

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125477Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 1254770/
Product Name: Cyramza

PMR/PMC Description: To submit the validation report for a sensitive and accurate assay for the detection of anti-ramucirumab binding antibodies in the presence of ramucirumab levels that are expected to be present in the serum or plasma at the time of patient sampling

PMR/PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: December 31, 2016
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Limited data were provided to demonstrate the anti-drug antibody assay was capable of detecting antibodies against ramucirumab at levels of drug expected to be present in serum samples at the time of collection. Given the safety profile observed in the clinical studies, the presence of anti-drug antibodies does not appear to be a significant safety issue.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Given the current validation data for the anti-drug antibody assay and the PK data from the clinical studies, it is not clear that the assay is capable of detection of anti-drug antibodies in serum samples that included drug at the higher end of the range identified. The study required under this PMR will provide assurance that anti-ramucirumab binding antibodies can be detected in patient samples characterized by the level of ramucirumab expected to be present at the time of sample collection.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Validation of a sensitive, accurate assay for the detection of anti-drug antibodies to ramucirumab or submission of additional data from the current partially validated assay to demonstrate sufficient sensitivity of the current assay.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Validation of a sensitive and accurate assay for detection of anti-ramucirumab binding antibodies.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
Clinical pharmacology study/Validation of an assay to assess immunogenicity
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

APPEARS THIS WAY ON ORIGINAL

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

/s/

MICHELE K DOUGHERTY
03/19/2014

CHANA FUCHS on behalf of SARAH B KENNETT
03/19/2014

JEFFERY L SUMMERS
03/20/2014

The goal of the study is to reliably determine the incidence of antibody development in patients receiving Cyramza and fully understand the impact of immunogenicity on safety, efficacy, and pharmacokinetics of ramucirumab.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

APPEARS THIS WAY ON ORIGINAL

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
03/18/2014

HONG ZHAO
03/18/2014
I concur.

JEFFERY L SUMMERS
03/19/2014

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125477/Cyramza
Product Name:

PMC #6 Description: To perform a shipping study to confirm validation of the commercial ramucirumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipment samples for product quality (purity by SEC, rSDS-PAGE, nrSDS-PAGE, IEX, (b)(4) and potency of ramucirumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 04/30/2015
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Shipping validation studies for drug product were performed (b)(4). The additional studies provide assurance of the safety and quality of the product when the finished commercial packaging configuration is shipped in the commercial shipping configuration.

2. Describe the particular review issue and the goal of the study.

Shipping validation studies did not evaluate the final commercial packaging and shipping configuration. In addition, product quality parameters were not directly assessed pre- and post-shipment but were inferred from release data. This study will provide validation of the commercial packaging and shipping configuration on product quality and the integrity of the commercial packaging system.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Assessment of product quality parameters and integrity of commercial packaging following shipment.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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

/s/

MICHELE K DOUGHERTY
03/14/2014

SARAH B KENNETT
03/14/2014

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125477/Cyramza
Product Name:

PMC #5 Description: To confirm product stability (b) (4)
using small scale studies. These studies will include testing (b) (4) for product quality (purity by (b) (4), and potency of ramucirumab).

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 11/30/2015
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

(b) (4) These studies provide additional assurance of the safety and quality of the product (b) (4)

2. Describe the particular review issue and the goal of the study.

(b) (4) In addition,
product quality parameters were not directly assessed
(b) (4)
(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
 Assay
 Sterility
 Potency
 Product delivery
 Drug substance characterization
 Intermediates characterization
 Impurity characterization
 Reformulation
 Manufacturing process issues
 Other

Describe the agreed-upon study:

Assessment of product quality (b) (4)
at small scale.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
 Are the objectives clear from the description of the PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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

/s/

MICHELE K DOUGHERTY
03/14/2014

SARAH B KENNETT
03/14/2014

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125477/Cyramza
Product Name:

PMC #3 Description: To re-evaluate ramucirumab drug substance lot release and stability specifications after (b)(4) lots have been manufactured using the commercial manufacturing process. Lilly will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 12/31/2015
Other: _____

PMC #4 Description: To re-evaluate ramucirumab drug product lot release and stability specifications after (b)(4) lots have been manufactured using the commercial manufacturing process. Lilly will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 12/31/2015
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The Drug Substance and Drug Product release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of ramucirumab for the initial marketed product. *Additional* manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

Cyramza Drug Substance and Drug Product release and shelf-life specifications are based on clinical and manufacturing experience *provided in the BLA and assessed* during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Statistical analysis of release data acquired following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

APPEARS THIS WAY ON ORIGINAL



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

/s/

MICHELE K DOUGHERTY
03/14/2014

SARAH B KENNETT
03/14/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 4, 2014

To: Sharon Sickafuse
Regulatory Project Manager
Division of Oncology Products 2

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **BLA# 125477**
CYRAMZA (ramucirumab) injection, for intravenous infusion
OPDP Review of Prescribing Information (PI), carton and
container labeling

Thank you for the opportunity to review and provide our comment on the proposed labeling for CYRAMZA (ramucirumab) injection, for intravenous infusion (Cyramza).

OPDP has reviewed the proposed PI for Cyramza (FDA version emailed on February 25, 2014) and our comments are incorporated therein (e.g., OPDP QVT. . .). We have no comment on the proposed carton and container labeling for Cyramza.

If you have any questions, please contact Quynh-Van Tran at (301) 796-0185, or quynh-van.tran@fda.hhs.gov.

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

QUYNH-VAN TRAN
03/04/2014



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Division of Monoclonal Antibodies
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date: January 23, 2013

Reviewer: Michele K. Dougherty, Ph.D.
Division of Monoclonal Antibodies

Through: Sarah Kennett, Ph.D.
Review Chief
Division of Monoclonal Antibodies

Kathleen A. Clouse, Ph.D.
Director
Division of Monoclonal Antibodies

Application: BLA 125477/0

Product: Cyramza (ramucirumab)

Applicant: Eli Lilly and Company

Submission Date(s): August 23, 2013

Executive Summary

The carton and container labels for Cyramza (ramucirumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 36. Labeling deficiencies initially identified were communicated to the sponsor. The sponsor agreed to revise the labels according to the recommendations discussed below and to provide the revised carton and container labels to the BLA by February 7, 2014. Comments are listed in the conclusions section. Pending receipt of the revised labels, the draft carton and container labels submitted on August 23, 2013, to be updated as requested, are acceptable

Background and Summary Description

STN 125477/0 for ramucirumab is an original Biologic License Application (BLA) indicated for the treatment of patients with advanced gastric cancer or gastro-esophageal

junction adenocarcinoma, as a single-agent after prior chemotherapy. The product is supplied as a 500 mg/ 50 ml and 100 mg/ 10 ml solution in a single-use vial.

Materials Reviewed:

Cyramza[®] (ramucirumab) Container Labels

500 mg vial and 100 mg vial

Cyramza[®] (ramucirumab) Carton Labels

500 mg vial carton and 100 mg vial carton

Start of Sponsor Material

Vial labels



(b) (4)

End of Sponsor Material

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name (established name) of the product, ramucirumab, is displayed along with the (proprietary name), Trade name, Cyramza[®]. *This conforms to the regulation.*

(2) The name, address, and license number of manufacturer are provided on the 500 mg and 100 mg container label. *This conforms to the regulation.*

(3) The lot number or other lot identification is provided on the 500 mg and 100 mg container label. *This conforms to the regulation. Note DMEPA recommendation to revise (b)(4) to “lot no.”*

(4) The expiration date is provided on the 500 mg and 100 mg container label. *This conforms to the regulation.*

(5) The recommended individual dose, for multiple dose containers. *The product is supplied as a single-use only vial, the regulation does not apply.*

(6) The statement: “Rx only” for prescription biologicals is provided on the 500 mg and 100mg container label. *This conforms to the regulation.*

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. *No mediation guide is supplied with the product. The regulation does not apply.*

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Each container is enclosed in a package (carton). This regulation does not apply.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the

proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *Each container bears a full label. The regulation does not apply.*

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Each container bears a full label. The regulation does not apply.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – *The sponsor provided pictures of the labeled 10mg and 50mg vials. The labels are designed and affixed in a manner that allows for adequate visual inspection. Conforms to the regulation.*

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; The National Drug Code (NDC) number is located at the top of the label. Per 21 CFR 207.35, the last five digits of the NDC number represent the Product-Package Code configuration in either a 3-2 or 4-1 configuration. The NDC code is listed as, “NDC 0002-XXXX-XX” in a 3-2 format. *Conforms to the regulation.*

C. 21 CFR 201.5 Drugs; adequate directions for use: A reference to the prescribing information is stated on each label as, “See package insert for full prescribing information for preparation and administration” is found on the 500 mg and the 100 mg container label. *Conforms to the regulation.*

D. 21 CFR 201.6 Drugs; misleading statements: The names that appear on the labels are the trade name (proprietary name), Cyramza[®] and the proper name (established name), ramucirumab.

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence]: The type print of the proper name (established name) in letters are at least half as large as the letters comprising the Trade name (proprietary name). The established name shall have a prominence commensurate with the prominence of the Trade name (proprietary name). *Conforms to the regulation.*

F. 21 CFR 201.15 Drugs; prominence of required label statements: *Conforms to regulation. Note DMEPA recommendation to revise certain label statements.*

G. 21 CFR 201.17 Drugs; location of expiration date: The expiration date appears with the lot/control number on the 500 mg and the 100 mg container label. *This conforms to the regulation.*

H. 21 CFR 201.25 Bar code: A bar code is found on the 500 mg and the 100 mg container label. *This conforms to the regulation.*

I. 21 CFR 201.50 Statement of identity: The proper name (established name), ramucirumab is stated on the label with the trade name (proprietary name), CYRAMZA. *This conforms to the regulation.*

J. 21 CFR 201.51 Declaration of net quantity of contents: The net quantity is declared, “100 mg/10 mL and 500 mg/50 mL” immediately followed by “(10 mg/mL)” on the vial label. *Conforms to the regulation. Note DMEPA recommendation to revise the presentation of the net quantity of contents to assure that all components are of similar font size and prominence.*

K. 21 CFR 201.55 Statement of dosage: A statement of dosage or a reference to a statement of dosage appears on the vial label. *This conforms to the regulation.*

L. 21 CFR 201.100 Prescription drugs for human use: A statement of dosage or a reference to a statement of dosage appears on the vial label. *This conforms to the regulation.*

Start of Sponsor Material

100 mg carton label

1 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

500 mg carton label

(b) (4)



End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label

- a) The proper name of the product (established name) of the product ramucirumab is displayed along with the proprietary name CYRAMZA[®] on the 100 mg and 500 mg carton labels. *This conforms to the regulation.*

- b) The name, addresses, and license number of manufacturer is provided on the 100 mg and 500 mg carton labels. *This conforms to the regulation.*

- c) The lot number or other lot identification is provided on the carton labels. *This conforms to the regulation. Note the DMEPA recommendation to replace “^{(b) (4)}” with “lot no.”*
- d) The expiration date is displayed along with the lot/control number on the container label. *This conforms to the regulation.*
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor: The words “no preservative” is provided on both the 100 mg and the 500 mg carton label. *This conforms to the regulation.*
- f) The number of containers, if more than one. *Not applicable*
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable. The amount of product is expressed as either 100 mg/10 mL or 500 mg/50 mL on the appropriate carton label. *This conforms to the regulation.*
- h) The recommended storage temperature. The statement “**Storage:** Refrigerated at 2° - 8°C (36° to 46°F)” is found on each container label. The statement “Protect from light.” is displayed on each carton label, separately from the storage statement. *This conforms to the regulation; however, the preference may be to locate the “protect from light” statement to appear with the storage statement. Note the DMEPA recommendation to include the storage statement on the principal display panel.*
- i) The words “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product are provided on the each carton label. *This conforms to the regulation.*
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container. *Not applicable.*
- k) The route of administration recommended, or reference to such directions in and enclosed circular. The route of administration is displayed as ^{(b) (4)} for Intravenous Infusion.” *This conforms to the regulation. Note the DMEPA*

recommendation to remove the word (b) (4)” OBP concurs with the recommendation.

- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information. *Not applicable*
- m) The type and calculated amount of antibiotics added during manufacture. *Not applicable.*
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information. A reference to the package insert is listed on each carton. *This conforms to the regulation.*
- o) The adjuvant, if present. *Not applicable.*
- p) The source of the product when a factor in safe administration. *Not applicable*
- q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. *Not applicable.*
- r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency.” The statement is found on each carton label. *This conforms to the regulation.*
- s) The statement “Rx only” for prescription biologicals. The statement is present on each carton label. *This conforms to the regulation.*
 - Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. *Not applicable.*

B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)*]

- a) Position. The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label.

b) Prominence. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.

c) Legible type. All items required to be on the container label and package label shall be in legible type. "Legible type" is type of a size and character which can be read with ease when held in a good light and with normal vision.

The product is a specified biologic and is exempt; the regulation does not apply.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown. *Not applicable.*

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. *Not applicable.*

E. 21 CFR 610.67 Bar code label requirements

Biological products must comply with the bar code requirements at §201.25 of this chapter. A barcode is found on each carton label. *This conforms to the regulation.*

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35]. The NDC code is found on the principal display panel at the top of the label on each carton label. *This conforms to the specification.*

G. 21 CFR 201.5 Drugs; adequate directions for use. The label states "**Dosage:** See package insert for full prescribing information and instructions for preparation and administration." *This conforms to the regulation.*

H. 21 CFR 201.6 Drugs; misleading statements. The trade name and established name are provided on each container label. *This conforms to the regulation.*

- I. 21 CFR 201.10 Drugs; statement of ingredients. The established name shall have a prominence commensurate with the prominence of the Trade name (proprietary name). *This appears to conform to the regulation.*
- J. 21 CFR 201.15 Drugs; prominence of required label statements. *This conforms to the regulations.*
- K. 21 CFR 201.17 Drugs; location of expiration date, it appears with the lot number. *This conforms to the regulation.*
- L. 21 CFR 201.25 Bar code label requirements. *This conforms to the regulation.*
- M. 21 CFR 201.50 Statement of identity. The proper name (established name), ramucirumab, is stated on the label with the trade name (proprietary name), Cyramza. *This conforms to the regulation.*
- N. 21 CFR 201.51 Declaration of net quantity of contents. The amount of product is expressed as either 100 mg/10 mL or 500 mg/50 mL on the appropriate carton label. *This conforms to the regulation.*
- O. 21 CFR 201.55 Statement of dosage. The label states “**Dosage:** See package insert for full prescribing information and instructions for preparation and administration.” *This conforms to the regulation.*
- P. 21 CFR 201.100 Prescription drugs for human use. *This conforms to the regulation.*

Conclusions

The labels submitted on August 23, 2013 meet regulatory requirements and appear to be acceptable. However, there are CDER preferences that have been recommended by the Division of Medication Error and Prevention. In addition, the DMEPA safety assessor deferred to DMA on whether ramucirumab should be labeled [REDACTED] (b) (4) [REDACTED] on the container and carton label. OBP has no objection to the statement as provided. The following clarifications were requested.

1. Container: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60.
2. Per USP 36/NF 31, <1091> Labeling of Inactive Ingredients, please list the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount).

Reviewer comment

The sponsor committed to revise the container and carton labels to list the names of inactive ingredients in alphabetical order and according the format specified above. Revised labels will be submitted to the BLA. Pending receipt of the revised carton and container labels, the response is acceptable.

APPEARS THIS WAY ON ORIGINAL

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

/s/

MICHELE K DOUGHERTY
01/23/2014

SARAH B KENNETT
01/23/2014

KATHLEEN A CLOUSE STREBEL
01/23/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, and Packaging Review

Date: January 21, 2014

Reviewer: Jibril Abdus-Samad, PharmD
Division of Medication Error Prevention and Analysis

Acting Team Leader: Chi-Ming Tu, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Cyramza (Ramucirumab)
Injection
100 mg/10 mL and 500 mg/50 mL

Application Type/Number: BLA 125477

Applicant: Eli Lilly and Company

OSE RCM #: 2013-1963

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	INTRODUCTION	1
1.1	Regulatory History	1
1.2	Product Information	1
2	METHODS AND MATERIALS REVIEWED	2
2.1	Literature Search	2
2.2	Labels and Labeling	2
2.3	Previously Completed Reviews	2
3	MEDICATION ERROR RISK ASSESSMENT	2
3.1	Integrated Summary of Medication Error Risk Assessment	2
4	CONCLUSIONS AND RECOMMENDATIONS	4
4.1	Comments to the Division	4
4.2	Comments to the Applicants	5
	Appendices	7

1 INTRODUCTION

This review evaluates the proposed container label, carton labeling, and prescribing information for Cyramza (Ramucirumab) BLA 125477 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted the container label, carton labeling, and prescribing information for Cyramza on August 23, 2013. On October 30, 2013, the Applicant submitted updated prescribing information.

1.2 PRODUCT INFORMATION

The following product information is provided in the August 23, 2013 submission.

- Active Ingredient: Ramucirumab
- Indication of Use: treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy.
- Route of Administration: Intravenous infusion
- Dosage Form: Injection
- Strength: 100 mg/10 mL and 500 mg/50 mL
- Dose and Frequency:

Usual Dose: 8 mg/kg every 2 weeks administered as an intravenous infusion over approximately 60 minutes (b) (4).

Dose Modification:

- Infusion Rate Reaction: reduce infusion rate by 50%
- Proteinuria:
 - Temporarily discontinue ramucirumab if urine protein level greater than or equal to 2 g/24 hours):.
 - 6 mg/kg once the urine protein level returns to normal
 - 5 mg/kg if a urine protein level greater than or equal to 2 g/24 hours reoccurs

Patients should continue CYRAMZA treatment until progression of the underlying disease or until unacceptable toxicity.

- How Supplied: 100 mg/10 mL and 500 mg/50 mL single-dose vials
- Storage: Refrigerate at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light. Do not freeze or shake the vial.
- Container and Closure System: Glass vials.

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Cyramza labels, labeling, and prescribing information submitted by the Applicant.

2.1 LITERATURE SEARCH

We searched PubMed on November 18, 2013 for medication error concerns with Ramucirumab, which yielded no publications.

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 23, 2013 (Appendix B)
- Carton Labeling submitted August 23, 2013 (Appendix C)
- Prescribing Information submitted October 30, 2013

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously completed a proprietary name review for Cyramza (OSE Review 2013-1964). There were no labeling concerns discussed in this review.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the risk assessment of the Cyramza product design as well as the associated label and labeling.

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

3.1.1 Administration Instructions

The instructions for rate of administration [(infuse over approximately 60 minutes ((b) (4) are ambiguous and prone to wrong rate of administration errors. (b) (4)

(b) (4) It is unclear whether the recommended (b) (4)

Additionally, the prescribing information recommends reducing the infusion rate by 50% for patients with Grade 1 or 2 infusion rate reactions (IRR). It is unclear whether (b) (4)

. We recommend the

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Applicant simplify the administration instructions to a specific time period (xx minutes) or rate of administration (xx mg/min) rather than providing both options.

Table 1: Cyramza Infusion Time

Cyramza Dose and Infusion Time
(b) (4)

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container and carton labeling may be improved to promote the safe use of the product because there is critical information missing from the principal display panel such as the need to dilute the product prior to use and to store in the refrigerator. Additionally, the prescribing information may be improved to facilitate practitioners in locating instructions for administration and dose modifications. Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA:

If you have further questions or need clarifications, please contact Kevin Wright, OSE project manager, at 301-796-3621.

4.1 COMMENTS TO THE DIVISION

- A. We note the side panels of the container label and carton labeling state (b) (4) We defer to the Division of Monoclonal Antibodies (DMA) to determine whether it is appropriate to label Cyramza a (b) (4).
- B. DMEPA's recommendations to the Prescribing Information are in Appendix D.

APPEARS THIS WAY ON ORIGINAL

4.2 COMMENTS TO THE APPLICANTS

- A. Carton Labeling - 100 mg/10 mL and 500 mg/50 mL
1. Delete “ (b) (4) ” from the top right-side of the principal display panel.
 2. Revise the statement, “ (b) (4) ”, to read, “Single-Dose Vial”. Additionally, relocate this statement from the top of the principal display panel to the lower portion to appear directly before the statement, “Discard unused portion”.
 3. Relocate the route of administration, “For Intravenous Infusion”, to appear below the strength statement.
 4. Delete the word (b) (4) from the dosage form statement. Thus, the dosage form should appear as “Injection”.
 5. Revise the strength presentation such that the numerals and letters share the identical font size and commensurate prominence. For example, **100 mg/10 mL** should read **100 mg/10 mL**.
 6. Increase the prominence of the concentration, (10 mg/mL), while maintaining the strength per total volume (**100 mg/10 mL** and **500 mg/50 mL**) should be the primary and prominent expression on the label.
 7. Add a statement to the principal display panel to alert practitioners to refrigerate Cyramza.
 8. Revise the statement, (b) (4) on the side panel to read, “Must Dilute Prior to Use”. Additionally, relocate this statement from the side panel to the principal display panel. Thus the principal display panel should appear in the following order:

Cyramza
Ramucirumab
Injection
XX mg/XX mL
(xx mg/mL)

For Intravenous Infusion Only
Must Dilute Prior to Use
Single-Dose Vial – Discard Unused Portion
Store in Refrigerator
 9. To create space on the other prominent information relocate the statement, “No US Standard of potency”, to the side panel and decrease the size of the Lilly logo.
 10. Revise the statement “ (b) (4) ” to read “Lot” as this is customary on US drug labels.
- B. Container Label - 100 mg/10 mL and 500 mg/50 mL
1. See comments A1 through A6.

2. Revise the statement, [REDACTED]^{(b) (4)}, on the side panel to read, “Must Dilute Prior to Use”. Additionally, relocate this statement from the side panel to the principal display panel. Thus, the principal display panel should appear in the following order:

Cyramza
Ramucirumab
Injection
XX mg/XX mL
(xx mg/mL)
For Intravenous Infusion Only
Must Dilute Prior to Use
Single-Dose Vial – Discard Unused Portion

3. See comments A9 and A10.

APPEARS THIS WAY ON ORIGINAL

APPENDICES

Appendix A: Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JIBRIL ABDUS-SAMAD
01/21/2014

CHI-MING TU
01/21/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 10, 2014

TO: Sharon Sickafuse, Regulatory Health Project Manager
Sandra Casak, M.D., Medical Officer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125477
APPLICANT: Eli Lilly and Company, Inc.

DRUG: Ramucirumab (Cyramza)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION(S): For the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy.

CONSULTATION REQUEST DATE: June 3, 2013 (Final Rolling BLA Component Received August 23, 2013)
INSPECTION SUMMARY GOAL DATE: January 23, 2014
DIVISION ACTION GOAL DATE: April 23, 2014
PDUFA DATE: April 23, 2014

I. BACKGROUND:

Eli Lilly and Company, seeks approval to market ramucirumab as a single agent for the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy. Ramucirumab is a human receptor-targeted antibody that specifically blocks vascular endothelial growth factor (VEGF) receptor 2. Therefore, ramucirumab inhibits ligand stimulated activation of VEGF receptor 2, and its downstream signaling components, resulting in the down-regulation of ligand-induced mitogenesis of human endothelial cells.

The application is supported by safety and efficacy results of the pivotal Phase 3 study IMCL CP12-0715/14T-IE-JVBD (REGARD), entitled, “A Phase 3, Randomized, Double-Blinded Study of IMC-1121B and Best Supportive Care (BSC) Versus Placebo and BSC in the Treatment of Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy”.

The REGARD study was a Phase 3, randomized, double-blinded study in which patients with metastatic gastric or GEJ adenocarcinoma received either ramucirumab at a dose of 8 mg/kg, administered as an intravenous infusion every 2 weeks (that is 1 cycle) plus BSC or an equivalent volume of ramucirumab placebo plus BSC, in a 2:1 ratio, respectively. There was no planned maximum duration of treatment. Patients were permitted to receive treatment according to the study protocol until there was evidence of progressive disease (PD), unacceptable toxicity, withdrawal of consent, or until other withdrawal criteria were met.

Approximately 348 subjects were planned, and 355 subjects were randomized to study treatment (236 ramucirumab; 117 placebo) at 119 sites in 29 countries. This study was conducted under IND 11856.

Three clinical sites were chosen for inspection: Site 852 (Dr. Lucas Vieira dos Santos, Sao Paulo, Brazil), Site 234 (Dr. Jae Yong Cho, Seoul, S. Korea), and Site 410 (Dr. Jaffer Ajani, Houston, Texas), based on enrollment of large numbers of study subjects and a relatively high rate of treatment responders. The study sponsor, Eli Lilly and Company, Inc., was also inspected because this application is for a new molecular entity.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: Cristina Abdalla Khatia (former: Lucas Vieira dos Santos) Hospital da Cancer de Barretos Rua Antenor Duarte Vilela 1331, Barretos Sao Paulo 14784-400 Brazil	Protocol: IMCL CP12-0715/14T-IE-JVBD (REGARD) Site Number: 852 Number of Subjects: 8	October 28-31, 2013	Pending Interim classification: NAI
CI#2: Jae Yong Cho Gangnam Severance Hospital 712 Eonju-Ro Gangnam-Gu Seoul 135 720 South Korea	Protocol: IMCL CP12-0715/14T-IE-JVBD (REGARD) Site Number: 234 Number of Subjects: 10	October 21-24, 2013	Pending Interim classification: NAI
CI#3: Jaffer A. Ajani University of Texas MD Anderson Cancer Center Unit 426 1515 Holcombe Blvd Houston, TX 77030	Protocol: IMCL CP12-0715/14T-IE-JVBD (REGARD) Site Number: 410 Number of Subjects: 13	September 25, 2013 – October 4, 2013	Pending Interim classification: NAI
Sponsor: Eli Lilly and Company, Inc. 33 ImClone Drive Branchburg, New Jersey 08876	Protocol: IMCL CP12-0715/14T-IE-JVBD (REGARD) Site Numbers/Subjects: 852, 234 and 410/All	December 4-12, 2013	Pending Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. CI#1: – Cristina Abdalla Khatia, M.D.

Hospital da Cancer de Barretos
Rua Antenor Duarte Vilela
1331, Barretos
Sao Paulo 14784-400
Brazil

- a. What was inspected:** The site screened 13 subjects, 8 subjects were enrolled, and 1 completed the study. The study records of all 13 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to BLA 125477, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability and monitoring reports.
- b. General observations/commentary:** The documented clinical investigator, Lucas Viera dos Santos, is no longer with the firm. Dr. Vieira dos Santos relocated to another city on January 3rd, 2013. The new clinical investigator for this location is Dr. Cristina Abdalla Khatia. Dr. Khatia served as a sub-investigator for Study IMCL CP12-0715/14T-IE-JVBD (REGARD) at this site and was available during the current inspection. Generally, the investigator's execution of the protocol was found to be adequate. Per the protocol, the primary efficacy endpoint for the study was overall survival. The source records audited at this site supported the site investigator-reported efficacy outcome measure. There was no evidence of underreporting of adverse events.

Eight subjects were enrolled in the study, six of whom were discontinued due to disease progression during the course of the study. One subject completed the study and one subject died less than 2 months after enrollment. There were a few minor inspectional observations, discussed with the site at the close out meeting. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data for Dr. Khatia's site, associated with Study IMCL CP12-0715/14T-IE-JVBD (REGARD) submitted to the Agency in support of BLA 125477, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI#2: – Jae Yong Cho

Gangnam Severance Hospital
712 Eonju-Ro Gangnam-Gu
Seoul 135 720
South Korea

- a. What was inspected:** The site screened 12 subjects, 10 subjects were enrolled, and 5 completed the study. All study records of all subjects were audited. The record audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to eCRFs and data listings submitted to BLA 125477, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability and monitoring reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Per the protocol, the primary efficacy endpoint for the study was overall survival. The source records audited at this site supported the site investigator-reported efficacy outcome measure. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. There were a few minor inspectional observations discussed with the site at the close out meeting. No Form FDA 483 was issued.
- c. Assessment of data integrity:** The data for Dr. Cho's site, associated with Study IMCL CP12-0715/14T-IE-JVBD (REGARD) submitted to the Agency in support of BLA 125477, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. CI#3: – Jaffer A. Ajani

University of Texas
MD Anderson Cancer Center
Unit 426
1515 Holcombe Blvd
Houston, TX 77030

- a. What was inspected:** The site screened 16 subjects, 3 subjects were screen failures, and 13 subjects were enrolled. Of those 13 enrolled subjects at least 10 subjects who received treatment were taken off study after two doses due to progressive disease. Portions of the study records of all subjects were audited. The record audit was conducted in accordance with the clinical investigator

compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to BLA 125477, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator assessed all informed consent documents, patient histories, laboratory results, drug accountability, concomitant medications, sponsor correspondence, progress notes and tumor measurements.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. Per the protocol, the primary efficacy endpoint for the study was overall survival. The source records audited at this site supported the site investigator-reported efficacy outcome measure. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. No Form FDA 483 was issued.
- c. Assessment of data integrity:** The data for Dr. Ajani's site, associated with Study IMCL CP12-0715/14T-IE-JVBD (REGARD) submitted to the Agency in support of BLA 125477, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

4. Sponsor: – Eli Lilly and Company, Inc.
33 ImClone Drive
Branchburg, New Jersey
08876

- a. What was inspected:** The sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection focused on adherence to protocol, and review of the firm's SOPs, monitoring reports and actions related to monitoring deficiencies. Ethics Committee/IRB approvals, completed Form FDA 1572s, and communications with the sites were also generally covered. The FDA field investigator specifically audited subject records from three clinical study sites, and assessed the AEs and primary efficacy endpoints. The three audited sites were the those sites listed in the table above; Site 852 (Dr. Cristina Abdalla Khatia; formerly Dr. Lucas Vieira dos Santos), Site 234 (Dr. Jae Yong Cho), and Site 410 (Dr. Jaffer A. Ajani).
- b. General observations/commentary:** Records and procedures were clear, and generally well organized. There were no discrepancies between audited subject CRFs and the data listings submitted to BLA 125477; primary endpoints and

SAEs from the CRFs appear to have been correctly reported in the CSR. There was no evidence of under-reporting of AEs/SAEs.

Overall the sponsor maintained adequate oversight of study conduct. Site monitoring appeared adequate. General monitoring procedures/oversight appeared to capture issues which were corrected during each monitoring visit or followed up appropriately at subsequent visits. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data generated at this site, as it pertains to Study IMCL CP12-0715/14T-IE-JVBD (REGARD) were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this sponsor submitted to the Agency in support of BLA 125477 appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Cristina Abdalla Khatia (Site 852), Dr. Jae Yong Cho (Site 234), Dr. Jaffer Ajani (Site 410) and the Sponsor, Eli Lilly and Company Inc., the Study IMCL CP12-0715/14T-IE-JVBD (REGARD) data appear reliable based on available information. The preliminary classification for clinical investigators Dr. Cristina Abdalla Khatia, Dr. Jae Yong Cho, Dr. Jaffer Ajani, and for the sponsor, Eli Lilly and Company Inc., is No Action Indicated (NAI).

The record audit of subject records at these clinical sites included comparison of source documentation to CRFs and data listings submitted to BLA 125477, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, the primary efficacy endpoint, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigators also assessed informed consent documents, test article accountability, and monitoring reports. Per the protocol, the primary efficacy endpoint was overall survival. The primary efficacy outcome measures reported in the application were verified with the source records generated at the sites. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no major discrepancies.

The inspection focused on adherence to the protocol, and review of the firm's SOPs, monitoring reports and actions related to monitoring deficiencies. Comparison of CRFs and the key data listings submitted to BLA 125477 found no discrepancies. Ethics Committee/IRB approvals, completed Form FDA 1572s, and communications with the sites were also generally covered.

Minor regulatory violations were noted by the FDA field investigators in the personal communications during inspection of each of the clinical sites audited. Based upon available

information they are unlikely to importantly impact primary safety and efficacy analyses. The overall data for Study IMCL CP12-0715/14T-IE-JVBD (REGARD) in support of this application may be considered reliable based on available information.

Note: The observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{ See appended electronic signature page }

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

LAUREN C IACONO-CONNORS
01/10/2014

JANICE K POHLMAN
01/10/2014

KASSA AYALEW
01/16/2014

**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: November 7, 2013

From: Candace Gomez-Broughton, Ph.D., OC/OMPQ/DGMP/BMAB
Michele Dougherty, Ph.D., OPS/OBP/DMA

To: BLA File, STN 125477/0

Through: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMP/BMAB

Subject: Biological License Application (BLA)

Applicant: Eli Lilly and Company

Facility: Eli Lilly and Company Indianapolis, IN 46285, USA (FEI # 1819470)

Product: Cyramza (ramucirumab)

Dosage: sterile solution for intravenous injection in glass vials at 100 mg/10ml or 500mg/50ml concentrations

Indication: For the treatment of patients with advanced gastric cancer of gastro-esophageal junction adenocarcinoma after prior chemotherapy

Waiver Recommendation

Based on the compliance history of the firm, the current GMP status, and the fact that Eli Lilly and Co. has been approved to manufacture multiple licensed products using the same manufacturing process, we recommend that the pre-approval inspection of the Eli Lilly and Co. drug product manufacturing facility in Indianapolis, IN 46285, USA (FEI # 1819470) be waived for STN 125477/0 (submission dated 23 August 2013).

Summary

BLA 125477/0 is for ramucirumab (proposed name: Cyramza®) which is indicated for patients with advanced gastric cancer or gastric-esophageal junction adenocarcinoma after prior chemotherapy. Ramucirumab drug product is supplied as a sterile liquid for intravenous injection in Type I glass vials. Ramucirumab will be available in two presentations: 100mg/10 ml and 500mg/50 ml.

The drug substance is a recombinant DNA-derived monoclonal antibody that targets the extracellular domain of the kinase insert domain receptor (KDR, also known as human vascular endothelial growth factor receptor-2 or VEGFR-2). (b) (4)

Facility Information

(b) (4)

Supporting Information

The following information is provided in support of waiving the pre-approval inspection:

1.

2.

(b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

CANDACE GOMEZ-BROUGHTON
11/21/2013

PATRICIA F HUGHES TROOST
11/21/2013

MICHELE K DOUGHERTY
11/21/2013

MARJORIE A SHAPIRO on behalf of KATHLEEN A CLOUSE STREBEL
11/26/2013

JOSEPH D DOLESKI
11/26/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: BLA 125477/0

Application Type: New BLA

Name of Drug: Cyramza (ramucirumab), 100 mg/10 mL and 500 mg/50 mL

Applicant: Eli Lilly and Co.

Submission Date: August 23, 2013

Receipt Date: August 23, 2013

1.0 Regulatory History and Applicant's Main Proposals

Treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma, as a single-agent after prior chemotherapy

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in filing letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by October 31, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment: Delete white space.

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

NO

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: Delete white space.

N/A

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- N/A** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- NO** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.
Comment: *Need bulleted subheadings.*

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.
Comment:
- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.
Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.
Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):
If a product **does not** have FDA-approved patient labeling:
- “**See 17 for PATIENT COUNSELING INFORMATION**”
- If a product **has** FDA-approved patient labeling:
- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
 - “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”
- Comment:**

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.
Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.
Comment:
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.
Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- NO** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment: *Statement is there but the words "full", "prescribing", and "information" need to be capitalized.*

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use

Selected Requirements of Prescribing Information (SRPI)

8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

Selected Requirements of Prescribing Information (SRPI)

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

SHARON K SICKAFUSE
10/16/2013

MONICA L HUGHES
10/16/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125477	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Cyramza Established/Proper Name: ramucirumab Dosage Form: injection, solution for intravenous infusion Strengths: 100 mg/10mL, 500 mg/50mL		
Applicant: Eli Lilly and Company Agent for Applicant (if applicable):		
Date of Application: August 23, 2013 Date of Receipt: August 23, 2013 Date clock started after UN:		
PDUFA Goal Date: April 23, 2014		Action Goal Date (if different):
Filing Date: October 22, 2013		Date of Filing Meeting: October 7, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Treatment of advanced gastric cancer and gastroesophageal junction adenocarcinoma after prior chemotherapy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 11856				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p> <p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan designation granted

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT consult request: 6-20-2013

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, specify consult(s) and date(s) sent:</i>				OSI consult request: 6-3-2013
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 5-28-2008	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 1-17-2013 – clinical, 1-23-2013 - CMC	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10-7-2013

BLA/NDA/Supp #: 125477/0

PROPRIETARY NAME: Cyramza

ESTABLISHED/PROPER NAME: ramcirumab

DOSAGE FORM/STRENGTH: 100 mg/10mL, 500 mg/50mL

APPLICANT: Eli Lilly and Company

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of advanced gastric cancer and gastroesophageal junction adenocarcinoma after prior chemotherapy

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sharon Sickafuse	Y
	CPMS/TL:	Monica Hughes Karen Jones	Y Y
Cross-Discipline Team Leader (CDTL)	Steven Lemery		Y
Clinical	Reviewer:	Sandra Casak	Y
	TL:	Steven Lemery	Y
Clinical Pharmacology	Reviewer:	Stacy Shord for Lillian Zhang	Y
	TL:	Stacy Shord for Hong Zhao	Y
Biostatistics	Reviewer:	Hui Zhang	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sachia Khasar	Y
	TL:	Whitney Helms	Y
Immunogenicity (assay/assay validation) (for BLAs/BLA efficacy supplements)	Reviewer:	Michele Dougherty	Y

Product Quality (CMC)	Reviewer:	Michele Dougherty	Y
	TL:	Sarah Kennett	Y
Quality Microbiology Review	Reviewer:	Kalavati Survarna - DS Candice Gomez-Broughton – DP	Y Y
	TL:	Patricia Hughes	N
CMC Labeling Review	Reviewer:	Lindsey Hennessey	Y
	TL:		
Facility Review/Inspection	Reviewer:	Kalavati Survarna - DS Candice Gomez-Broughton – DP	Y Y
	TL:	Patricia Hughes	N
OSE/DMEPA (proprietary name)	Reviewer:	Jabril Abdus-Samad	Y
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:	Suzanne Robottom	Y
	TL:	Cynthia LaCivita	N
Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connors	Y
	TL:		
OPDP	Reviewer:	Quynh-Van Tran	N
Other attendees	Pat Keegan, DOP2 Director Richard Pazdur, OHOP Director Lola Fashoyin-Aje, clinical reviewer Sue Kang, OSE RPM Mimi Biable, RPM Sarah Dorff, Genomics and Targeted Therapeutics Tracy Salaam, OSE/DPVII team leader Afrouz Nayernama, OSE/DPVII reviewier		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues: 	<input checked="" type="checkbox"/> Not Applicable

<ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> ● Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> ● Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p> <ol style="list-style-type: none"> 1. Please provide a statement whether all sites described in the Audit Summary for Study 14T-IE-JVBD conducted the study according to good clinical practices. 2. Please submit the following to the original BLA in regards to the top-line results from the RAINBOW trial: <ol style="list-style-type: none"> a. Datasets that allow the Agency to reproduce efficacy findings for <i>overall survival</i> in the ITT population and in relevant subgroups. b. A copy of the pre-Phase 3 meeting minutes in reference to the RAINBOW trial. c. Copies of the protocol, all amendments, and the statistical analysis plan. d. <i>Brief</i> report describing the major efficacy findings of the primary and secondary endpoints and overall survival estimates in relevant subgroups. 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p>e. Safety information, <i>only</i> if the information would strengthen the Warnings and Precautions section of the label (i.e., indicate increased severity of a specific adverse reaction or include a new adverse reaction) and/or that would change the risk/benefit assessment of ramucirumab.</p>	
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease as Lilly will submit data from a second study that conforms the overall survival effect observed in the REGARD trial.
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

Comments:	<input type="checkbox"/> REFUSE TO FILE
• Clinical pharmacology study site(s) inspections(s) needed?	<input type="checkbox"/> Review issues for 74-day letter
	<input type="checkbox"/> YES
	<input checked="" type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable
	<input checked="" type="checkbox"/> FILE
	<input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable
	<input checked="" type="checkbox"/> FILE
	<input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	<input type="checkbox"/> Not Applicable
	<input checked="" type="checkbox"/> FILE
	<input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter

PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable
	<input checked="" type="checkbox"/> FILE
	<input type="checkbox"/> REFUSE TO FILE
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
1.  (b) (4)	

<p>2. Provide the reports for all safety testing performed on the ramucirumab MCB and working cell banks (WCBs).</p> <p>3. Information provided regarding testing performed on the cells cultured to the limit of in vitro age in section 3.2.S.2.3.2.7 and table 3.2.S.2.3.2.2.7-1 do not describe testing to confirm the authenticity of the cells; per Points To Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997), end of production cells should be tested once to confirm authenticity.</p> <p>4. The source or manufacturer and representative certificates of analysis for (b) (4)</p> <p>3.2.S.2.3 Control of Materials. Provide the information for the (b) (4) used in the manufacture of ramucirumab to the BLA.</p> <p>5. (b) (4)</p> <p>6. (b) (4)</p>	
---	--

<p>7.</p>	
<p>8.</p>	
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments: Please provide information on  (b) (4)</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): December 2, 2013

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

On September 26, Lilly announced positive results from a Phase 3 study (RAINBOW, I4T-IE-JVBC, IMCL CP12-0922) of ramucirumab in combination with paclitaxel for the treatment of patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma after prior chemotherapy.

Clinical and statistical team members are scheduled to have a teleconference with Lilly on October 10th in which Lilly will share the topline RAINBOW results and discuss the proposed content and format to submit these data to FDA.

A decision on whether to present at ODAC will be made after the October 10th teleconference.

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.

	<p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input checked="" type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

SHARON K SICKAFUSE
10/16/2013

MONICA L HUGHES
10/16/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: BLA 125477/0

Application Type: New BLA

Name of Drug: Cyramza (ramucirumab), 100 mg/10 mL and 500 mg/50 mL

Applicant: Eli Lilly and Co.

Submission Date: August 23, 2013

Receipt Date: August 23, 2013

1.0 Regulatory History and Applicant's Main Proposals

Treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma, as a single-agent after prior chemotherapy

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in filing letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by November 12, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

N/A

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

N/A 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- NO** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.
Comment: Need bulleted subheadings.

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.
Comment:
- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.
Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.
Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):
- If a product **does not** have FDA-approved patient labeling:
- “**See 17 for PATIENT COUNSELING INFORMATION**”
- If a product **has** FDA-approved patient labeling:
- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
 - “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”
- Comment:*

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.
Comment: Delete the word "Revised" as this is the initial approval.
-

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.
Comment:
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.
Comment:
- YES**

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

SHARON K SICKAFUSE
09/18/2013

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

BLA	125477
Brand Name	Cyramza
Generic Name	Ramucirumab
Sponsor	Eli Lilly and Company
Indication	Treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma, as a single agent after prior chemotherapy
Dosage Form	IV infusion
Drug Class	Monoclonal antibody-VEGF blocker
Therapeutic Dosing Regimen	8 mg/kg IV every 2 weeks (<i>q2w</i>) until disease progression or unacceptable toxicity
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	13 mg/kg q1w. No MTD established for <i>q2w</i> and <i>q3w</i> regimens
Submission Number and Date	SDN 002, 19 Jun 2013
Review Division	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of ramucirumab (10 mg/kg/3 weeks) was detected in this QT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between ramucirumab (10 mg/kg/3 weeks) and placebo were below 10 ms. Participants in the moxifloxacin group showed the expected QTc profile under moxifloxacin treatment as illustrated in Figure 5. Assay sensitivity, however, was not established because moxifloxacin was not administered in the same period as study drug and was not administered to all patients. In the review of the protocol (09/28/2009), QT-IRT noted that administration of moxifloxacin was not recommended for this study.

In this multicenter, open-label, single-active arm, monotherapy study that enrolled 68 patients with advanced cancer (of solid tumor origin), the first 16 patients received a single oral dose of moxifloxacin 400 mg, while 66 patients received at least 1 dose of ramucirumab 10 mg/kg/3 weeks. Fifteen patients discontinued study treatment prior to completing 9 weeks of study drug therapy and the remaining 51 patients received at least 9 weeks of therapy. The primary reason for discontinuation of study treatment was progressive disease.

An overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Ramucirumab 10 mg/kg/3 weeks and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	Δ QTcF (ms)	90% CI (ms)
Ramucirumab 10 mg/kg/3 weeks	1.25	3.3	(1.4, 5.1)
Moxifloxacin 400 mg*	4	16.1	(12.0, 20.2)

* Multiple endpoint adjustment was not applied..

There was no statistically significant relationship between ramucirumab concentrations and Δ QTcF. The 10-mg/kg *q3w* dose selected for this QT study produces C_{max} values (mean C_{max} of 571 μ g/mL at cycle 3- third dose) which are higher than that with the intended therapeutic dose of 8 mg/kg *q2w* (geometric mean C_{max} of 282 μ g/mL and maximum individual C_{max} of 318 μ g/mL at cycle 2- third dose; Ref: Phase 1b trial I4T-IE-JVBW [IMCL CP12-1026]).. The results from Phase 3 (REGARD) data suggest that age, hepatic status, and renal function did not influence ramucirumab PK considerably. Gender was a significant covariate for PK even after accounting for body weight in multiple linear regression analysis, with females having 77% higher C_{min} than males..

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL:



Reviewer's Comment: The proposed labeling language is acceptable.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Ramucirumab DP is a recombinant human monoclonal antibody that blocks the interaction of VEGFR-2 and the ligand, vascular endothelial growth factor-A (VEGF-A; hereafter referred to as VEGF); inhibits VEGF-stimulated activation of VEGFR-2 and p44/p42 mitogen-activated protein kinases; and neutralizes VEGF-induced mitogenesis of human endothelial cells.

3.2 MARKET APPROVAL STATUS

Ramucirumab is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

No studies as per ICH S7B guidance were submitted.

3.4 PREVIOUS CLINICAL EXPERIENCE

Until December 2011 approximately 1200 patients were exposed to ramucirumab. No syncope, seizures, sudden cardiac death or ventricular arrhythmias were reported during ramucirumab clinical program. No clinically relevant ECGs were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of ramucirumab's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 11856. The sponsor submitted the study report 7I4T-IE-JVBK for ramucirumab, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Study to Evaluate the Relationship Between Ramucirumab (IMC-1121B) Therapy and Corrected QT (QTc) Interval Changes in Patients with Advanced Cancer

4.2.2 Protocol Number

I4T-IE-JVBK (IMCL CP12-0712)

4.2.3 Study Dates

Date of first patient visit: November 30, 2009

Date of data cutoff: October 3, 2012

4.2.4 Objectives

The primary objective of this study was to determine if treatment with ramucirumab caused prolongation of the QT/QTc interval in patients with advanced cancer. The secondary objectives of this study were to assess the safety and tolerability of ramucirumab therapy as well as evaluate the pharmacokinetic (PK) characteristics of ramucirumab.

4.2.5 Study Description

4.2.5.1 Design

This was a multicenter, open-label, single-active arm, monotherapy study that enrolled 68 patients with advanced cancer (of solid tumor origin). Patients received ramucirumab 10 mg/kg, administered as an intravenous (IV) infusion over 60 minutes, once every 3 weeks for a minimum of 9 weeks. The first 16 patients enrolled in the study received 1 dose of moxifloxacin (400 mg orally [PO]), an antibiotic associated with mild QTc prolongation, followed by a 1-week washout period to assess the assay sensitivity in this patient population.

4.2.5.2 Controls

The Sponsor used a positive (moxifloxacin) control in the study.

4.2.5.3 Blinding

The study was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

This was a single arm study in which patients received a ramucirumab dose of 10 mg/kg.

4.2.6.2 Sponsor's Justification for Doses

Nonclinical data obtained from a murine BxPC-3 xenograft model have demonstrated that the efficacy of DC101, a murine analogue to ramucirumab, was evident in vivo at trough concentrations of 18 µg/mL. The target serum concentration for ramucirumab is hypothesized to be one that maintains ramucirumab at trough plasma concentrations at ≥ 18 µg/mL. Preliminary PK data from Studies CP12-0401 and CP12-0402, for patients treated on the weekly- and every-2-week regimens, indicate that the minimum 18-µg/mL target trough concentrations are attainable. Although data from the dosing regimen of ramucirumab every 3 weeks (Study CP12-0402) are limited, PK modeling of data derived from the above studies suggests that the 18-µg/mL minimum trough levels can be achieved readily. In the every-other-week protocol, following the initial dose of 10 mg/kg, the ramucirumab maximum observed serum concentration (C_{max}) is approximately 406 µg/mL (range: 249-685 µg/mL, n=7). Using the derived half-life following the initial 10-mg/kg ramucirumab infusion (206 hours) and this C_{max} , the predicted trough levels of drug at the end of 3 weeks would be approximately 74 µg/mL. To provide a suitable margin above the 18 µg/mL ramucirumab target concentration, the proposed dose and regimen of ramucirumab is 10 mg/kg given every 3 weeks.

Ramucirumab has been administered in Phase 2 and Phase 3 investigations at doses of 6 mg/kg/week, 8 mg/kg/2 weeks, and 10 mg/kg/3 weeks. The 10-mg/kg/3 week dose was chosen for the current (QTc) study because it was hypothesized that the highest of the doses utilized (irrespective of schedule) would be associated with higher peak (post-infusion) drug levels, and that the largest potential for induction of QTc abnormalities would be associated with this dose, relative to the other doses/schedules evaluated in the Phase 2 and Phase 3 studies.

Source: Sponsor's study report (Section 5.3.2, Page 22)

Reviewer's Comment: The 10-mg/kg q3w dose selected for this study produces C_{max} values (mean C_{max} of 571 µg/mL at cycle 3- third dose) which are higher than that with the intended therapeutic dose of 8 mg/kg q2w (geometric mean C_{max} of 282 µg/mL and maximum individual C_{max} of 318 µg/mL at cycle 2- third dose). Thus the dose evaluated in this study covers the expected therapeutic concentration range and is appropriate. The results from Phase 3 (REGARD) data suggest that age, hepatic status, and renal function did not influence ramucirumab PK considerably. Gender was a significant covariate for PK even after accounting for body weight in multiple linear regression analysis, with females having 77% higher C_{min} than males. There are no DDI studies conducted yet to explore any potential higher exposure scenario that exceeds the range covered by 10 mg/kg q3w.

4.2.6.3 Instructions with Regard to Meals

Reviewer's Comment: There is no necessity of instructions with regard to meals, since the drug is to be administered as an i.v. infusion.

4.2.6.4 ECG and PK Assessments

Serial PK samples were taken from patients following their initial infusion (Cycle 1) and subsequent infusion cycles (Cycles 2, 3, 4) at following time points:

0 h on Pretreatment Day -1 (treatment of diphenhydramine infusion alone);

2.25, 3.25, 4.25, 72, 168, 336, and 504 h from start of 15 min diphenhydramine infusion in Cycle 1 (Ramucirumab 1 h infusion being started at 0.25 h);

1.25 h from start of 15 min diphenhydramine infusion in Cycle 2 (Ramucirumab 1 h infusion being started at 0.25 h);

0, 1.25, 2.25, 3.25, 4.25, 72, 168, 336, and 504 h from start of 15 min diphenhydramine infusion in Cycle 3 (Ramucirumab 1 h infusion being started at 0.25 h);

1.25 h from start of 15 min diphenhydramine infusion in Cycle 4 (Ramucirumab 1 h infusion being started at 0.25 h);

ECG assessments in triplicate were done at all the above timings and additionally at the following times:

0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6 and 8 h on Pretreatment Day -7 (during moxifloxacin treatment in some subjects);

0.25, 1.25, 2.25, 3.25 h on Pretreatment Day -1 (treatment of diphenhydramine infusion alone);

0, and 0.25 h from start of 15 min diphenhydramine infusion in Cycle 1 (Ramucirumab 1 h infusion being started at 0.25 h);

0.25 h from start of 15 min diphenhydramine infusion in Cycle 2, Cycle 3 and Cycle 4 (Ramucirumab 1 h infusion being started at 0.25 h);

Source: Sponsor's Report (Table JVBK.5.1, Page 19)

Reviewer's Comment: Frequent ECG measurements were carried out around Tmax (~2 h) of this drug. Thus, the timing of ECGs was reasonable.

4.2.6.5 Baseline

Time-matched ECG measure at Day -1 was used as baseline.

4.2.7 ECG Collection

Triplicate electrocardiograms (ECGs; 3 consecutive ECG tests recorded within 4 minutes) were collected at multiple time points after the initial dose, and at the steady state.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 68 patients, 37 male and 31 female, between the ages of 19 and 86 years enrolled in this study. Of the 66 patients who received at least 1 dose of ramucirumab, 51 patients received 9 weeks of therapy stipulated as the complete QTc evaluation period.

Fifteen patients discontinued study treatment prior to completing the 9 weeks of therapy stipulated as the complete QTc evaluation period; 51 patients received at least 9 weeks of therapy.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

On Day -1, patients were administered diphenhydramine 25 to 50 mg as an IV infusion, and ECGs (in triplicate) were collected according to the schedule in Table JVBK.5.1. These Day -1 ECGs were considered as the time-matched baseline values for the ECGs collected after ramucirumab treatment (study baseline).

Pretreatment with diphenhydramine (25-50 mg IV) was required before the administration of ramucirumab for Cycles 1 to 4. Each patient was to be administered a consistent dose of diphenhydramine prior to each ramucirumab infusion during Cycles 1-4 (for example, a patient who received 25 mg of diphenhydramine at Cycle 1 was to receive this same dose at Cycles 2-4).

Patients received ramucirumab 10 mg/kg, administered as an IV infusion over 60 minutes, once every 3 weeks for a minimum of 9 weeks. ECGs (in triplicate) were collected according to the schedule in Table JVBK.5.1.

The 90% CI of change from time-matched baseline (Day -1) for QTcF at Cycle 3 is shown in Figure JVBK.7.4. The diphenhydramine infusion occurred between 00:00 hour and 00:15 hour, and the ramucirumab infusion occurred between 0:15 hour and 1:15 hour. Using the time-matched QTcF values from Day -1 as the baseline, repeated-measures ANCOVA showed that the upper limit of the 2-sided 90% CI of the least square means of change from baseline for QTcF values was less than 10 msec at all study time points in Cycle 3.

4.2.8.2.2 Assay Sensitivity

The first 16 patients enrolled in the study received 1 dose of moxifloxacin (400 mg PO), an antibiotic associated with mild QTc prolongation, to assess the assay sensitivity.

ECGs (in triplicate) were collected for 8 hours after moxifloxacin administration according to the schedule in Table JVBK.5.1.

The 90% CI of change from baseline for QTcF after moxifloxacin treatment is shown in Figure JVBK.7.3. In the assay sensitivity analyses, repeated-measures analysis of covariance (ANCOVA) using baseline QTcF as a covariate and gender and visit as factors showed that there was a statistically significant prolongation of QTcF at 9 time points between 01:00 and 08:00 hours postdose (Table JVBK.11.12). The mean QTcF prolongation exceeded 10 msec and the lower 90% CIs exceeded 5 msec at 8 postdose time points on Day -7 between 01:30 to 08:00 hours. Thus, assay sensitivity was demonstrated in the present study. Peak QTcF prolongation was seen at 03:30 hours postdose and a steady decline was seen thereafter, demonstrating the typical time course of the moxifloxacin effect (Bloomfield et al. 2008).

4.2.8.2.3 Categorical Analysis

Categorical outliers analysis for Cycle 3 showed 2 patients (3 time points) with a QTcF value >450 msec and ≤ 480 msec. No patient had a QTc value >480 msec or QT, QTcB, or QTcF value ≥ 500 msec in this population.

An increase in QTcF of >30 msec and ≤ 60 msec was seen in 3 patients (5 time points) in Cycle 3. A QTcF change from baseline value of more than 60 msec was reported in one 79-year-old male patient (CP12-0712/004-0405) at the Cycle 3, Day 1/Week 1, 03:15-hour and Cycle 3, Day 1/Week 1, 04:15-hour time points in all 3 replicates after receiving diphenhydramine + ramucirumab treatment. This patient had the shortest baseline QTcF value (347 msec) among all patients participating in the study. The absolute QTcF values at these visits were 412 msec at Cycle 3, Day 1/Week 1, 03:15 hour and 431 msec at Cycle 3, Day 1/Week 1, 04:15 hour. None of these QTc values exceeded 450 msec.

There were 2 patients with observed treatment-emergent morphological abnormalities in this study.

The first patient was a 69-year-old male (CP12-0712/004-0404) who had episodes of ventricular bigeminy after diphenhydramine and ramucirumab treatment in Cycle 3, Day 1. This patient additionally had an episode of trigeminy at 1 time point (and only in 1 replicate) in Cycle 3, Day 4, which also showed limb lead error. At subsequent visits, ECGs showed a normal sinus rhythm. This patient also demonstrated atrial premature complexes, which were not considered treatment emergent

because they were present during the moxifloxacin evaluation (Day -7), at study baseline (diphenhydramine Day -1), and during therapy with diphenhydramine and ramucirumab (Cycle 3). This patient had metastatic non-small cell lung cancer with bilateral lung tumor at time of study entry, and extensive mediastinal lymphadenopathy. The patient had received prior right lung radiation therapy and multiple lines of chemotherapy, including both paclitaxel and docetaxel, and investigational MDX-1106 (anti-PD-1 antibody) during the month prior to initial treatment on Study CP12-0712. There was also a history of prior rheumatic fever, diabetes, and hypertension. This patient received investigational ramucirumab on Study CP12-0712 beginning on 19 February 2010; investigational therapy was discontinued approximately 9 months later because of disease progression/symptomatic deterioration.

The second patient was a 53-year-old male (CP12-0712/007-0708) who had an episode of atrial fibrillation after diphenhydramine and ramucirumab treatment at the Cycle 3, Day 4/Week 1, 72:00-hour time point. This patient had premature ventricular complexes at Cycle 3, Day 1 and Cycle 3, Day 8. This patient also had left atrial enlargement at baseline (diphenhydramine Day -1), which was not considered treatment emergent. This patient had metastatic gastroesophageal junction cancer with metastasis to lymph nodes, including mediastinal lymph nodes. The patient had received multiple prior lines of chemotherapy involving 6 different cytotoxic agents including epirubicin, which was administered in the month prior to initial treatment on Study CP12-0712. There was also a history of pericarditis. The patient received investigational ramucirumab on Study CP12-0712 beginning on 09 March 2010; investigational therapy was discontinued because of disease progression on 01 June 2010. Both prior to and during study therapy, the patient received multiple additional medications, including transdermal scopolamine (anticholinergic agent) that was begun on 20 April 2010.

4.2.8.3 Safety Analysis

Of the 66 patients who were treated with ramucirumab, 16 patients died during the study. Eleven patients died within 30 days of the last dose of ramucirumab; 5 patients died more than 30 days after the last dose of ramucirumab. Disease progression was indicated as the primary cause for all of these deaths.

None of the serious AE reported was linked to QT prolongation.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results and mean concentration-time profiles are presented in Table 2 and Figure 1 for Ramucirumab administered at 10 mg/kg every 3 weeks as an i.v. infusion over 1 hour. The 10-mg/kg *q3w* dosing tested in this QT study covers the expected range of concentrations with the intended clinical dose of 8 mg/kg *q2w*. Mean C_{max} values in the thorough QT study with 10-mg/kg *q3w* dosing were approximately 2-fold the mean C_{max} values with 8 mg/kg *q2w* observed in a Phase 1b study (although the analytical assays in both these studies were slightly different).

Table 2: Sponsor's Results for Pharmacokinetic Parameters

Predose and End of Infusion serum concentration of Ramucirumab administered at 10 mg/kg every 3 weeks as an i.v. infusion over 1 hour

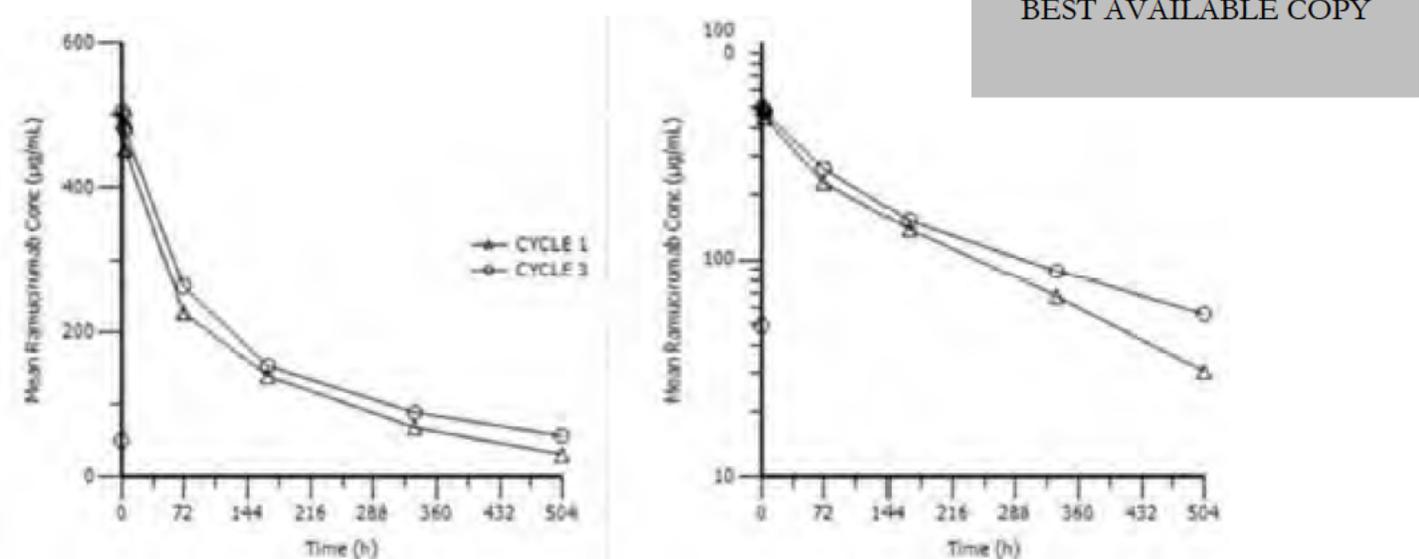
Ramucirumab 10 mg/kg Every 3 Weeks				
Cycle	2	3	4	5
Predose Serum Concentrations ($\mu\text{g/mL}$)				
N	48	43	22	12
Min	3.18	8.23	19.0	23.6
Max	81.3	202	151	151
Geo Mean	25.1	38.9	46.9	67.0
Geo CV%	82	80	62	74
End of Infusion Serum Concentrations ($\mu\text{g/mL}$)				
N	38	39	17	
Min	246	150	244	
Max	881	1060	1475	
Geo Mean	510	476	581	
Geo CV%	31	37	41	

Summary of PK parameters in Cycle 1 and Cycle 3

	Ramucirumab Serum Parameters Geometric Mean ^a (Geometric CV%)	
	10 mg/kg Every 3 Weeks	
	Cycle 1 First Dose (N _{PK} =61) ^b	Cycle 3 Third Dose (N _{PK} =47) ^c
C _{max} or C _{max,12} ($\mu\text{g/mL}$)	485 (43)	571 ^c (41)
t _{max} or t _{max,12} ^a (h)	2.13 (1.45 – 4.20)	2.03 ^c (0.95-4.58)
t _{1/2} (h)	148 ^b (36)	189 ^c (33)
AUC(0-∞) or AUC _{t,12} ($\mu\text{g}\cdot\text{h/mL}$)	67400 ^b (38)	69900 ^c (41)
CL or CL ₁₂ (mL/hr)	11.6 ^b (35)	10.7 ^c (41)
V ₁₂ (mL)	2290 ^b (36)	2560 ^c (46)
R _{A,Cmax}		1.12 ^c (57)
R _{AAUC}		1.11 ^c (38)

Source: Table JVBK.7.1, and JVBK.7.2 of sponsor's study report

Figure 1: Mean Ramucirumab concentration-time profiles (linear in left and semi-log in right panel) in Cycle 1 and Cycle 3 with dose of 10 mg/kg every 3 weeks as an i.v. infusion over 1 hour

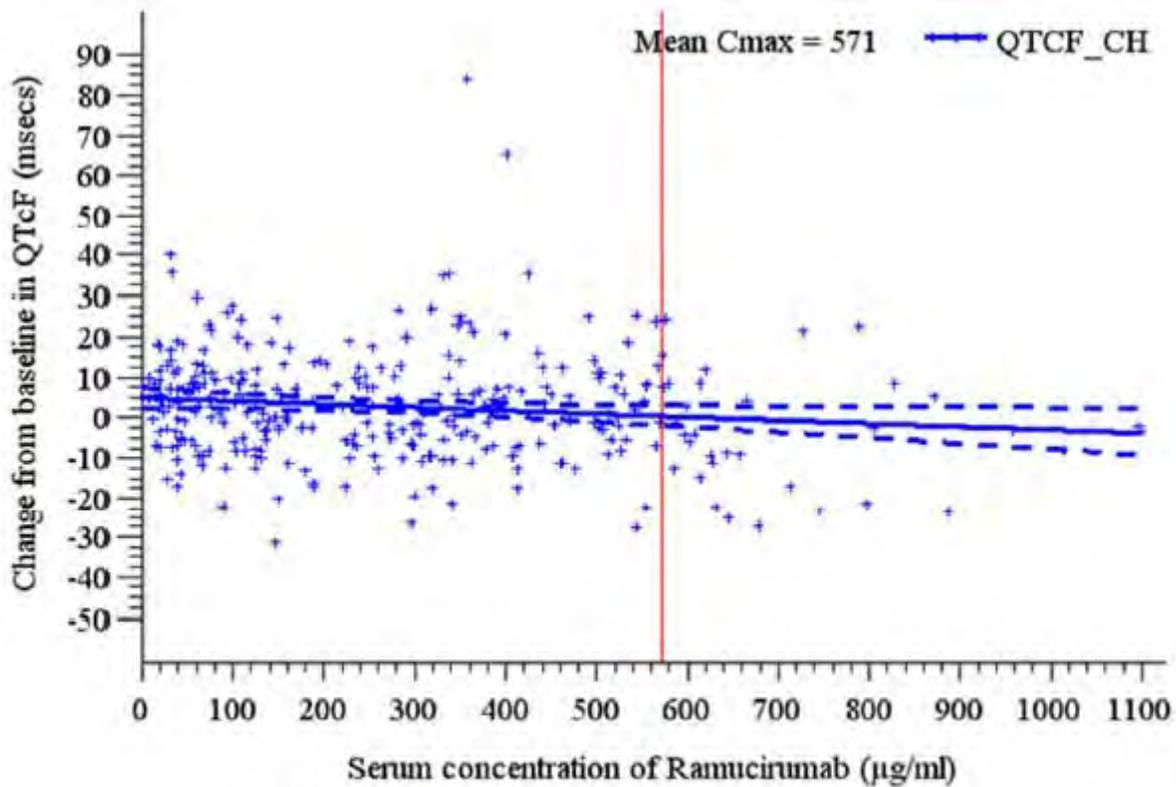


Source: Figure JVBK.7.2 of sponsor's study report

4.2.8.4.2 Exposure-Response Analysis

The Sponsor used a linear mixed model to quantify the relationship between serum concentrations and Δ QTcF, with serum concentration as a covariate as well as intercept and serum concentration as subject-specific random effects. This analysis was performed for data from Cycle 3. The estimated slope of the model was -0.00207 and was not statistically significantly different from 0 (Figure 2). The parameter estimates of the model and predicted Δ QTcF at geometric mean C_{max} of 571 μ g/mL in Cycle 3 are displayed in Table 3 and Figure 2 respectively.

Figure 2: Δ QTcF versus Ramucirumab Concentrations in Cycle 3



Regression Equation

$$\Delta\text{QTcF} = 3.9 - (0.002 * \text{Concentration})$$

Mean Δ QTcF at mean Cmax (90%CI) = 2.8 msec (-3.8, 9.5)

Abbreviations: QTc = corrected QT; QTcF = QT corrected by Fridericia's formula.

Source: Table 14.3.18.21.1.1; Table JVBK.7.2.

Source: Figure JVBK.7.5 of sponsor's study report

Table 3: Parameter Estimates from Linear Mixed Model

Table 14.3.18.21.1.1: Estimates from concentration Electrocardiographic QTcF Parameter analysis - Primary QTc-Evaluable Population using nominal Time for cycle 3 [EGT011] N=66						
Treatment	Parameter	Estimate	SE	90% C.I.		p-value
				Lower	Upper	
Diphenhydramine + Ramucirumab	Change in QTcF (Intercept)	3.9132	1.5608	1.2980	6.5385	0.0161
Diphenhydramine + Ramucirumab	Change in QTcF (Slope)	-0.00207	0.004357	-0.00939	0.005262	0.6379

Source: Table JVBK.7.4 of Sponsor's study report

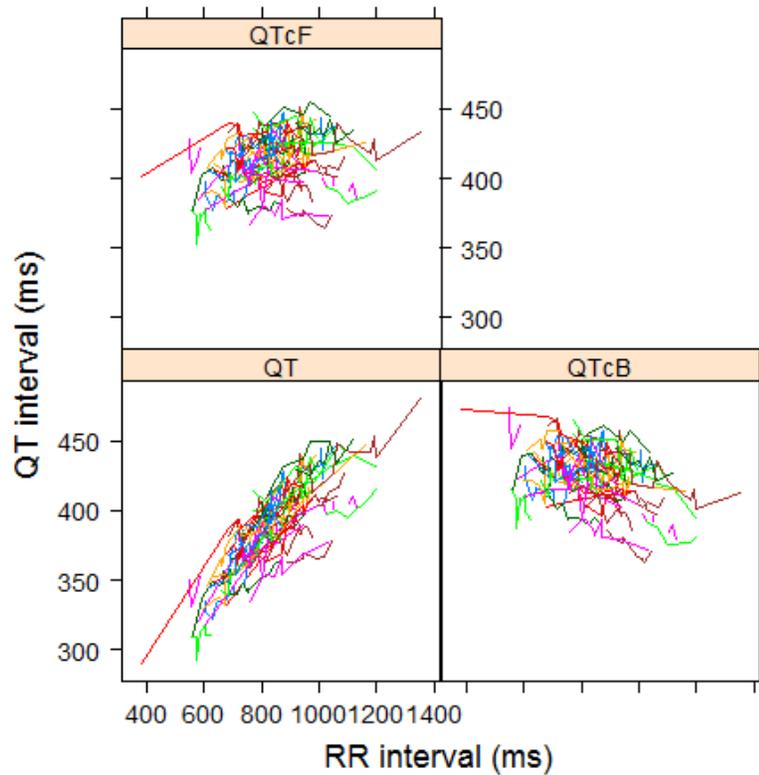
Reviewer's Analysis: A plot of Δ QTcF vs. Ramucirumab concentrations in Cycle 3, from Reviewer's analysis, is presented in Figure 6. Across the studied concentration range, there appears to be no concentration-QTc relationship, with the linear slope being not statistically significantly different from 0.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used ANOVA model to analyze the Δ QTcF effect. The analysis results are listed in the following tables.

Table 4: Analysis Results of Δ QTcF for Treatment Group = Diphenhydramine + Ramucirumab

	Δ QTcF: diphenhydramine + ramucirumab	
Time/(hr)	Mean	90%CI
0	1.6	(-0.2, 3.5)
0.25	2.8	(1.5, 4.2)
1.25	3.3	(1.4, 5.1)
2.25	-0.6	(-2.4, 1.2)
3.25	2.0	(0.0, 4.0)
4.25	0.3	(-2.0, 2.5)
72	-1.3	(-3.3, 0.7)
168	-0.7	(-2.8, 1.3)
336	2.0	(-0.1, 4.2)
504	3.0	(1.1, 4.8)

The largest upper bound of the 2-sided 90% CI for the mean change from baseline of diphenhydramine + ramucirumab was 5.1 ms.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin data. The results are presented in Table 5. The largest unadjusted 90% lower confidence interval was 12.0 ms .

Table 5: Analysis Results of Δ QTcF for Moxifloxacin

	Δ QTcF: moxifloxacin	
Time/(hr)	Mean	90%CI
0.5	2.0	(-2.5, 6.4)
1	6.0	(1.4, 10.6)
1.5	8.6	(5.1, 12.2)
2	10.5	(5.7, 15.2)
2.5	12.8	(8.2, 17.3)
3	14.5	(10.4, 18.6)
3.5	14.4	(10.5, 18.3)
4	16.1	(12.0, 20.2)
6	13.7	(10.6, 16.8)
8	10.0	(5.5, 14.6)

* Bonferroni method was not applied for multiple endpoint.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figures display the time profile of $\Delta\Delta$ QTcF for different treatment groups.

(Note: CIs are all unadjusted including moxifloxacin)

Appears this way on original

Figure 4: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse for Diphenhydramine + Ramucirumab

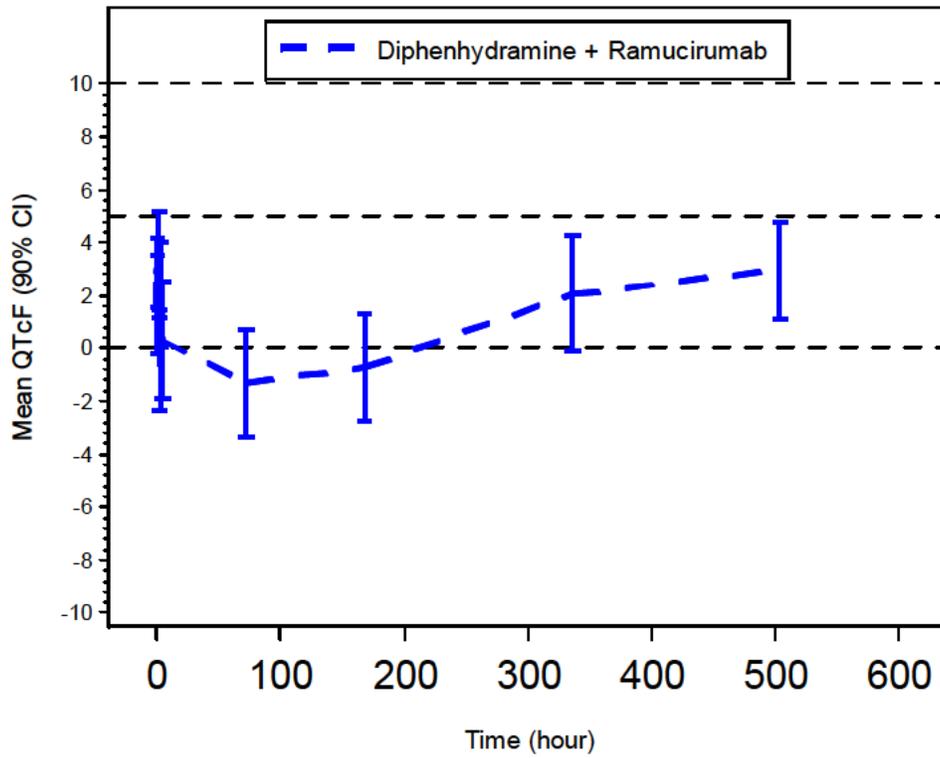
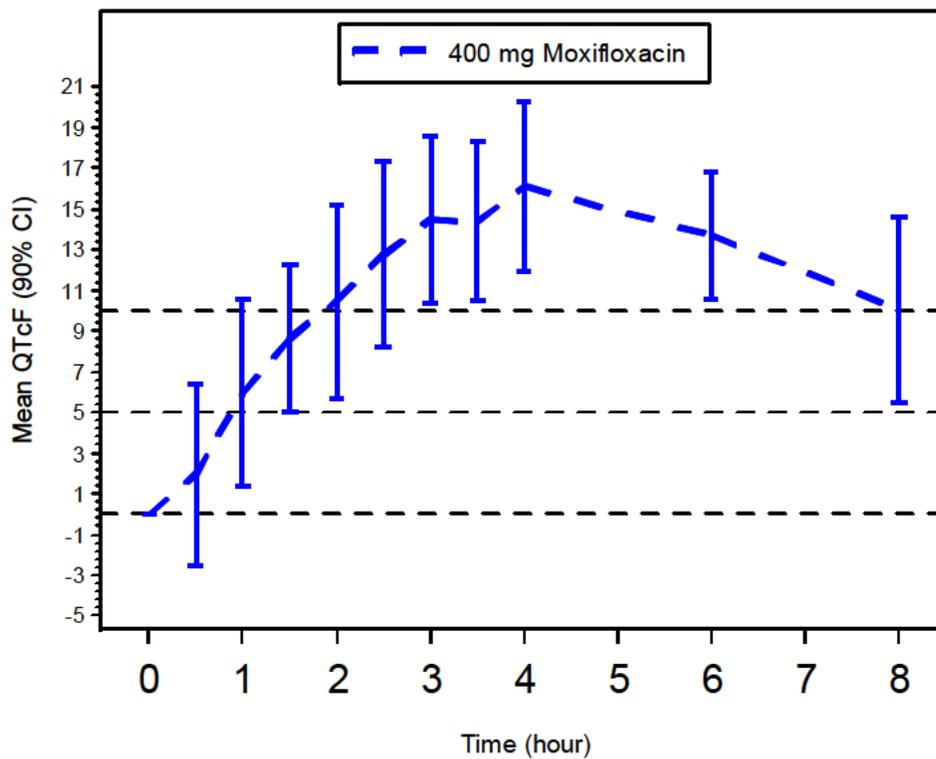


Figure 5: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse for Moxifloxacin



5.2.1.4 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are \leq 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 6: Categorical Analysis for QTcF

Treatment Group	Total N		Value \leq 450 ms		450 ms<Value \leq 480 ms		480 ms<Value \leq 500 ms		Value>500	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Diphenhydramine + Ramucir	66	1148	63 (95.5%)	1143 (99.6%)	3 (4.5%)	5 (0.4%)	0 (.%)	0 (0.0%)	0 (.%)	0 (0.0%)

Table 7 lists the categorical analysis results for Δ QTcF. One subject has 2 changes from baseline above 60 ms.

Table 7: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Value \leq 30 ms		30 ms<Value \leq 60 ms		Value>60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Diphenhydramine + Ramucir	64	1113	57 (89.1%)	1100 (98.8%)	6 (9.4%)	11 (1.0%)	1 (1.6%)	2 (0.2%)

5.2.2 HR Analysis

The statistical reviewer used ANOVA model to analyze the Δ HR effect. The analysis results are listed in the following table. The largest upper bound of the 2-sided 90% CI for the mean change from baseline of diphenhydramine + ramucirumab was 4.2 bpm. The outlier analysis results for PR are presented in Table 13

Table 8: Analysis Results of Δ HR and $\Delta\Delta$ HR for for Treatment Group = Diphenhydramine + Ramucirumab

Δ HR: diphenhydramine + ramucirumab		
Time/(hr)	Mean	90%CI (bpm)
0	-1.3	(-2.6, 0.0)
0.25	-1.2	(-2.1, -0.3)
1.25	-2.6	(-3.9, -1.3)
2.25	-0.9	(-2.3, 0.4)
3.25	-1.1	(-2.3, 0.2)
4.25	-1.0	(-2.4, 0.4)
72	1.9	(-0.3, 4.0)
168	1.1	(-0.5, 2.7)
336	2.6	(1.0, 4.2)
504	-1.3	(-2.8, 0.3)

Table 9: Categorical Analysis for HR

Treatment Group	Total N		Value≤100 bpm		Value>100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Diphenhydramine + Ramucir	66	1072	54 (81.8%)	1040 (97.0%)	12 (18.2%)	32 (3.0%)

5.2.3 PR Analysis

The statistical reviewer used ANOVA model to analyze the Δ PR effect. The analysis results are listed in the following table. The largest upper bound of the 2-sided 90% CI for the mean change from baseline of diphenhydramine + ramucirumab was 8.1 ms.

The outlier analysis results for PR are presented in Table 12

Table 10: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = Diphenhydramine + Ramucirumab

Time/(hr)	Δ PR: diphenhydramine + ramucirumab	
	Mean	90%CI (ms)
0	0.3	(-1.4, 2.0)
0.25	3.4	(1.0, 5.8)
1.25	2.4	(0.6, 4.2)
2.25	2.5	(0.9, 4.1)
3.25	3.6	(1.7, 5.5)
4.25	2.9	(0.9, 4.8)
72	-1.8	(-4.1, 0.5)
168	-1.0	(-4.0, 1.9)
336	-1.9	(-4.9, 1.1)
504	3.5	(-1.1, 8.1)

Table 11:**Table 12: Categorical Analysis for PR**

Treatment Group	T		Value≤200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Diphenhydramine + Ramucir	66	1066	58 (87.9%)	962 (90.2%)	8 (12.1%)	104 (9.8%)

5.2.4 QRS Analysis

The statistical reviewer used ANOVA model to analyze the Δ QRS effect. The analysis results are listed in the following table. The largest upper bound of the 2-sided 90% CI for the mean change from baseline of diphenhydramine + ramucirumab was 1.1 ms.

The outlier analysis results for QRS are presented in Table 13

Table 13: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = Diphenhydramine + Ramucirumab

	Δ QRS: diphenhydramine + ramucirumab	
Time/(hr)	Mean	90%CI (ms)
0	-1.2	(-1.9, -0.5)
0.25	-0.5	(-1.2, 0.2)
1.25	-0.4	(-1.2, 0.4)
2.25	0.3	(-0.4, 0.9)
3.25	0.2	(-0.6, 0.9)
4.25	0.3	(-0.6, 1.1)
72	-0.4	(-1.4, 0.6)
168	-0.7	(-1.8, 0.4)
336	-0.6	(-1.5, 0.4)
504	-0.5	(-1.3, 0.3)

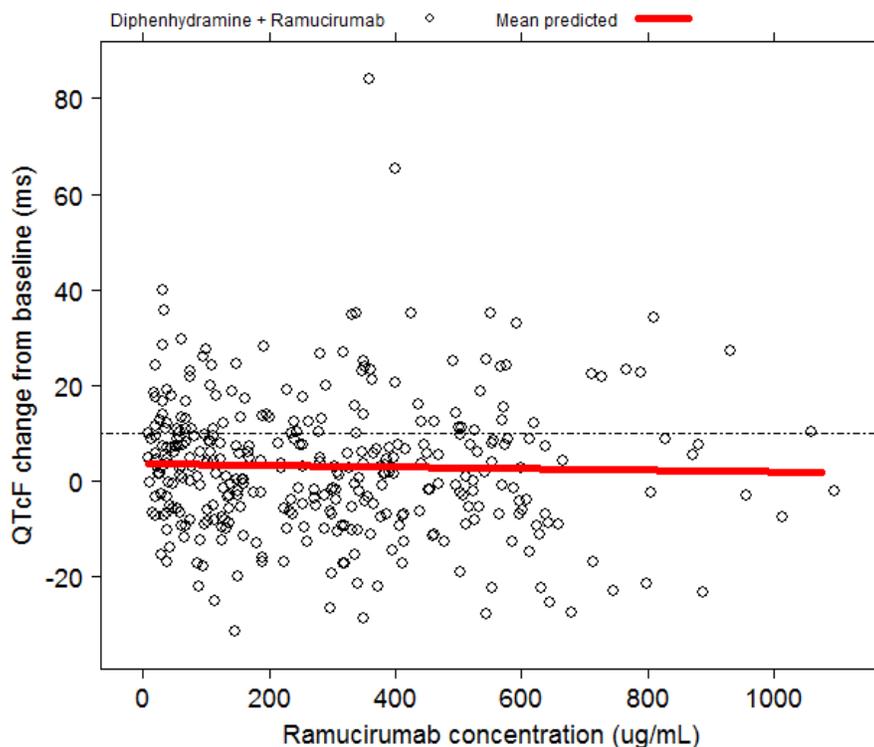
Table 14: Categorical Analysis for QRS

Treatment Group	T		Value \leq 100 ms		100 ms<Value \leq 110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Diphenhydramine + Ramucir	66	1071	42 (63.6%)	852 (79.6%)	18 (27.3%)	164 (15.3%)	6 (9.1%)	55 (5.1%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between Δ QTcF and ramucirumab concentrations in Cycle 3 with dosing of 10 mg/kg *q3w* is visualized in Figure 6 with no evident exposure-response relationship.

Figure 6: Δ QTcF vs. Ramucirumab concentration together with the Population Predictions (solid red line)



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

Hypertension was reported in 10 subjects, 4 of them were grade ≥ 3 .

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 98 % of the ECGs were annotated in multiple leads (PR annotations in lead II, QRS in V2 and QT in V5), with less than 3% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Eight subjects in the treatment group had PR > 200 ms at baseline. Six subjects had QRS > 110ms, 4 of them at baseline (two subjects had baseline values >130 ms). Post-baseline increases in QRS duration of approximately 15% were reported.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology	
Therapeutic Name	Ramucirumab (LY3009806; IMC-1121B)

Therapeutic dose	8mg/kg IV q2w, 10 mg/kg IV q3w	
Maximum tolerated dose	Clinical: 13 mg/kg Q1w in (I4T-IE-JVBM [IMCL CP12-0401]) No MTD established for q2w and q3w regimens (I4T-IE-JVBN [IMCL CP12-0402])	
Principal adverse events	<p>Dose limiting Adverse Events observed in Phase 1- I4T-IE-JVBM (IMCL CP12-0401): one patient with hypertension, one patient with deep vein thrombosis</p> <p>Adverse Events of Special Interest-</p> <p>Adverse events considered potentially associated with anti-angiogenic agents or therapeutic monoclonal antibodies: infusion-related reactions, hypertension, proteinuria, arterial thromboembolic event (ATEs), venous thromboembolic event (VTEs), bleeding/hemorrhagic events, intestinal perforation</p>	
Maximum dose tested	Single Dose	20 mg/kg IV (I4T-IE-JVBN (IMCL CP12-
	Multiple Dose	<ul style="list-style-type: none"> - 16 mg/kg IV q1w; median number of infusions (range): 4 (1-93); (I4T- IE-JVBM [IMCL CP12-0401]) - 10 mg/kg IV q2w; median number of infusions (range): 25.5 (17-31); (I4T-IE-JVBN [IMCL CP12-0402]) - 20 mg/kg IV q3w; median number of infusions (range):
Exposures Achieved at Maximum Tested Dose ^a	Single Dose	<ul style="list-style-type: none"> - Cmax: 763 µg/mL (25) [Geometric mean (%CV)] at 20 mg/kg IV dose - AUC (0-505): 120000 µg*h/mL (31) [Geometric mean (%CV)] at
	Multiple Dose	<ul style="list-style-type: none"> - 16 mg/kg q1w following the fourth infusion: (I4T-IE-JVBM [IMCL CP12-0401]) <ul style="list-style-type: none"> o Cmax: 934 µg/mL (63) [Geometric mean (%CV)]; o AUC(TAU): 71400 µg*h/mL (51) [Geometric

Approval Date: 13-Jun-2013 GMT

		infusion: (I4T-IE-JVBN [IMCL CP12-0402]) <ul style="list-style-type: none"> o Cmax: 476 µg/mL (18) [Geometric mean (%CV)];
Range of linear PK	Ramucirumab exhibited nonlinear PK between 2 and 6 mg/kg and linear PK at doses 8 mg/kg and above (I4T-IE- JVBM [IMCL CP12-0401])	
Accumulation at steady state ^b	Accumulation ratio calculated by AUC: 1.52 and 1.53 at 8 mg/kg IV q2w (following the third infusion) (I4T-IE-JVBW [IMCL CP12-1026])	
Metabolites	No studies on the metabolism of ramucirumab have been performed in humans or in animals. Metabolism studies are not generally performed for monoclonal antibodies because they are proteins which are degraded into amino acids that are then recycled into other proteins.	
Absorption Absolute/Relative Bioavailability	Ramucirumab is administered intravenously (IV).	
Tmax	Not applicable (IV administration)	
Distribution	Vss	Not available
	% bound	Not determined
Elimination Route	Therapeutic proteins are generally cleared through their interaction with specific receptors on the target cell surfaces, as well as interaction with the FcγR receptors on the hepatic epithelial cells. Proteins are also cleared nonspecifically through proteolysis by proteases and peptidases. These specific and nonspecific mechanisms of clearance are the presumed primary expected routes of elimination for ramucirumab.	
Terminal t _{1/2}	8 d (6– 9 d) [Geometric Mean (range) at 8 mg/kg IV (following single dose) (I4T-IE-JVBW [CP12-1026])	
CL/F or CL	Not available	

<p>Intrinsic Factors Age Sex Race e Hepatic & Renal Impairment</p>	<p>No formal Studies have been conducted No formal Studies have been conducted No formal Studies have been conducted No formal Studies have been conducted</p> <p>Results based upon multiple linear regression analysis of C_{min} data in REGARD (I4T-IE-JVBD (IMCL CP12-0715)) suggested that age, gender, hepatic status, and renal function did not appear to influence ramucirumab PK to an</p>
<p>Extrinsic Factors Drug Interactions Food Effects</p>	<p>DDI Studies with common co-meds, including paclitaxel, docetaxel, and FOLFIRI are currently ongoing.</p>
<p>Expected High Clinical Exposure Scenario</p>	<p>In general, excessively high clinical exposure scenarios are not expected for ramucirumab. An example of a worst case high clinical exposure scenario would be overdose due to a miscalculation of the appropriate dose. The maximum tolerated dose (MTD) for weekly administration was identified as 13mg/kg/week, which is substantially higher than the doses utilized in phase 2-3 evaluation (6mg/kg/week; 8mg/kg/2 week; 10mg/kg/3 week). No MTD was identified for every 2-3 week dosing and doses up to 20mg/kg/3 week were evaluated in phase 1 study. Dose miscalculations observed to-date have not exceed the identified MTD and are not likely events because of the considerable window between phase 2-3 doses and MTD.</p> <p>Safety data are not available for clinical exposure at doses greater than those studied in phase 1-3.</p>

^a: PK data in I4T-IE-JVBM (IMCL CP12-0401) and I4T-IE-JVBN (IMCL CP12-0402) were derived by the original assay and are considered supportive.

^b: PK data in I4T-IE-JVBW (IMCL CP12-1026) were derived by the modified assay and are considered primary.

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

/s/

DHANANJAY D MARATHE
08/12/2013

KEVIN M KRUDYS
08/12/2013

QIANYU DANG
08/18/2013

MONICA L FISZMAN
08/18/2013

NORMAN L STOCKBRIDGE
08/19/2013