CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125477Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

BLA	STN 125477/0
Submission Type	BLA-NME
Submission Date(s) (Rolling Submission)	3/26/2013, 4/30/2013, 6/19/2013, 7/29/2013, 8/21/2013, 8/23/2013
Review Classification	Priority (Orphan Indication, Fast Track Designation)
PDUFA Due Date	4/23/2014
Brand Name	CYRAMZA®
Generic Name	Ramucirumab
Proposed Indication	Advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy
Formulation	A sterile solution at concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials
Proposed Dosing Regimen	8 mg/kg Q2W, IV infusion over 60 minutes
Related IND	11,856
Applicant	Eli Lilly and Company
OCP Reviewer	Lillian H. Zhang, Ph.D.
OCP Team Leader	Hong Zhao, Ph.D.
OCP Division	Division of Clinical Pharmacology V (DCPV)
Clinical Division	Division of Oncology Products 2 (DOP2)

This is an Addendum to the clinical pharmacology review (DARRTS, 1/23/2014) of the original BLA submission regarding immunogenicity testing.

In the original clinical pharmacology review, a clinical pharmacology post-marketing requirement (PMR) was requested for the Applicant to accurately analyze patient serum samples from the Cyramza clinical trials for the presence of anti-ramucirumab antibodies (ARAs) and neutralizing antibodies (NAbs) using the more sensitive and validated assays because the current assays used in detecting ARAs and NAbs might be interfered by the presence of ramucirumab in the patients' serum samples.

At the Late-Cycle Meeting (LCM) held on February 11, 2014, the Applicant stated that it may be difficult to improve the drug tolerance of the current NAb assay. With the current assay, NAbs were detected in 1 of the 33 patients who tested positive for ARAs in ten clinical trials. As the incidence of NAb development is perceived to be small and its clinical impact on safety, efficacy and pharmacokinetics of ramucirumab is considered minimal based on the current data (see details in clinical pharmacology review in DARRTs), the team has decided to not request the Applicant to develop a new assay for NAbs assessment.

For the ARA assay, the further validation data indicate that the assay can detect ARAs at a high level (b) (4) in the presence of ramucirumab at clinically relevant concentrations. However, there is no data available to support that the assay can detect a level of ARA that is lower than (b) (4). The FDA guidance on assay development for immunogenicity testing recommends that the assay be able to detect 250-500 ng/ml ARA since these antibody concentrations have been associated with clinical events. Thus, the Applicant was asked at the LCM to fulfill the PMR by submitting adequate data on the drug tolerance of the current ARA assay or by re-analyzing patient serum samples with a newly validated assay if the data on the drug tolerance of the current assay is not acceptable.

Signatures:

Lillian H. Zhang, Ph.D. Clinical Pharmacology Reviewer Division of Clinical Pharmacology 5	Hong Zhao, Ph. D. Clinical Pharmacology Team Leader Division of Clinical Pharmacology 5

Cc: DOP2: CSO – **S Sickafuse**; MTL – **S Lemery**; MO – **S Casak**

DCPV: Reviewers – **LH Zhang**; TL – **H Zhao**; Division Deputy Director – **B Booth**; Division Director - **A Rahman**

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/s/

LILLIAN H ZHANG
03/14/2014

HONG ZHAO
03/14/2014
I concur.

Clinical Pharmacology Review

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1 EXECUTIVE SUMMARY

CYRAMZA (ramucirumab) is a recombinant human monoclonal antibody (mAb) of the immunoglobulin G subclass 1 (IgG1) that specifically binds to vascular endothelial growth factor receptor 2 (VEGF R2) and blocks the activation of this receptor. This original BLA submission seeks marketing approval for ramucirumab to be used as a single agent for the treatment of patients with advanced gastric or gastro-esophageal junction (GEJ) adenocarcinoma after prior chemotherapy. The recommended dosing regimen is 8 mg/kg every two weeks (q2w) administered as an intravenous (IV) infusion over 60 minutes.

Efficacy of ramucirumab has been demonstrated in a Phase 3, randomized, double-blind, placebo-controlled registration trial (REGARD). In the trial, the primary efficacy endpoint, overall survival (OS), was significantly improved in patients (N = 238) receiving ramucirumab plus best supportive care (BSC) as compared to patients (N = 117) receiving placebo plus BSC (hazard ratio [HR] 0.78; 95% CI: 0.60 to 1.00; $p = 0.047$), corresponding to a 37% longer median survival in the ramucirumab arm (5.2 months versus 3.8 months). An acceptable safety profile of ramucirumab has also been observed. The most common adverse events (AEs) observed with ramucirumab at a rate $\geq$ 10% and at a higher rate than placebo are abdominal pain, diarrhea, and hypertension.

The limited concentration data collected in the PK subgroup (N = 58) in REGARD showed that following the dosing regimen of 8 mg/kg q2w, the geometric mean minimum concentrations (C_{min}) of ramucirumab were 50 µg/mL (6-228 µg/mL) and 74 µg/mL (14-234 µg/mL) after the administration of the 3rd and 6th dose, respectively, in patients with advanced gastric or GEJ cancer. Approximately 95% of patients (55/58) in the PK subgroup achieved C_{min} >18 µg/mL, the targeted serum concentration that was associated with inhibition of tumor growth in the preclinical xenograft model. Age, gender, body weight did not appear to influence ramucirumab PK to an extent that would warrant any dose adjustment. The apparent mean half-life of ramucirumab following a single dose of 8 mg/kg was approximately 8 days (range 6-9 days) in Japanese patients with gastric cancer.

The incidence of antibody development in patients receiving ramucirumab has not been adequately determined because the assays used in detecting anti-ramucirumab antibodies (ARA) and neutralizing antibodies (NAb) were interfered by the presence of ramucirumab in the patients' serum samples.

(b) (4)

1.1 RECOMMENDATIONS

This BLA is acceptable from a clinical pharmacology perspective provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends approval of this BLA.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

PMR:

> To accurately analyze patient serum samples from the Cyramza clinical trials for the presence of anti-ramucirumab antibodies and neutralizing antibodies using the more sensitive and validated assays

PMRs for improving the anti-ramucirumab antibody assay and the neutralizing antibody assay will be requested by the CMC review team.

Although the PK data contained in this submission are limited, no PMR or PMC studies are required at this time (b) (4)

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DCPV: Reviewers – **LH Zhang**; TL – **H Zhao**; Division Deputy Director – **B Booth**; Division Director - **A Rahman**
OCP: Office Director **– Issam Zineh**

A Clinical Pharmacology (CP) briefing was not held for this BLA as clinical pharmacology information contained in the submission is limited and there are no issues for discussion at the CP briefing.

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

***Product Property and Mechanism of Action*:** Ramucirumab is a recombinant human receptor targeted mAb of the IgG1 subclass. Ramucirumab has an approximate molecular weight of 146.8 kDa. It specifically binds to VEGF R2 and inhibits ligand (VEGF-A, VEGF-C, and VEGF-D) stimulated activation of VEGF R2 and its downstream signaling components, including p44/p42 mitogen-activated protein kinases, neutralizing ligand-induced proliferation and migration of human endothelial cells.

***Registration Trial Design*:** REGARD was a Phase 3, randomized, double-blind trial to evaluate ramucirumab as a single agent in the treatment of patients with advanced gastric or GEJ adenocarcinoma after disease progression during or following prior chemotherapy. A total of 355 eligible patients were randomly assigned in a 2:1 ratio to receive

- Ramucirumab 8 mg/kg IV q2w + BSC (N = 238); or
- Placebo (buffer solution) + BSC (N = 117)

Therapy was continued until there was evidence of progressive disease, unacceptable toxicity, withdrawal of consent, or other withdrawal criteria were met.

***Efficacy Results*:** REGARD met its primary objective, demonstrating that ramucirumab improved overall survival (OS) as compared to the placebo. The median OS was 5.2 months (95% CI: 4.4, 5.7) for the ramucirumab arm and 3.8 months (95% CI: 2.8, 4.7) for the placebo arm with a HR of 0.78 (95% CI: 0.60, 1.00; *p*-value =0.047).

Safety Profiles: The most common adverse events (AEs) at all grades observed in ramucirumab-treated patients at a rate ≥10% compared to placebo are abdominal pain, diarrhea, and hypertension. An increased incidence of severe hypertension (Grade 3-4) was reported in patients receiving ramucirumab (8%) as compared to placebo (3%). In most cases hypertension was managed using standard antihypertensive treatment.

Dose Selection: Weekly doses (qw) of ramucirumab ranging from 2 to 16 mg/kg were evaluated in a Phase 1 dose escalation trial. Preliminary clinical activity (disease control) was observed at all dose levels studied and a maximum tolerated dose (MTD) was identified as 13 mg/kg. Administration regimens of once every-2-weeks (q2w, 6 to 10 mg/kg) and once every-3-weeks (q3w, 15 to 20 mg/kg) were evaluated in another Phase 1, dose-ranging trial. All dosing regimens were tolerated with no MTD identified and disease control was observed in some dose groups. Two dosing regimens, 8 mg/kg q2w and 10 mg/kg q3w, were then selected for subsequent Phase 2 trials and Phase 3 trials. In the registration trial REGARD, the ramucirumab dose of 8 mg/kg q2w was clinically efficacious and tolerable. Approximately 95% of patients (55/58) in the PK subgroup achieved minimum concentrations (C_{min}) of ramucirumab >18 µg/mL, the targeted serum concentration that was associated with inhibition of tumor growth in the preclinical xenograft model.

***Pharmacokinetics (PK)*:** Analysis of the trough concentration data obtained in 58 patients (25% of the total patients on ramucirumab in REGARD) indicated that following the dosing regimen of 8 mg/kg q2w, the geometric mean C_{min} of ramucirumab was 50 µg/mL (6-228 µg/mL) and 74 µg/mL (14-234 µg/mL) after the 3rd and 6th dose, respectively, which are higher than the targeted serum concentration (18 µg/mL) that was associated with inhibition of tumor growth in the preclinical xenograft model. Results based on multiple linear regression analysis of the C_{min} data suggested that age (range: 40 to 86 years), gender (41 male, 17 female), body weight (range: 45

to 113 kg) did not appear to influence ramucirumab PK to an extent that would warrant any dose adjustment. The apparent mean half-life of ramucirumab following a single dose of 8 mg/kg in Japanese patients (N = 6) with gastric cancer was approximately 8 days (range 6-9 days).

***Immunogenicity*:** In clinical trials, 33 of 480 patients (6.9%) developed treatment emergent anti-ramucirumab antibodies (ARA) and 1 patient (0.2%) developed neutralizing antibody (NAb). However, the reported incidence is likely to underestimate the incidence of ARAs and NAbs because the assays used for the detection of ARAs and NAbs are interfered by the presence of ramucirumab in patients' serum samples.

QT/QTc Evaluation: In a dedicated QT study, no clinically relevant QTc prolongation of ramucirumab (10 mg/kg every 3 weeks) was detected in patients with advanced solid tumors.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTITES

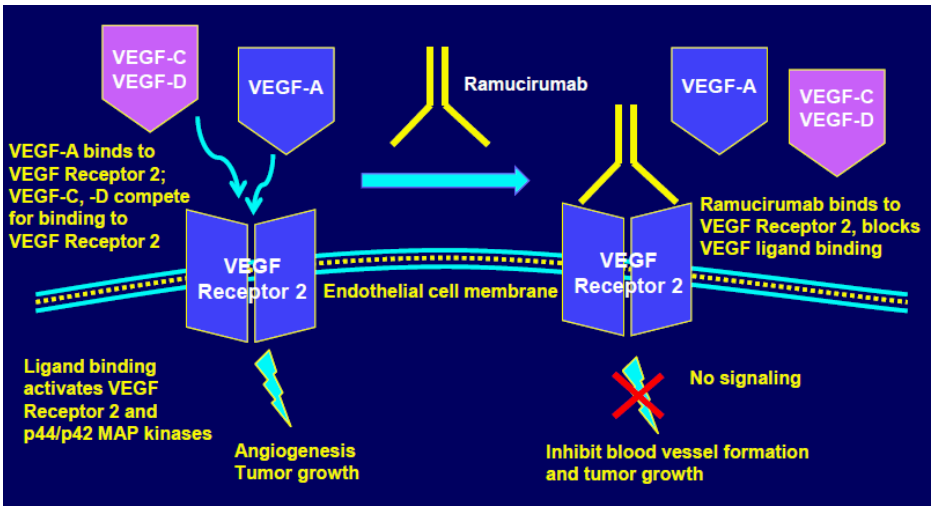
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology review?

Ramucirumab drug substance is a recombinant human mAb of IgG1 subclass produced in murine NS0 cells by recombinant DNA technology. It is composed of 4 polypeptide chains: 2 identical heavy (γ) chains consisting of 446 amino acids each and 2 identical light (κ) chains consisting of 214 amino acids each (see Figure 1). The measured molecular weight for the entire antibody is 146.8 kDa. The drug product is supplied as a sterile, preservative-free solution at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials for IV infusion following dilution.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Vascular endothelial growth factor receptor 2 (VEGF R2) is the key mediator of VEGF induced angiogenesis. Ramucirumab is designed to bind the extracellular domain of VEGF R2, preventing the interaction of VEGF R2 with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits ligand-stimulated activation of VEGF R2 and its downstream signaling components, including p44/p42 mitogen-activated protein kinases, neutralizing ligand-induced proliferation and migration of human endothelial cells (see Figure 2).

Figure 2 Ramucirumab Mechanism of Action



The indication is to use ramucirumab as a single agent for the treatment of patients with advanced gastric cancer or GEJ adenocarcinoma after prior chemotherapy. Currently, there are no FDA-approved 2nd-line treatments of advanced gastric cancer in the USA.

2.1.3 What are the proposed dosage and route of administration?

The recommended dosing regimen of ramucirumab as a single-agent is 8 mg/kg q2w administered as an IV infusion over approximately 60 minutes.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The efficacy of ramucirumab in the proposed patient population was demonstrated by the data from the registration trial REGARD (14T-IE-JVBD). The design feature of REGARD is presented in the table below:

Table 1 Summary of Study Design of REGARD

Study Description	Phase 3 , randomized, double-blind, placebo-controlled
Primary Objective	Overall survival (OS)
Patient Population	Patients with advanced gastric or GEJ adenocarcinoma after disease progression during or following first-line platinum- or fluoropyrimidine-containing therapy
Treatment	• Ramucirumab 8 mg/kg IV q2w + BSC (best supportive care) *or* • Placebo (an equivalent volume buffer solution IV q2w) + BSC
No. of Patients	• Ramucirumab arm: N = 238 • Control arm: N = 117

In the trial, eligible patients were randomized on a 2:1 basis to receive ramucirumab + BSC or placebo + BSC. BSC could include antiemetic agents, opiate and non-opiate analgesic agents, appetite stimulants, and other supportive care agents. Patients were treated until there was evidence of progressive disease, unacceptable toxicity, withdrawal of consent, or until other withdrawal criteria were met.

Clinical Studies with PK Data

A total of nine clinical studies containing ramucirumab concentration data (including REGARD) were submitted. Of those studies, only the PK data from the registration trial REGARD and a Phase 1 Study JVBW are deemed reliable to support labeling because serum concentrations of ramucirumab were measured using a validated modified enzyme-linked immunosorbent assay [ELISA] only in these two trials.

During the drug development, the original assay was modified to optimize performance (b) (4) The results of a cross-assay comparison using serum samples from Study JVBW showed large discrepancies between the two assays (see details in bioanalytical methods performance in Section 2.6). Due to the lack of concordance between the original assay and the modified new assay, concentration data from the seven early Phase 1 & 2 studies using the original assay were deemed uninterpretable. Therefore, only the data from the REGARD (N=58, 25% of the total patients on ramucirumab) and JVBW (N=6) studies provide PK information to the labeling.

2.2.2 What is the basis for selecting the clinical endpoint or surrogate and how are they used to assess efficacy in the pivotal clinical study? What is the clinical outcome in terms of efficacy and safety?

Primary Clinical Endpoint: The primary clinical endpoint in REGARD was OS defined as the interval between the date of randomization and the date of death from any cause. Patients received assigned study treatment every 2 weeks and were evaluated radiographically every 6 weeks until documented disease progression. Radiologic disease progression and response were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0). The

study met its primary objective, showing improved OS for patients treated with ramucirumab plus BSC compared to patients on the placebo plus BSC control arm (see Table 2).

Table 2 Summary of the Primary Efficacy Result

	Ramucirumab (N = 238)	Placebo (N = 117)
OS (median, month) (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)
HR (95% CI)	0.78 (0.60, 1.00)	
***P*-value**	0.047	

Secondary Efficacy Endpoint: The key secondary clinical endpoint is progression-free survival (PFS) defined as the time from the date of randomization until the date of objectively determined progressive disease or death due to any cause, whichever was first. Treatment with ramucirumab significantly reduced the risk of disease progression or death by 52% (HR = 0.48; 95% CI: 0.38, 0.62; p<0.0001), resulting in a 62% longer median time to disease progression in the ramucirumab arm (2.1 months vs. 1.3 months)

Safety

The most common AEs (all grades) observed in ramucirumab-treated patients at a rate ≥10% and at a higher rate than placebo are abdominal pain (31 vs. 30%), diarrhea (14% vs. 9%), and hypertension (16% vs. 8%). An increased incidence of severe hypertension (Grade 3-4) was reported in patients receiving ramucirumab (8%) as compared to placebo (3%). In most cases hypertension was managed using standard antihypertensive treatment.

2.2.3 What is the basis of the dose selection?

Weekly dosing of ramucirumab from 2 to 16 mg/kg was evaluated in Phase 1 Study JVBM. Preliminary clinical activity (disease control) was observed at all dose levels studied (see Table 3) and a maximum tolerated dose (MTD) was identified as 13 mg/kg.

Administration regimens of once every-2-weeks (q2w, 6 to 10 mg/kg) and once every-3-weeks (q3w, 15 to 20 mg/kg) dosing regimens were evaluated in another dose-ranging trial (Study JVBN). All dose regimens were tolerated with no MTD identified and disease control was observed in some dose groups (see Table 3).

Two dosing regimens, 8 mg/kg q2w and 10 mg/kg q3w, were then selected for subsequent Phase 2 (e.g. in renal cell carcinoma and melanoma, respectively) and Phase 3 trials (in a variety of patient populations including gastric cancer). In REGARD, the ramucirumab dose of 8 mg/kg q2w was clinically efficacious and tolerable. Approximately 95% of patients (55/58) in the PK subgroup achieved ramucirumab C_{min} >18 µg/mL, the targeted serum concentration that was associated with inhibition of tumor growth in preclinical xenograft model.

Table 3 Observed Clinical Activities and C_{min}

Trial No.	Dose (mg/kg)	Disease Control [Complete Response (CR) + Partial Response (PR) + Stable Disease (SD)], N (CR/PR/SD) (%)	C_{min} (µg/mL)
JVBM			*Cycle 1 pre-dose #5*
	2 (qw)	2 (0/0/2) (33.3)	14.3
	4 (qw)	4 (0/2/2) (100)	35.2
			Cycle 1 pre-dose #4
	6 (qw)	2 (0/0/2) (50.0)	59.0
	8 (qw)	3 (0/1/2) (60.0)	159.4
	10 (qw)	5 (0/0/5) (71.4)	120.2
	13(qw)	5 (0/1/4) (100)	218.4
	16 (qw)	3 (0/0/3) (50.0)	112.0
JVBN			*Cycle 1 pre-dose #4*
	6 (q2w)	2 (0/0/2) (50.0)	25.0
	8 (q2w)	1 (0/0/1) (20.0)	26.3
	10 (q2w)	4 (0/0/4) (100)	56.7
			Cycle 2 pre-dose #2
	15 (q3w)	2 (0/0/2) (33.3)	56.3
	20 (q3w)	6 (0/0/6) (100)	78.4
REGARD	8 (q2w)	OS statistically significant > placebo	> targeted 18 µg/mL in 55/58 patients in PK subgroup

2.2.4 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Ramucirumab concentrations in serum samples were measured by ELISA methods. The performance of the bioanalytical methods is reviewed in Section 2.6.

2.2.5 Exposure-response

The available data does not allow for a reliable assessment of the relationships between exposure and efficacy or safety of ramucirumab because PK samples only collected from 58 patients (25% of the total patients on ramucirumab) in the registration trial REGARD.

2.2.6 Does ramucirumab prolong the QTc interval?

The effect of ramucirumab (10 mg/kg, q3w for a minimum of 9 weeks) on QT interval was evaluated in a multicenter, open-label, single-agent trial (Study JVBK) in 66 patients with advanced solid tumors. No clinically relevant changes in the mean QTc interval were detected. The largest upper bounds of the 2-sided 90% CI for the mean difference between ramucirumab (10 mg/kg q3W) and placebo were below 10 ms and no subject's QTcF was above 480 nm.

There was no notable correlation between ramucirumab concentrations and ΔQTcF. Please see IRT-QTc review in DARRTS for more information.

Being a mAb, ramucirumab does not penetrate cell membranes. It is unlikely that ramucirumab would directly inhibit the function of hERG or other ion channels responsible for cardiac repolarization. (b) (4)

(b) (4)

2.2.7 Pharmacokinetic (PK) characteristics of the drug and its major metabolites

2.2.7.1 What are the single dose (SD) and multiple dose (MD) PK parameters?

As discussed in Section 2.2.1, PK data contained in this application for ramucirumab are limited due to the modified assay only used in two studies (trial JVBW and trial REGARD).

PK Characterization

PK of ramucirumab in Japanese patients with gastric cancer was evaluated in an open-label, single-arm Phase 1b trial (Study JVBW). In the trial, 6 patients received ramucirumab, 8 mg/kg IV infusion over 1 hour on Days 1 and 15, and paclitaxel, 80 mg/m^2 IV infusion over 1 hour on Days 1, 8, and 15 in 28-day treatment cycles. Serum samples were collected in Cycles 1&2 prior to the 1st dose and up to 336 hours following the infusion (prior to the next dose). From Cycle 2 onwards, serum samples were collected at pre-dose and 1 hour post-end-of-infusion. Serum concentrations of ramucirumab were measured by the modified ELISA method. The mean serum concentration *vs.* time profiles following the 1st (in Cycle 1) and 3rd (in Cycle 2) IV infusions are depicted in Figure 3. The PK parameters determined are presented in Table 4.

Figure 3 **Mean Serum Ramucirumab Concentration-Time Profiles following 1st (in Cycle 1) and 3rd (in Cycle 2) IV Infusions on a Normal Scale (left) and a Semi-log Scale (right)**

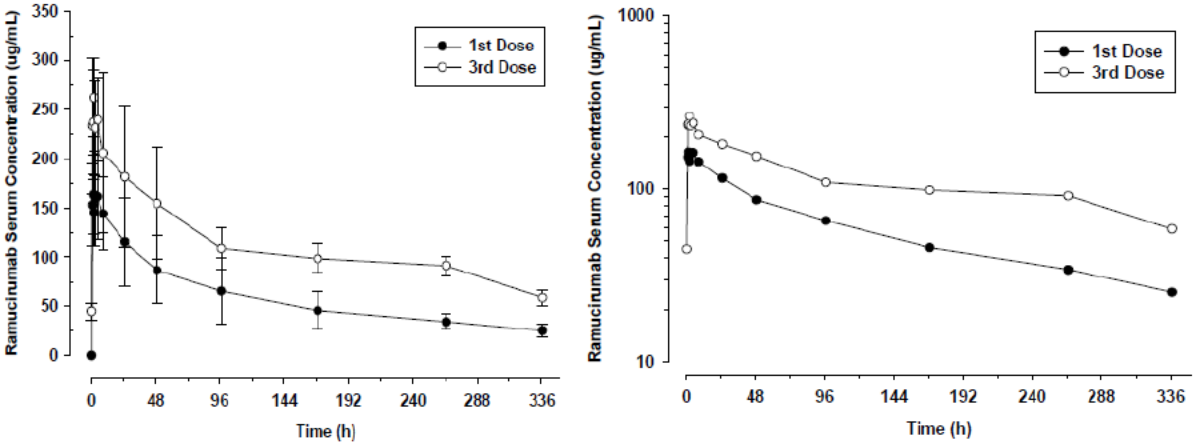


Table 4 **PK Parameters of Ramucirumab following 1st and 3rd IV Infusions in Japanese Patients with Gastric Cancer**

PK Parameter	1st Dose (n = 6) Geometric Mean (CV %)	3rd Dose (n = 4) Geometric Mean (CV %)
C_{max} (µg/mL)	171 (26)	282 (15)
$AUC_{0\text{-last}}$ (µg*h/mL)	18,300 (35)	--
$AUC_{0\text{-}\tau}$ (µg*h/mL)	18,300 (35)	41,300, 42,600*
$t_{1/2}$ (h)	181 (138 – 225)**	--
CL (mL/h/kg)	0.43 (35)	0.19, 0.19*
V (mL/kg)	97.1 (67)	44.1 (22)
R_A, AUC***	--	1.52, 1.53*

* Individual subject values; ** N = 4; *** R_A,AUC = $AUC_{(0\text{-}\tau,cycle2)}/AUC_{(0\text{-}\tau,cycle1)}$

Note that the geometric mean of half-life ($t_{1/2}$) (approximately 8 days, range 6 – 9 days) following the 1st dose is calculated based on the PK data collected up to 336 h (14 days) post dose, thus the terminal elimination phase have not been completely captured and accurately estimated. The accumulation ratio based on AUC (R_A, AUC) was approximately 1.5 following the third dose. However, the sample size is limited following multiple doses.

Summary statistics of the mean C_{min} and C_{1h} (1-hour post-infusion) values over the study period are presented in Table 5. Results suggests that from Cycle 2 Day 1 onwards, the serum levels of ramucirumab observed pre-dose and 1-hour post end-of-infusion appeared to stabilize.

Table 5 Summary of Ramucirumab C_{min} and C_{1h} in Japanese Patients with Gastric Cancer by Time Window

Study Day	Cycle 1 Day 1 (1st dose)	Cycle 1 Day 15 (2nd dose)	Cycle 2 Day 1 (3rd dose)	Cycle 2 Day 15 (4th dose)	Cycle 3 Day 1 (5th dose)	Cycle 4 Day 1 (7th dose)
N	6	6	4	2	3	2
C_{min} (µg/mL)*	N/A	24.6 (23)	44.2 (21)	53.2, 64.0**	66.6 (25)	16.5, 87.4**
C_{1h} (µg/mL)	142 (23)	--	260 (15)	--	291 (20)	294, 294**

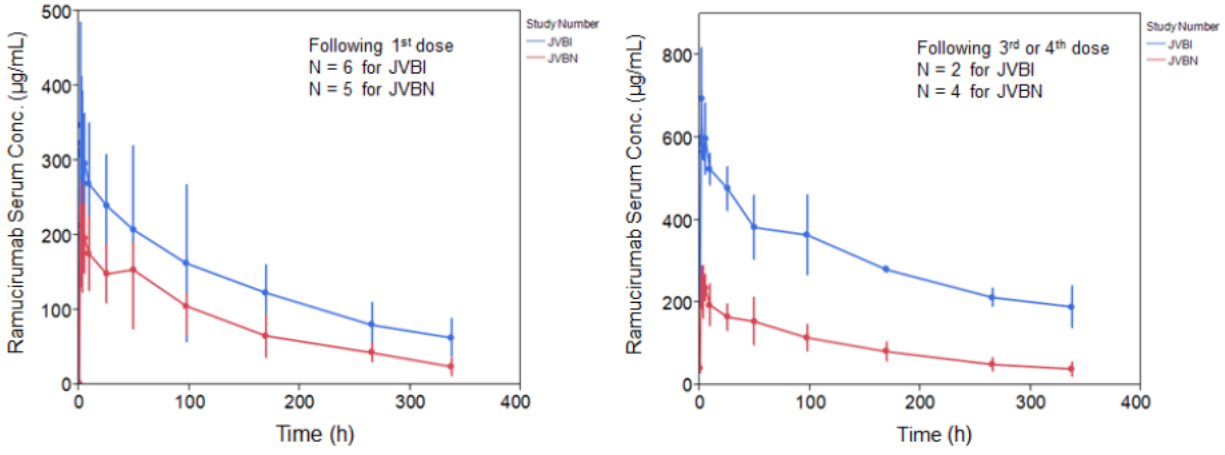
* Geometric mean (CV%)
N/A: below the limit of quantification (BLOQ)
**Data from two subjects

Although ramucirumab was given in combination with paclitaxel in this study, it is unlikely to have significant metabolism-based drug-drug interactions (DDI) between the two drugs given that ramucirumab is a mAb.

Japanese vs. Non-Japanese Patients

There were no data available with the modified assay to assess if there was any difference in PK between Japanese and non-Japanese patients. A cross-study comparison of the PK profiles generated using the original assay in Study JVBI (Japanese patients with solid tumors) and Study JVBN (non-Japanese patients with solid tumors) following 1st dose (Figure 4, left panel) and 3rd or 4th dose (Figure 4, right panel) IV administration of ramucirumab at 8 mg/kg q2w suggests that Japanese patients had notable higher exposure than that of the non-Japanese patients. Therefore, the PK information obtained from Study JVBW in Japanese patients may not represent that in non-Japanese patients in the indicated patient population. (b) (4)

Figure 4 Mean Serum Ramucirumab Concentration-Time Profiles in Japanese (Study JVBI-blue color) and in Non-Japanese Patients (Study JVBN-red color)



Trough Concentrations in REGARD Trial

The serum samples collected in 58 patients before Cycles 4 and 7 for immunogenicity assessment were used to determine C_{min} of ramucirumab after the 3rd and 6th doses. Of those 58

patients, 29 had concentration data at both sampling time points, 24 had concentration data only before Cycle 4 and 5 had concentration data only before Cycle 7 (Table 6).

Table 6 Summary of Ramucirumab C_{min} following 8 mg/kg Q2W IV Administration in Patients in REGARD Trial

	Prior to Cycle 4 (Post-3rd dose)	Prior to Cycle 7 (Post-6th dose)
N	53	34
C_{min} (µg/mL)*	49.5 (80.6)	74.4 (58.3)
Conc. Range (µg/mL)	6.3 - 228	13.8 - 234

*Geometric mean (CV %)

The limited concentration data collected in REGARD showed that of those 58 patients (25% of the total patients on ramucirumab), 55 had C_{min} values observed after either the 3rd and/or 6th doses above 18 µg/mL, a minimum ramucirumab concentration targeted for human studies as this concentration was associated with anti-tumor activity in preclinical xenograft model. The Applicant is requested to conduct PopPK analysis to generate ramucirumab PK parameters using the sparse PK samples collected in REGARD.

Based on the results generated from trial REGARD, the labeling language recommended by the Agency (in Blue) for Section 12.3 is provided below:

12.3 Pharmacokinetics

(b) (4)

[redacted]

2.2.7.2 How does the PK of the drug and its major active metabolites in healthy volunteers compared to that in patients?

Ramucirumab has not been evaluated in healthy volunteers.

2.2.7.3 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study has been conducted for ramucirumab. Mass balance studies are not generally performed for biologic products because they are degraded into amino acids that then recycled into other proteins.

2.2.7.4 What are the characteristics of drug metabolism?

Metabolism studies are not generally performed for biologic products because they are degraded into amino acids that are then recycled into other proteins.

2.2.7.5 What are the characteristics of drug excretion?

Excretion studies are not generally performed for monoclonal antibodies because their large molecular size prevents them from excreting via the kidney and/or bile as an intact form.

Reviewer's Note:

(b) (4)

[redacted]

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

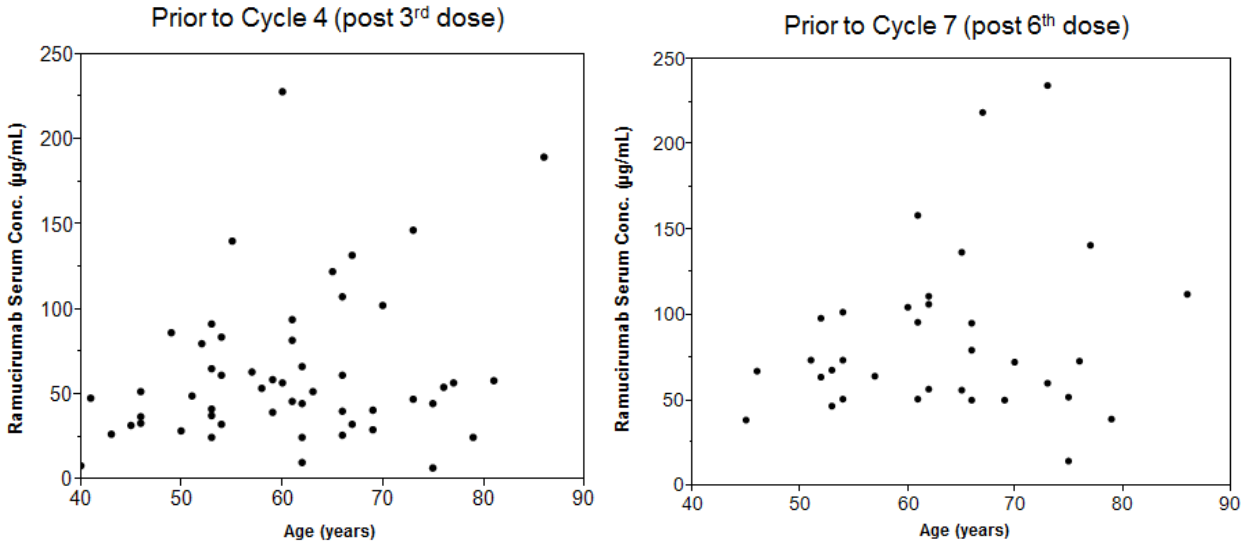
No formal studies have been conducted to assess the effect of age, gender, body weight, and race on the PK and/or response of ramucirumab. Results based upon multiple linear regression analysis of the limited C_{min} data generated in REGARD suggested that age (range: 40 to 86 years), gender (41 male, 17 female), body weight (range: 45 to 113 kg) did not appear to influence ramucirumab PK to an extent that would warrant any dose adjustment. Trough concentrations appeared to be comparable between White and Asian. However, no conclusion can be made based on the limited data. Thus, no labeling statement should be included with respect to these covariates.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

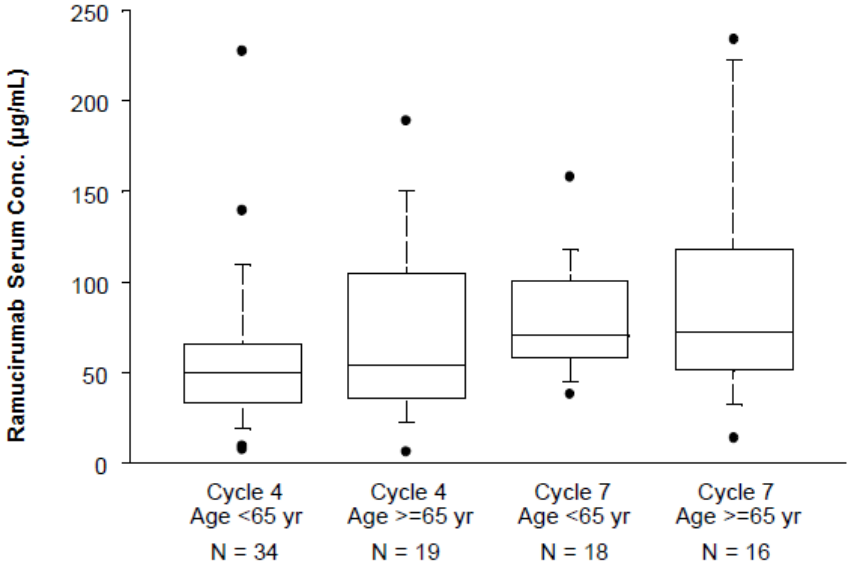
No formal studies have been performed to evaluate the effect in elderly patients. The distribution of individual C_{min} with respect to age is shown in Figure 5. The scatter pattern of the individual concentrations versus age suggests that age would not have a significant effect on ramucirumab C_{min}. The multiple regression analysis also demonstrated that age is not a significant covariate.

Figure 5 Effect of Age on Ramucirumab C_{min} in Patients with Gastric Cancer following 8 mg/kg Q2W IV Administration



Available data in REGARD suggest that patients at ages ≥65 years have similar median C_{min} value as that at ages <65 years (see Figure 6).

Figure 6 Effect of Elderly Patients on Ramucirumab C_{min} in Patients with Gastric Cancer following 8 mg/kg Q2W IV Administration



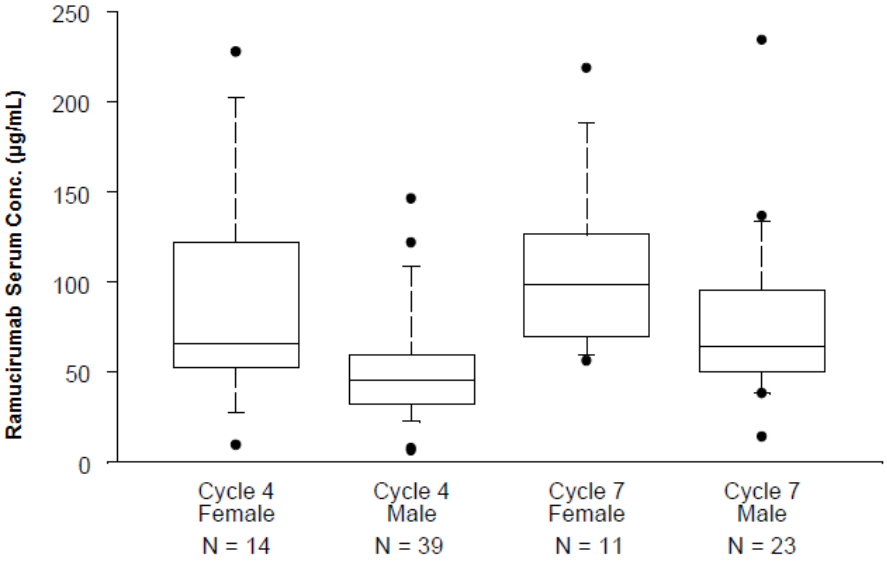
2.3.2.2 Pediatric patients

Safety and effectiveness of ramucirumab have not been established in pediatric patients. As ramucirumab is designated as an orphan drug for the treatment of gastric cancer, it is exempt from the requirement to assess the safety and effectiveness of the product for the claimed indication in all pediatric age categories under 21 CFR 314.55 (d), Exemption for Orphan Drugs.

2.3.2.3 Gender

The box-plot of C_{min} with respect to gender shown in Figure 7 suggests that median C_{min} value in females is higher than that in males. The multiple regression analysis also indicates that gender is a significant covariate; however, the higher exposure in female does not result in a better efficacy or a higher adverse event rate in female than that in male. Thus, the differences in exposure observed by gender are unlikely to have clinical implications, and no dose adjustment based on gender is recommended.

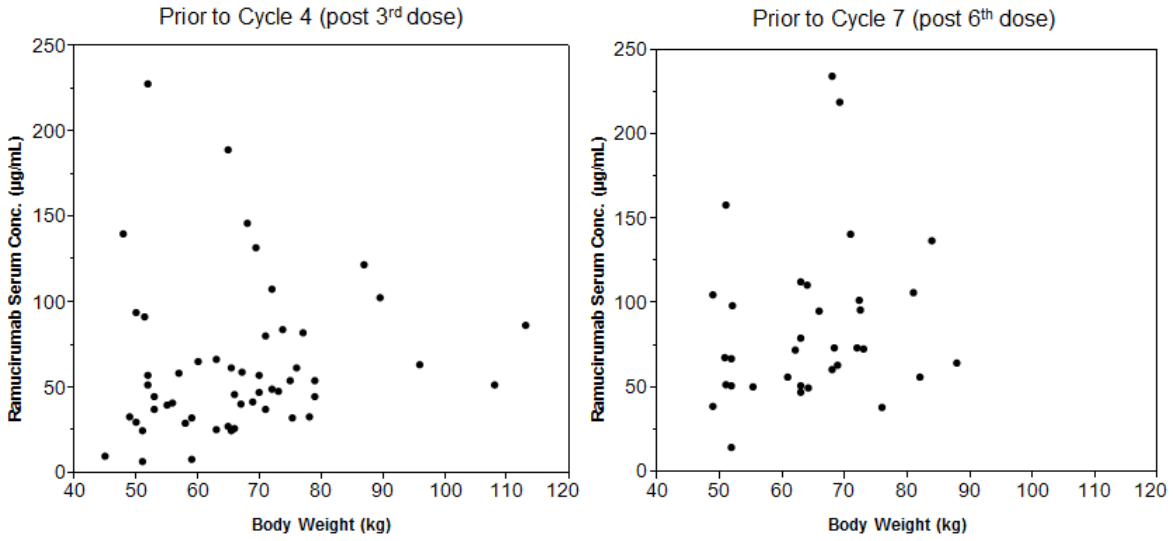
Figure 7 Effect of Gender on Ramucirumab C_{min} in Patients with Gastric Cancer following 8 mg/kg Q2W IV Administration



2.3.2.4 Body Weight

The distribution of individual C_{min} with respect to body weight is presented in Figure 8. The multiple regression analysis demonstrated that body weight is a significant covariate. The current dosing is already body weight based and the target concentration of 18 µg/mL is achieved even at the low end of body weight range.

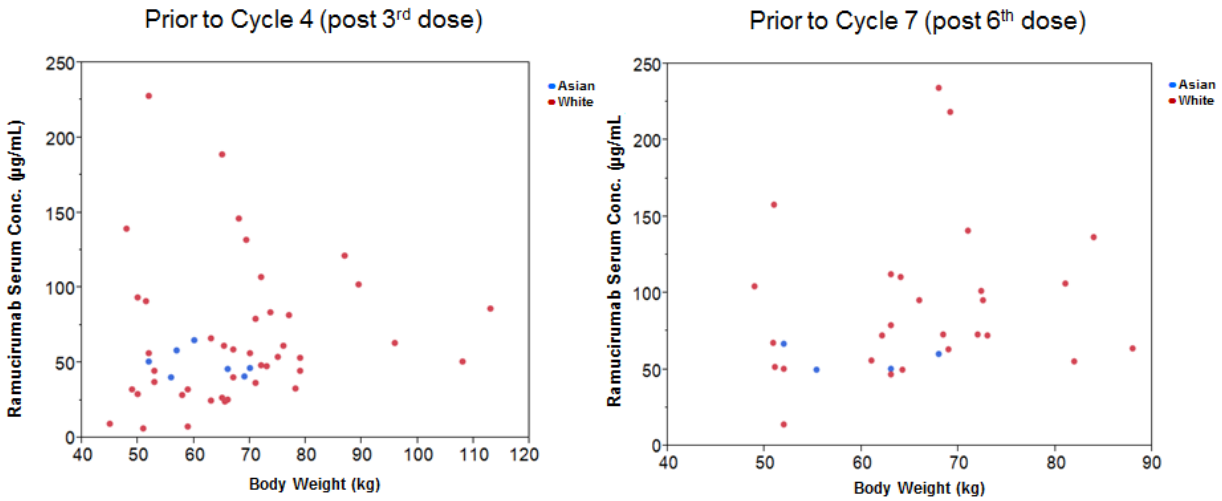
Figure 8 Effect of Body Weight on Ramucirumab C_{min} in Patients with Gastric Cancer following 8 mg/kg Q2W IV Administration



2.3.2.5 Race

The distribution of individual C_{min} with respect to race presented in Figure 9 suggests that C_{min} values for Asian were within the range of that for White; however the sample size of Asian is small (N = 7) and no conclusion can be made.

Figure 9 Effect of Race on Ramucirumab C_{min} in Patients with Gastric Cancer following 8 mg/kg Q2W IV Administration



2.3.2.6 Renal impairment

No specific studies of ramucirumab in patients with renal impairment have been conducted. As a mAb with a 146.8 kDa molecular weight, ramucirumab is not expected to be excreted via the kidney, but rather through proteolytic degradation. Thus renal impairment study is considered unnecessary.

2.3.2.7 Hepatic impairment

No specific studies of ramucirumab in patients with hepatic impairment have been conducted. Ramucirumab is a mAb that is eliminated by proteolytic degradation not by hepatic metabolism, thus hepatic impairment study is considered unnecessary.

2.3.2.8 What pregnancy and lactation use information is there in the application?

No animal studies have been specifically conducted to evaluate the effect of ramucirumab on female reproduction and fetal development. It is also not known whether ramucirumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Based on ramucirumab's mechanism of action, it is likely that ramucirumab will inhibit angiogenesis and may potentially result in adverse effects during pregnancy and postnatal development. Avoid the use of ramucirumab in pregnant women and only use if the potential benefit to the mother justifies the potential risk to the fetus or its postnatal development. No studies have been conducted to assess ramucirumab's impact on milk production, its presence in breast milk, or its effects on the breast-fed child. It is not known whether ramucirumab is excreted in human milk. Human IgG is excreted in human milk and due to potential risks to the nursing infant, it is recommended to discontinue nursing or discontinue ramucirumab.

2.3.2.9 What are other factors important to understand the drug's efficacy and safety?

Immunogenicity: The immunogenicity of ramucirumab was assessed in nine clinical trials presented in Table 2 as well as in a Phase 2 trial JVBR in patients with ovarian cancer. In those ten trials, blood samples for analysis of the presence of anti-ramucirumab antibodies (ARAs) were collected at baseline (prior to first dose of ramucirumab), in the early treatment courses (typically after 1-3 cycles or 2 to 6 weeks), after several doses/cycles (4 to 12 weeks), and at follow-up visit. ARAs were detected using an ELISA method. A ligand-binding competitive assay format was developed to detect neutralizing antibodies (NAb) to ramucirumab.

Of the 551 patients in the ten clinical trials who received ramucirumab and whose serum samples were collected for the evaluation of immunogenicity, 480 patients had serum samples analyzed for the presence of ARAs post-ramucirumab treatment. Of those 480 patients, 33 patients (6.9%) had treatment-emergent (TE) ARAs and 1 patient (0.2%) developed NAb to ramucirumab. In the registration trial REGARD, 6 patients (3.4%) in the ramucirumab arm developed TE ARAs. None of the patients developed NAb (see Table 7).

Table 7 Summary of Anti-ramucirumab Antibody Results in Clinical Trials

Study No.	Dosing Regimen (Cycle Length)	Incidence of Patients with TE ARAs	Time-point	No. of Patient with NAb Detected
REGARD	8 mg/kg Q2W, IV (2W)	6/175	cycle 4; 30-day follow up	0
JVBW	8 mg/kg Q2W, IV (4W)	0/6	--	0
JVBM	2, 4, 6, 8, 10, 13, and 16 mg/kg QW, IV (Cycle 1 = 6W; Cycles >1 = 4W)	1/36	30-day follow up	0
JVBN	6, 8, 10 mg/kg Q2W (Cohorts 1, 2, and 3); 15&20 mg/kg Q3W (Cohorts 4 and 5), IV (Cohorts 1 to 3: Cycle 1 = 6W; Cycles >1 = 4W; Cohorts 4 and 5: 3W)	3/25	cycle 2; 30-day follow up	0
JVBI	6 and 8 mg/kg Q2W or 10 mg/kg Q3W, IV (6W)	0/15	--	0
JVBK	10 mg/kg Q3W, IV (3W)	1/52	cycle 2	0
JVBO	10 mg/kg Q3W, IV with or without 1000 mg/m^2 dacarbazine Q3W, IV (3W)	10/74	cycle 1; cycle 3; end of therapy; 30-day follow up	0
JVBP	8 mg/kg Q2W, IV (2W)	3/32	end of therapy; 30-day follow up	0
JVBQ	8 mg/kg Q2W, IV (2W)	6/17	cycle 2; cycle 3; cycle 4; cycle 7; end of therapy; 30-day follow up	1
JVBR	8 mg/kg Q2W, IV (4W)	3/48	cycle 2; cycle 3	0
Total		33/480		1

Effect of Immunogenicity on Efficacy
The impact of immunogenicity on ramucirumab efficacy could not be assessed due to the low incidence of patients developed TE ARAs.

Effect of Immunogenicity on PK
The limited data do not permit the evaluation of the impact of immunogenicity on ramucirumab exposure. PK data were collected only in 15 of the 33 patients tested positive ARAs and 10 patients didn't develop ARAs until the end of therapy or the scheduled 30-day follow-up visit.

Effect of Immunogenicity on Safety
The immunogenicity was not associated with the observed infusion related reactions (IRRs). Of the 33 patients with TE ARAs, only six patients (18%) experienced IRRs. Of the 30 patients who experienced IRRs and had ARA tested, only 6 patients (20%) were ARAs positive. In REGARD, none of the six patients with TE ARAs experienced an IRR.

However, the incidence of antibody development in patients receiving ramucirumab has not been reliably determined because both assays have substantial limitations in detecting ARAs and NAb in the presence of ramucirumab. For the ARA assay, the validation data indicate that the assay can detect as little as (b) (4) of the positive control antibody in the presence of (b) (4) ramucirumab. For the NAb assay, the data indicate that the assay can detect (b) (4) of NAb in the presence of (b) (4) ramucirumab. The serum concentrations of ramucirumab observed in patients at the post-third and post-sixth dose sampling time points in REGARD trial were much higher than the drug tolerance level of either assay.

Based on the reviewer's further analysis of the immunogenicity data collected in REGARD trial, of the 44 patients with serum ramucirumab concentration collected at 30-day follow-up visit, 21 had serum concentration values greater than 3.9 µg/ml. Thus, the reported incidence is likely to underestimate the incidence of ARAs and NAbs in patients receiving ramucirumab.

Please see CMC review in DARRTS for more information on the ARA and NAb assays performance.

The labeling recommendation regarding immunogenicity provided by the Agency is presented below (in Blue):

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for (b) (4) immunogenicity. In clinical trials, 33/ (b) (4) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies using an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibody was detected in 1 of those 33 patients. However, due to limitations in assay performance, the incidence of antibody development in patients receiving CYRAMZA has not been reliably determined. (b) (4)

(b) (4)

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. (b) (4)

(b) (4) For these reasons, comparison of incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No dedicated studies were conducted to evaluate the impact of extrinsic factors on the PK and/or PD of ramucirumab. Given that ramucirumab is a mAb and is intravenously administered, the influence of extrinsic factors on dose-exposure and/or response is anticipated to be minimal, if any.

2.4.2 Drug-drug interactions

No studies on the metabolism of ramucirumab have been performed *in vitro* or in humans. Like most therapeutic proteins, ramucirumab is not expected to be metabolized by liver cytochrome P450 (CYP) or other drug metabolizing enzymes and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction. Therefore, ramucirumab is unlikely to have clinically relevant metabolism-based drug-drug interactions (DDI).

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

No, given that ramucirumab is a mAb.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

No, given that ramucirumab is a mAb.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes? Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No, given that ramucirumab is a mAb.

2.4.2.4 Are there other metabolic/transporter pathways that may be important?

No. As biologics are degraded into amino acids that then recycled into other proteins, classical biotransformation studies performed for small molecule drugs are generally not needed for biologics.

2.4.2.5 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No. For the proposed indication, ramucirumab will be used as a monotherapy.

2.4.2.6 What other co-medications are likely to be administered to the target patient population?

A variety of supportive medicines and nutritional supplements include antiemetic agents, opiate and non-opiate analgesic agents, appetite stimulants, and other supportive care agents are likely to be given to the targeted patient population. With hypertension occurrence observed in REGARD trial, antihypertensive drugs will be administered as well.

2.4.2.7 Are there any other in vivo drug-drug interaction (DDI) studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable because ramucirumab is a therapeutic mAb given by IV route.

2.5.2 What is the composition of the to-be-marketed formulation?

Ramucirumab is supplied as a sterile, preservative-free solution at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials with excipients of (b) (4) histidine, (b) (4) histidine monohydrochloride, sodium chloride, glycine, polysorbate 80, and Water for Injection, USP. The composition of the drug product is presented in Table 8.

Table 8 Unit Formula for Ramucirumab Drug Product, 500 mg/50 mL and 100 mg/10 mL

Ingredient	Quantity (mg/mL)	Function
Active Ingredient		
Ramucirumab	10	Active Ingredient
Other Ingredients		
(b) (4) Histidine	0.65	(b) (4)
Histidine Monohydrochloride	1.22	
Glycine	9.98	
Sodium Chloride	4.38	
Polysorbate 80	0.10	
Water for Injection	(b) (4)	

2.5.3 What moieties should be assessed in bioequivalence studies?

Not applicable.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

Not applicable.

2.6 ANALYTICAL SECTION

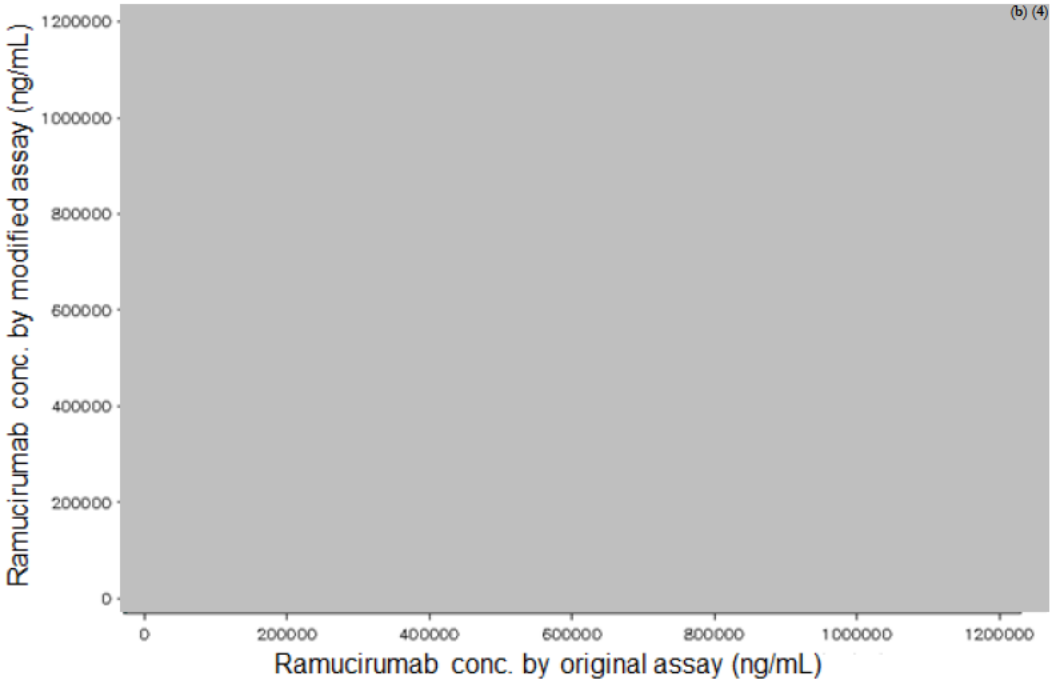
2.6.1 Were the active moieties identified and measured in the clinical pharmacology studies?

Yes. The serum concentrations of the active moiety, ramucirumab, were measured by a validated bioanalytical method in trials REGARD and JVBW.

2.6.2 *What bioanalytical procedures and methods were used to determine drug concentrations? Are they acceptable for this BLA?*

As mentioned in Section 2.2.1, the serum concentrations of ramucirumab were measured by an original and a modified ELISA method during drug development. The modifications were introduced during the assay transfer from in-house (ImClone) (b) (4) to optimize performance (b) (4). Results of a cross-assay comparison using serum samples from Study JVBW showed discrepancies between the two assays (b) (4) (see Figure 10 below).

Figure 10 Plot of JVBW Ramucirumab Concentration Results (ng/mL) Using the Original vs. Modified Assay



(b) (4)

(b) (4) Due to the lack of comparability between the two assays and deficiencies in validation package for the original assay (i.e. lack of specificity and selectivity assessment, lack of RE% acceptance criteria for standard curves, and lack of intra-assay performance at lower limit of quantitation), only the data from REGARD and JVBW trials using the modified assay deemed reliable to provide PK information to the labeling.

Modified ELISA

(b) (4)

Table 9 Summary of Bioanalytical Method Validation for Ramucirumab

Study No.	JVBW, REGARD (runs 1-24)	REGARD (runs 25 – 27)
Analyte	Ramucirumab	
Matrix	Human Serum	
Standard Curve Range (ng/mL)	1.6 - 200	2.5 – 100
Regression Type	Five parameter curve fit	
Lower limit of quantification (LLOQ) (ng/mL)	5.0 (2,500 with the minimum required dilution of 1:500 applied)	
Upper limit of quantification (ULOQ) (ng/mL)	108 (54,000 with the minimum required dilution of 1:500 applied)	55.0 (27,500 with the minimum required dilution of 1:500 applied)
QC Samples (ng/mL)	5, 30, 90	10, 20, 40
Precision (%CV)		
Intra-Assay	0.9 to 35.1	0.6 to 15.5
Inter-Assay	4.9 to 11.2 (LLOQ)	2.7 to 8.5
Accuracy (%RE)		
Intra-Assay	-35.3 (LLOQ) to 25.1	-16.2 to 8.7
Inter-Assay	-18.1 (LLOQ) to 3.9	-9.3 to -3.6
Stability		
Storage	12 months @ -20^{o}C, 30 months @ -70^{o}C.	
Bench-Top	24 hours @ ambient temperature	
Freeze-Thaw	5 cycles @-70^{o}C	

As shown in the table above, the validation performance of the modified assay does not meet the regulatory standard as the intra-assay accuracy/precision fell outside the acceptance range. This method is considered acceptable for initial PK characterization; however, this assay needs to be improved before it can be used for any future PK comparability study if the manufacturing changes warrant such a study.

3 APPENDIX - OCP FILING REVIEW FORM

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

BLA Number	STN 125477	**Brand Name**	Cyramza®
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Ramucirumab
Medical Division	Oncology/DOP2	**Drug Class**	A recombinant human receptor targeted monoclonal antibody of the IgG1 class
OCP Reviewer	Lillian Hua Zhang, Ph.D.	**Indication**	For the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy
OCP Team Leader	Hong Zhao, Ph.D.	**Dosage Form**	A sterile solution at concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials
Date of Submission (rolling)	3/26/2013, 4/30/2013, 6/19/2013, 7/29/2013, 8/21/2013, 8/23/2013	**Dosing Regimen**	8 mg/kg every 2 weeks administered as an intravenous (IV) infusion over approximately 60 min
Due Date of OCP Review	January, 2014	**Route of Administration**	IV infusion
Priority Classification	Priority	**Sponsor**	Eli Lilly and Company
PDUFA Due Date	April 23, 2014		

Clinical Pharmacology Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**5**		Two assay validation reports, one methods cross comparison report, and two bioanalytical study reports
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	**3**		Studies JVBM, JVBN, JVBI
multiple dose:	**X**	**1**		Study JVBW
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

In-vivo effects of primary drug:				
In-vitro:				
in-silico				
Subpopulation studies -				
ethnicity:				
gender:				
geriatrics:				
renal impairment:				
hepatic impairment:				
pediatrics:				
PD:				
Phase 2:	**x**	**4**		Studies JVBO, JVBP, JVBQ, JVBR
Phase 3:	**x**	**1**		Study REGARD
QT study	**x**	**1**		Study JVBK
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**x**	**1**		REGARD
II. Biopharmaceutics				
Compatibility	**x**	**1**		BDZ00030 in monkeys (comparability of drug product from Process B – used in phase 2 trials to Process C0 – used in phase 3 trials
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References				
Total Number of Studies		**17**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	N/A. To-be-marketed product was used in the pivotal clinical trial.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	N/A. IV Formulation
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		Insufficient data
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	N/A. Orphan Drug
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		
	General				

18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes, the application is fileable from a clinical pharmacology perspective.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

The following pharmacometrics information requests were sent to the Applicant on 8/19/2013 and the responses from the Applicant were received on 8/21/2013:

1. *Dataset under the folder i4t-ie-jvbn is not the correct dataset for Study CP12-0402. The folder only includes the data for Study CP12-0401. Submit the correct dataset.*
2. *We could locate data for CP-12-0715 (i4t-ie-jvbd) but noted that they are only from 15 subjects. However, in the clinical pharmacology summary of your submission (Clin-pharm-sum-us-gastric, page16), it states that 58 patients were evaluable for Cmin. Please submit the complete dataset.*
3. *We noted that you used "C" as a flag for excluded observations in the dataset for CO12-1705. For an adequate analysis, this flag should be located in a separate column (i.e., first column of the dataset).*

The following clinical pharmacology information request was sent to the Applicant on 9/24/2013 and the responses from the Applicant were received on 9/27/2013:

1. *Submit the bioanalytical study reports for the modified assay for trials REGARD and JVBW.*

Lillian H. Zhang, Ph.D.	30-Sept-2013
Reviewing Clinical Pharmacologist	Date
Stacy Shord, Pharm.D.	30-Sept-2013
Acting Team Leader	Date

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

/s/

LILLIAN H ZHANG
01/23/2014

HONG ZHAO
01/23/2014
I concur.

NAM ATIQUR RAHMAN
01/23/2014

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

BLA Number	STN 125477	**Brand Name**	Cyramza®
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Ramucirumab
Medical Division	Oncology/DOP2	**Drug Class**	A recombinant human receptor targeted monoclonal antibody of the IgG1 class
OCP Reviewer	Lillian Hua Zhang, Ph.D.	**Indication**	For the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy
OCP Team Leader	Hong Zhao, Ph.D.	**Dosage Form**	(b) (4)
Date of Submission (rolling)	3/28/2013, 4/30/2013, 6/20/2013, 8/26/2013	**Dosing Regimen**	8 mg/kg every 2 weeks administered as an intravenous (IV) infusion over approximately 60 min
Due Date of OCP Review	December, 2013	**Route of Administration**	IV infusion
Priority Classification	Priority	**Sponsor**	Eli Lilly and Company
PDUFA Due Date	April 27, 2014		

Clinical Pharmacology Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**5**		Two assay validation reports, one methods cross comparison report, and two bioanalytical study reports
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	**3**		Studies JVBM, JVBN, JVBI
multiple dose:	**X**	**1**		Study JVBW
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
in-silico				
Subpopulation studies -				
ethnicity:				
gender:				
geriatrics:				
renal impairment:				
hepatic impairment:				
pediatrics:				
PD:				
Phase 2:	**x**	**4**		Studies JVBO, JVBP, JVBQ, JVBR
Phase 3:	**x**	**1**		Study REGARD
QT study	**x**	**1**		Study JVBK
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**x**	**1**		REGARD
II. Biopharmaceutics				
Compatibility	**x**	**1**		BDZ00030 in monkeys (comparability of drug product from Process B – used in phase 2 trials to Process C0 – used in phase 3 trials
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References				
Total Number of Studies		**17**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	N/A. To-be-marketed product was used in the pivotal clinical trial.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	N/A. IV Formulation
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		Insufficient data
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	N/A. Orphan Drug
16	Did the applicant submit all the pediatric exclusivity data, as			x	

	described in the WR?				
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes, the application is fileable from a clinical pharmacology perspective.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

The following pharmacometrics information requests were sent to the Applicant on 8/19/2013 and the responses from the Applicant were received on 8/21/2013:

1. *Dataset under the folder i4t-ie-jvbn is not the correct dataset for Study CP12-0402. The folder only includes the data for Study CP12-0401. Submit the correct dataset.*
2. *We could locate data for CP-12-0715 (i4t-ie-jvbd) but noted that they are only from 15 subjects. However, in the clinical pharmacology summary of your submission (Clin-pharm-sum-us-gastric, page16), it states that 58 patients were evaluable for Cmin. Please submit the complete dataset.*
3. *We noted that you used "C" as a flag for excluded observations in the dataset for CO12-1705. For an adequate analysis, this flag should be located in a separate column (i.e., first column of the dataset).*

The following clinical pharmacology information request was sent to the Applicant on 9/24/2013 and the responses from the Applicant were received on 9/27/2013:

1. *Submit the bioanalytical study reports for the modified assay for trials REGARD and JVBW.*

Lillian H. Zhang, Ph.D. — 30-Sept-2013

Reviewing Clinical Pharmacologist — Date

Stacy Shord, Pharm.D. — 30-Sept-2013

Acting Team Leader — Date

Clinical Pharmacology - BLA Filing Memo

BLA:	**STN 125477/S0000-S0003 Original Submission IND: 11,856**
Product:	**CYRAMZA® (ramucirumab) Injection; solution for intravenous infusion in single-use vials**
Sponsor:	**Eli Lilly and Company**
Filing Date:	**October 7, 2013**
Reviewer:	**Lillian Zhang, Ph.D.**

Background and Mechanism of action: This rolling submission is the original BLA for Cyramza® (ramucirumab) for the treatment of patients with advanced gastric cancer or gastro-esophageal junction (GEJ) adenocarcinoma after prior chemotherapy. Ramucirumab is a human monoclonal receptor-targeted antibody with a molecular weight of 146.8 kilo Daltons. Ramucirumab specifically blocks VEGF Receptor 2 (VEGFR2), preventing the interaction of VEGFR2 with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits ligand-stimulated activation of VEGFR2 and its downstream signaling components, including p44/p42 mitogen-activated protein kinases, neutralizing ligand-induced proliferation and migration of human endothelial cells.

Formulation and Proposed Dosage: Cyramza is supplied as a sterile solution at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials for intravenous (IV) infusion following dilution. The recommended dose of Cyramza as a single-agent is 8 mg/kg every 2 weeks (q2w) administered as an IV infusion over approximately 60 minutes.

Clinical Studies:

The efficacy claim of ramucirumab in the proposed patient population was primarily supported by the data from a Phase 3 trial REGARD (Table 1).

TABLE 1. Summary of REGARD

Study No	Study description, population	Objectives	Treatments	No. of patients
REGARD (14T-IE-JVBD)	Phase 3 , randomized, double-blind, placebo-controlled Metastatic gastric or GEJ adenocarcinoma 2nd-line	**Primary:** • OS **Key Secondary:** • PFS (including 12-week PFS) • ORR • DOR • Safety • Immunogenicity	Ramucirumab: 8 mg/kg IV q2w + best supportive care (BSC) *versus* Placebo + BSC	Ramucirumab arm: N = 238 Control arm: N = 117

Efficacy

REGARD met its primary efficacy endpoint of overall survival (OS). Based on the applicant's analysis, OS was statistically significantly improved in patients receiving ramucirumab as compared with patients receiving placebo (hazard ratio [HR] 0.78; 95% CI: 0.6 to 1.0; p=0.047), corresponding to a 37% longer median survival in the ramucirumab arm (5.2 months versus 3.8 months). The key

secondary efficacy end point, progression-free survival (PFS), was statistically significantly improved in patients receiving ramucirumab as compared with patients receiving placebo (HR 0.48; 95% CI: 0.38 to 0.62; p<0.0001).

Safety

The rates of adverse events (AEs) in the ramucirumab arm were comparable to that in the placebo arm with a similar rate of Grade 3-5 AEs observed between the two arms. The most common adverse reactions observed in ramucirumab-treated patients at a rate ≥10% and at a higher rate than placebo are abdominal pain (28.85 vs. 27.8%), diarrhea (14.4% vs. 8.7%), and hypertension (16.1% vs. 7.8%).

Dose selection

Weekly doses of ramucirumab ranging from 2 to 16 mg/kg were evaluated in Phase 1 Study JVBM. A maximum tolerated dose (MTD) for weekly dosing was identified as 13 mg/kg. Preliminary efficacy was observed across a range of doses, including the 2 mg/kg dose. Pharmacokinetic (PK) results from Study JVBM showed nonlinear PK profiles between 2 and 8 mg/kg and linear PK profiles at doses of 8 mg/kg and above, suggesting saturation of the target-mediated (VEGFR2) clearance pathway. Every-2-week (6 to 10 mg/kg) and every-3-week (q3w, 15 to 20 mg/kg) dose regimens were evaluated in another dose-ranging trial (Study JVBN). All dose regimens were tolerated with no MTD identified and preliminary clinical efficacy was observed in some dose groups. Two dose regimens, 8 mg/kg q2w and 10 mg/kg q3w, were then selected for subsequent Phase 2 and Phase 3 studies. The applicant states that the ramucirumab dose of 8 mg/kg q2w was clinically efficacious and tolerated in the Phase 3 REGARD trial and approximately 95% patients in the PK subpopulation (N = 58) had trough concentrations (C_{trough}) above 18 µg/mL, the target C_{min} associated with antitumor activity in preclinical models.

Clinical studies with PK data

The clinical pharmacology package contains ramucirumab concentration data from 9 clinical studies (Table 2) with the primary PK data from REGARD and Study JVBW to support the submission and labeling.

Of the 9 trials, serum ramucirumab concentrations were determined either by the original enzyme-linked immunosorbent assay (ELISA) developed in-house by ImClone or the modified ELISA developed (b) (4) (b) (4) were used in the two assays. The applicant states that modifications were introduced during the assay transfer to optimize performance (b) (4). Cross-assay comparison was conducted using serum samples from Study JVBW in which discrepancies were observed (b) (4) between the results from the two assays. According to the applicant, due to the lack of comparability between the two assays and the known deficiencies in the original validation package (i.e. lack of specificity and selectivity assessment, lack of RE% editing/acceptance criteria for standard curves in the validation and sample analysis, and lack of intra – assay performance at lower limit of quantitation), the data from the two studies, REGARD and JVBW, using the modified bioanalytical assay, are deemed more reliable and provide the PK data to support the labeling. Data derived from the original bioanalytical assay will be used as supportive evidence and will be discussed on an individual study basis.

TABLE 2. Clinical studies containing PK data

Study	Population	Design	Ramucirumab Dose Regimen	PK Data	Bioanalytical Assay
REGARD (Pivotal)	Advanced gastric cancer	Phase 3	8 mg/kg q2w	Sparse, C_{trough} n=58	Modified
JVBW	Japanese advanced gastric cancer	Phase 1b, single-arm, with paclitaxel	8 mg/kg q2w	Intensive n=6	Modified
JVBM	Advanced solid tumors	Phase 1 dose escalation	2, 4, 6, 8, 10, 13, and 16 mg/kg qw	Intensive n=37	Original
JVBN	Advanced solid tumors	Phase 1 dose escalation	6, 8, 10 mg/kg q2w; 15 and 20 mg/kg q3w	Intensive n=25	Original
JVBI	Japanese advanced solid tumors	Phase 1 dose escalation	6 and 8 mg/kg q2w; or 10 mg/kg q3w	Intensive n=15	Original
JVBK	Advanced solid tumors	QT	10 mg/kg q3w	Intensive n=61	Original
JVBO	Melanoma	Phase 2	10 mg/kg q3w	Sparse n=17	Original
JVBP	RCC	Phase 2	8 mg/kg q2w	Sparse n=32	Original
JVBQ	HCC	Phase 2	8 mg/kg q2w	Sparse n=9	Original

The applicant derived PK parameters using data from Study JVBW and assessed the effect of age, gender, body weight, hepatic status, and renal function on the PK of ramucirumab using data from REGARD by multiple linear regression analysis.

Immunogenicity

Based on a pooled analysis of immunogenicity data from 10 studies (9 presented in Table as well as a Phase 2 Study JVBR in ovarian cancer), 33 (5.1%) of 551 patients had positive treatment-emergent (TE) anti-product antibodies (APA) and one (0.2%) was positive for neutralizing antibodies (NAb). In Study REGARD, six of 207 patients treated with ramucirumab (2.9%) developed TE-APAs and none developed NAb.

QTc Prolongation

The potential for ramucirumab to prolong QTc interval was assessed in patients with advanced solid tumors in Study JVBK. No clinically relevant changes in the mean QTc interval were detected.

Recommendation: The Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation 5 finds that BLA STN 125477 is fileable.

Signatures

Lillian Hua Zhang, Ph.D.	Stacy Shord, Ph.D.
Reviewer	Acting Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DOP2: CSO – **S Sickafuse**; MTL – **S Lemery**; MO – **S Casak**
DCP5: Reviewer – **LH Zhang; A**TL – **S Shord;** Deputy DD - **B Booth**
DD - **A Rahman**

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

/s/

LILLIAN H ZHANG
09/30/2013

STACY S SHORD
09/30/2013