ramucirumab without requiring dose reductions or permanent discontinuation.

The clinical reviewer determined the safety database to be adequate for the intended indication given the overall survival effect observed in Trial JVBD (and subsequently confirmed in Trial JVBE); a total of 236 patients received ramucirumab in trial JVBD, and approximately 570 patients received ramucirumab as a single agent across multiple clinical trials. Based on the poor prognosis of patients with previously treated gastric cancer and the modest effect of ramucirumab, treatment duration was limited in Trial JVBD; patients received ramucirumab for a median treatment duration of 8 weeks compared to a median duration of 6 weeks in the placebo arm.

The most important adverse reactions caused by ramucirumab (as monotherapy) included adverse reactions typically understood in the setting of anti-VEGF axis treatment. Such adverse reactions included hemorrhage, arterial thrombotic events, hypertension, proteinuria, and gastrointestinal perforation. Infusion-related reactions can also occur following treatment with ramucirumab.

Although ramucirumab can cause serious (and potentially life-threatening) toxicities, the overall risk benefit profile was considered favorable based on the demonstrated improvement in overall survival in a patient population with terminal cancer. Most of the toxicities are

familiar to trained oncologists, and it is standard practice to monitor for these adverse reactions, institute treatment as necessary, and to dose modify therapy or discontinue therapy if necessary. Additionally, in general, most patients tolerated monotherapy with ramucirumab and few patients permanently discontinued ramucirumab due to adverse events. The incidence rate of many adverse events was similar to that observed in the placebo arm.

Comment: This reviewer agreed with the major conclusions in the clinical review. The incidence of adverse events in the clinical review was, in general, similar to (or the same as) those of the applicant. Small differences in the incidence rates of certain adverse events were not clinically significant.

9. Advisory Committee Meeting

Although FDA planned for an advisory committee meeting upon submission of the application (based solely on the results of Trial JVBD), the review team determined that an ODAC meeting was not necessary following the submission of data from Trial JVBE that confirmed the OS results observed in Trial JVBD. FDA review staff considered the effects on OS to be (statistically) robust based on the results observed in two trials, and trained oncologists are familiar with the types of toxicities caused by ramucirumab.

10. Pediatrics

This BLA is exempt from the requirement to assess the safety and effectiveness of this product for the claimed indication in all pediatric age groups because FDA granted orphan-drug designation to the ramucirumab active moiety for the treatment of patients with gastric cancer on 16 Feb 2012.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

The BLA contained a statement signed by the Senior Director of Global Regulatory Affairs (U.S.) from Eli Lilly that certified that Eli Lilly did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11.2 Financial disclosures

The majority of investigators reported that they did not enter into any financial arrangements whereby the value of compensation to the investigator would be expected to affect the outcome of the study as defined in 21 CFR 54.2(a). The applicant certified that the listed investigators referenced on Form 3454 did not disclose financial interests as defined in 21 CFR 54.2(b) or significant payments as described in 21 CFR 54.2(f). Lilly also reported that the six members of the IDMC were in compliance with the requirement for financial clarification and disclosure information (21 CFR, Part 54).

Eli Lilly reported obtaining financial disclosure forms from all but two investigators / sub-investigators. Lilly reported contacting the sub-investigators (one in New Zealand and one in Spain) multiple times via electronic mail and telephone and also attempted to contact the

primary investigators at these sites. Despite these attempts, Lilly could not obtain the financial information prior to departure from their respective institutions. Lilly subsequently conducted an internal record of payments and did not identify a record of disclosable payments to these individuals.

Two sub-investigators disclosed reportable financial interests. Lilly stated that these interests did not, in any way, influence the outcome of the clinical trial. One sub-investigator reported receiving $27,725 in honorariums. The site (of this sub-investigator) randomized (b) (6) to the placebo arm whose overall survival was longer that the median OS among patients receiving placebo (and thus did not appear to bias the study towards a favorable result for the ramucirumab arm).

A second sub-investigator (b) (6) reported receiving honorariums of $34,100. This site randomized (b) (6) to each arm. There were (b) (4) potential outliers at this site who lived longer than 24 months; (b) (4) Additionally the overall mean and median survival between the (b) (4) patients in each arm at this site were similar (within one month for each analysis). Based on these findings, and because these constituted a minority of the patients enrolled in Study JVBD (a large multi-center study with the primary endpoint of overall survival), this reviewer agrees that these reported interests did not influence the primary outcome of the clinical trial.

11.3 GCP issues

Lilly provided an audit certificate that stated that 13 investigational sites (from Study JVBD) were audited. Lilly included a statement in the JVBD final study report that the PI or designee promptly submitted the protocol to applicable Ethical Review Boards (ERBs). The ERBs provided written approval of both the protocol and informed consent document. Eli Lilly submitted the name and address of each ERB (or IRB) in an appendix to the clinical study report.

Lilly also included a statement in the JVBD clinical study report that the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and consistent with good clinical practices (GCPs) and applicable laws and regulations.

In general, the numbers of protocol violations were similar between arms. One patient in each arm received the wrong treatment. Although there were entry criteria violations reported in each arm, the types of violations were unlikely to have had a major impact on the overall study results.

11.4 OSI audits

Because ramucirumab is an NME, DOP2 requested OSI inspections of clinical sites. DOP2 and OSI selected three clinical sites based on site-specific efficacy results, protocol violations, or patient enrollment at each site. OSI inspected sites in Brazil, South Korea, and Texas and classified all three (interim classification) as NAI (no action indicated). OSI found no evidence of underreporting of adverse events at the study sites. OSI also inspected the

applicant's records and found clear procedures and records. Lilly received an interim classification of NAI.

11.5 Late-Cycle meeting

Lilly and FDA met on 11 Feb 2014 to discuss outstanding issues related to BLA 125477. Much of the discussion pertained to potential Postmarketing Commitments (PMCs) and Postmarketing Requirements (PMRs). The Agency and Lilly initially discussed the PMR that would require Lilly to develop a validated, sensitive, and accurate assay for the detection of binding antibodies to ramucirumab, including procedures for 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. Lilly asked whether additional data could be submitted to support the use of the current assay. Based on Lilly's request, FDA stated that the intent of the PMR could be satisfied *either* by developing a new assay or by providing data showing acceptable drug tolerance of the ADA assay between (b) (4) of ADA. Additionally, if the current assay is sufficient, then Lilly will not need to re-test 300 patient samples using the new assay.

In regards to the neutralizing assay PMR, Lilly stated that it may be difficult to improve the drug tolerance of the current assay. Lilly provided summary validation data stating that the sensitivity of the assay exceeds the 2009 FDA guidance for sensitivity of the neutralizing ADA. FDA (OCP) stated that the Agency would further discuss the PMRs regarding neutralizing assays internally and determine whether they were necessary.

During the meeting, Lilly agreed to provide timelines regarding Postmarketing Commitments (PMCs) pertaining to drug substance and drug product release and stability specifications, product stability (b) (4), and to perform a shipping study.

11.6 Other discipline consults

11.6.1 DRISK

DRISK concurred with DOP2 that a REMS is not necessary for ramucirumab.

11.6.2 OPDP

DOP2 did not agree with the OPDP labeling recommendation to remove the following statement: As with all therapeutic proteins, there is the potential for immunogenicity. This is a standard statement included in labeling of monoclonal antibodies. DOP2 also did not agree with the provision to include all warnings in the patient counselling information section because this section should focus on major risks of the drug and how the patient may mitigate or manage them. For example, mitigation of infusion reactions is the responsibility of the treating physician and not the patient (e.g., through the administration of intravenous antihistamines or corticosteroids).

11.6.3 Drug name review (DMEPA)

During the review of this application, DMEPA sent a letter on 25 Oct 2013 informing Lilly that the proposed trade name of Cyramza was (conditionally) acceptable. The DMEPA review considered the name from a promotional perspective in consultation with DOP2 and OPDP.

DMEPA also considered the name Cyramza from a safety perspective (i.e., performed assessments for look-alike and sound-alike drugs) and found the name acceptable.

12. Labeling

FDA sent draft labeling recommendations to Lilly on 25 Feb 2014 prior to the date stipulated by the 21st Century Review Process (24 Mar 2014). Labeling recommendations described below should not be considered final as labeling negotiations are ongoing.

In general, DOP2 revised all sections of the label for brevity and clarity (*this reviewer acknowledges that Lilly facilitated FDA's review process by submitting their initial label following the spirit of PLR*). The remainder of this section of the review will only focus on high-level issues regarding the label submitted by Lilly. Numbering below is consistent with the applicable sections in product labeling. This review will not comment on all sections of the label (for example, if only minor edits were made to a section). This reviewer agreed with the recommendations made by the review teams that are described below.

1. Indication and Usage: FDA recommended revising the indication to specify the prior chemotherapy regimen for patients with gastric cancer.

2. Dosage and Administration: FDA review staff, including DMEPA, recommended re-ordering sections under Dosage and Administration. DMEPA also recommended revising the dose modification section to ensure consistency with other labels.

5. Warnings and Precautions: FDA recommended inclusion of a boxed warning for hemorrhage. However, the incidence of gastrointestinal perforation and compromised wound healing *as monotherapy* did not support the inclusion of a boxed warning for these two adverse reactions (which are described in Section 5 of the label).

The clinical reviewer recommended the addition of a warning for Reversible Posterior Leukoencephalopathy Syndrome (RPLS) based on reports in a ramucirumab trial along with evidence of RPLS occurring following the use of other anti-VEGF therapies. *Comment: During the Late-Cycle meeting, held after the completion of the clinical review, FDA was informed by Lilly that the reported cases were from a clinical trial that remains blinded as to the treatment assignment. Therefore, as of the completion of this review, it is uncertain whether this adverse event should be included as a separate warning in product labeling.*

FDA recommended describing the incidence rate of adverse reactions in the Warnings section of the label.

FDA recommended including information regarding the lack of data regarding concomitant ramucirumab and NSAID use (in the hemorrhage warning).

6. Adverse Reactions: FDA recommended describing certain exclusion criteria of Trial JVBD in order to contextualize the safety information contained in the label. FDA also added exposure information and information regarding the most common

serious adverse reactions and adverse reactions resulting in treatment discontinuation. FDA also recommended removal of statements regarding (b) (4) from the label and revised the Immunogenicity section to provide information regarding the assay used to test ADAs.

8.1. Pregnancy: FDA recommended inclusion of a statement that ramucirumab may cause fetal harm based on animal models linking inhibition of VEGF to critical aspects of female reproduction, embryofetal development, and postnatal development.

8.4. Pediatric Use: FDA recommended inclusion of animal data pertaining to pediatric use (specifically effects on epiphyseal growth plates).

8.5. Geriatric use: FDA revised this section because insufficient numbers of patients were enrolled in Trial JVBD to determine whether differences in safety or efficacy existed in this subpopulation of patients.

8.8. Females and Males of Reproductive Potential: FDA added this section and included information regarding fertility and contraception.

11. Description: DMA recommended deleting information regarding mechanism of action because this information is described in Section 12.1 of the label.

(b) (4)

14. Clinical Studies: FDA recommended removal of information regarding (b) (4) FDA added number of deaths in the efficacy results table to provide information regarding the maturity of the analysis.

FDA recommended removal of the PFS Kaplan-Meier curves from the label. Although (for brevity) the Division recommended removal of the Kaplan-Meier curves, the Division does not object to the use of the curves (proposed in the label) in promotional materials (as otherwise permitted in the United States under current law) and recognizes that the PFS effect was statistically significant (i.e., substantial evidence was submitted in the application to support the presentation of the PFS curves).

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

This reviewer recommends regular approval of BLA 125477 based on substantial evidence from two adequate and well controlled trials (JBVD and JVBE) establishing that ramucirumab can prolong the overall survival of patients with previously treated, locally advanced,

unresectable or metastatic gastric cancer. This approval recommendation is contingent upon reaching agreement on labeling, PMCs, and PMRs.

The submission of data from confirmatory Study JVBE during the review addressed two major deficiencies in the application: reliance on data from a single study (JVBD) with a p value just under 0.05 and the possibility that ramucirumab could harm women. In the confirmatory trial, JVBE, the point estimate for the OS HR in women was lower than the point estimate for OS in men. The female subgroup in JVBE was also larger (n=193) than the female subgroup in JVBD (n=107). Thus, the most likely explanation for the gender effect observed in JVBD was chance (e.g., due to imbalances in demographic variables).

Given the effects observed on overall survival, this reviewer agrees that regulatory discretion can be exercised in approving ramucirumab (as a single agent) prior to the receipt of the full clinical study report for JBVE. FDA previously exercised such discretion when the Agency approved ipilimumab for the treatment of patients with metastatic melanoma on 25 Mar 2011 (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125377Orig1s000SumR.pdf, accessed on 24 Dec 2013). In an amendment to BLA 125477, Lilly provided demographic and survival datasets from Trial JBVE to confirm the summary survival analyses. Lilly also provided the protocol, protocol amendments, and statistical analysis plan in the amended BLA.

13.2 Risk-benefit assessment

The recommendation for approval of this application is based on a statistically significant (but clinically modest) improvement on OS observed in two trials, JVBD and JVBE. According to the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf; accessed on 23 Dec 2013), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.

Because metastatic (or locally advanced, unresectable) gastric cancer is an incurable disease, the goals of treatment are to prolong life or improve quality of life. In JVBD, patients who received ramucirumab in combination with best supportive care lived a median 1.4 months longer than patients who received placebo in combination with best supportive care [HR = 0.776 (0.603, 0.998), p = 0.047]. This treatment effect on overall survival was confirmed in Trial JVBE where patients lived a median 2.3 months longer than patients in the placebo arm [HR = 0.807 (0.678, 0.962), p = 0.017)].

The effects on OS were supported by a statistically significant effect on progression free survival in Trial JVBD [HR 0.483 (0.376, 620), p < 0.0001]. The estimated difference in median PFS was 0.8 months; however, the timing of scans in Trial JBVD likely affected the estimates and the curves appeared to further separate after the medians. Nevertheless, the effects on PFS should be considered supportive of the OS results rather than as evidence of direct clinical benefit.

Adverse events observed in the JVBD trial were generally considered in-line with toxicities observed following the administration of other anti-VEGF monoclonal antibodies. Nevertheless, multiple factors may have contributed to differences in adverse event rates between ramucirumab and other approved monoclonal antibodies that target the VEGF pathway. In addition to specific product-related factors (e.g., differences in targets), other factors included brief duration (median of 8 weeks) of ramucirumab exposure in JVBD; monotherapy indication for ramucirumab (as opposed to use in combination with chemotherapy with other products); and accumulated knowledge regarding the use of other anti-VEGF inhibitors (e.g., resulting in more proactive management of toxicities including hypertension). The eligibility criteria in JVBD may have also mitigated some of the serious toxicities related to ramucirumab (e.g., exclusion of patients receiving NSAIDS).

Importantly, the risk-benefit profile in Trial JVBD was studied in a patient population with ECOG PS 0 and 1. This reviewer cannot extrapolate the survival benefit (observed in JVBD) to patients with ECOG PS 2 or greater. The hazard for death is sufficiently high in these patients that the risk-benefit profile may differ compared to patients with less co-morbidity. As such, this reviewer recommends that Section 14 of the label describe the population studied in JVBD (i.e., ECOG PS 0-1).

This reviewer acknowledges that the 1.4 month improvement in median overall survival represents a modest effect and that based on this modest effect, a reasonable person may decide whether or not to receive ramucirumab (e.g., versus no treatment, alternative treatment, or enrollment into a clinical trial). However, because an effect on OS was observed in two trials, this reviewer believes that there is substantial evidence to support the claim that ramucirumab *does* (modestly) improve overall survival. Although, this FDA reviewer recommends approving this application (and has recommended approval of other applications that demonstrated a 1.4 month median improvement in overall survival in patients with advanced cancer), this reviewer hopes that, in the future, sponsors target drug development to products intended to demonstrate larger treatment effects.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

The review teams did not identify any REMS as necessary prior to a marketing authorization for ramucirumab. Ramucirumab will be prescribed by oncologists who are trained how to monitor, diagnose, and manage serious toxicities caused by anti-neoplastic drugs including VEGF-targeted therapies. Standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

13.4 Recommendation for other postmarketing requirements and commitments

All PMCs and PMRs were recommended by the Division of Monoclonal Antibodies or the Office of Clinical Pharmacology. These PMCs and PMRs are described elsewhere in this review (e.g., Section 11.5).

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/s/

STEVEN J LEMERY
03/14/2014