CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761038Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: September 26, 2016

FROM: Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Review Designation memo

Sponsor:	Eli Lilly and Company (Lilly)
Product:	Lartruvo (olaratumab) injection, for intravenous use
Proposed Indication:	LARTRUVO™ is indicated, in combination with doxorubicin, for the treatment of advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery.

TO: BLA 761038

The review status of this file submitted as an original BLA is designated to be:

☐ Standard (12 Months) ☒ Priority (8 Months)

BACKGROUND

This BLA relies on efficacy results from a single clinical trial, I5B-IE-JGDG (IMCL CP15-0806), entitled "*A Phase 1b/2 Randomized Phase 2 Study Evaluating the Efficacy of Doxorubicin With or Without a Human Anti-PDGFRα Monoclonal Antibody (IMC-3G3) in the Treatment of Advanced Soft Tissue Sarcoma.*" Lilly reports that the trial demonstrated a statistically significant improvement in overall survival [HR 0.463 (95% CI: 0.301, 0.710); p=0.0003], a key secondary endpoint. The median overall survival time was 26.5 months for the olaratumab plus doxorubicin arm and 14.7 months for the doxorubicin alone arm. The trial also demonstrated a statistically significant effect on the primary endpoint of progression-free survival (based on the protocol-specified Type I error rate of 0.2, two-sided) both by investigator-assessment and independent review, however the effect on progression-free survival was not clinically important. There was

also a significant improvement in overall response rates between the two arms (18.2 vs. 7.5%), based on independent review.

Lilly requested priority review designation on the following basis "The efficacy and safety results from Study JGDG represent a significant advance in the treatment of advanced STS and therefore, meet the criteria for evaluation of a priority review designation by FDA."

ASSESSMENT OF REQUEST

In evaluating the review designation for Lilly's BLA, I considered their rationale including the summary results of Study I5B-IE-JGDG and the following FDA Guidance and MAPP:

- CDER MAPP 6020.3, Priority Review Policy (version 2)
- Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

As stated in these FDA documents (above), an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. In addition, specific statutory provisions provide for priority review for various types of applications

On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition compared to available therapies.

Significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

For purposes of determining whether a significant improvement exists over available therapy, FDA generally considers *available therapy* (and the terms *existing treatment* and *existing therapy*) as a therapy that:

- Is approved or licensed in the United States for the same indication being considered for the new drug and
- Is relevant to current U.S. standard of care (SOC) for the indication

FDA's available therapy determination generally focuses on treatment options that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed. In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies (e.g., National Comprehensive

Cancer Network, American Academy of Neurology) based on clinical evidence and other reliable information that reflects current clinical practice. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic mutation), the SOC for the broader population, if there is one, generally is considered available therapy for the subset, unless there is evidence that the SOC is less effective in the subset.

A drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by post-approval studies.

Assessment*:*
This Biologic License Application (BLA) was not submitted under the statutory provisions for which priority review designation is required by statute.

Criterion 1: the drug treats a serious condition

In 2016, there will be an estimated 12,310 new cases of soft tissue sarcomas (STS) and 4,990 deaths due to STS.[1] Survival is correlated with the extent of disease; using the NCI's staging system the 5-year survival rates are 83% for those with localized disease, 54% for those with regional disease, and 16% for those with distant metastatic disease.[2] The indicated population (metastatic or unresectable soft tissue sarcoma (STS) for the treatment of advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery) would include all of the 16% of patients with STS diagnosed with distant metasatic disease and some fraction of the 19% of patients who present with regional disease.

Based on the 5-year survival rate of 16% for patients diagnosed with metastatic disease, I concur that the indicated population has a serious, life-threatening disease.

Criterion 2: the drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis compared to available therapies

The only FDA-approved drug approved for the initial treatment of patients with soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery is to doxorubicin.

Doxorubicin was approved in 1974 and is indicated for the treatment of "metastatic soft tissue sarcoma."

Dactinomycin is approved for the treatment of Ewing's sarcoma and rhabdosarcoma in children; these subtypes of sarcoma do not fall within the proposed indication.

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[1] http://www.cancer.org/cancer/sarcoma-adultsofttissuecancer/detailedguide/sarcoma-adult-soft-tissue-cancer-key-statistics
[2] http://www.cancer.org/cancer/sarcoma-adultsofttissuecancer/detailedguide/sarcoma-adult-soft-tissue-cancer-survival-rates

NCCN Practice Guidelines: The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend single agent treatment with an anthracycline (doxorubicin, epirubicin, or liposomal doxorubicin), ifosfamide, gemcitabine, dacarbazine, temozolomide, or vinorelbine or combination chemotherapy (doxorubicin plus dacarbazine; doxorubicin, ifosfamide, and mesna; mesna, doxorubicin, ifosfamide, dacarbazine; ifosfamide, epirubicin, and mesna; gemcitabine and docetaxel; gemcitabine and vinorelbine; gemcitabine and dacarbazine). These recommendations are for STS other than GIST, alveolar soft parts sarcoma, well-differentiated/dedifferentiated liposarcoma (WD-DDLS) arising in the retroperitoneum, pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT), solitary fibrous tumor/hemangiopericytoma, inflammatory myofibroblastic tumor (IMT) with Anaplastic Lymphoma Kinase (ALK) Translocation, and PEComa/ recurrent angiomyolipoma/lymphangioleiomyomatosis

The NCCN guidelines note that anthracycline-based regimens are preferred in the neoadjuvant and adjuvant setting and that temozolomide and vinorelbine are recommended only for use in the palliative setting.

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As noted in FDA's Guidance for Industry (referenced above) "Generally, if there is an available therapy (see section III.B.), sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority relating to either safety or effectiveness. Alternatively, sponsors could show the drug's ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy."

The proposed drug (olaratumuab) was studied in combination with doxorubicin, an FDA-approved drug for this indication that has been used as a single agent for over 40 years and has been the backbone of multiple combination chemotherapy regimens. To date, multiple trials have failed to demonstrate that the addition of other drugs to doxorubicin improves survival, including trials comparing the addition of (b) (4)

In the randomized trial conducted by Lilly, the addition of olartumumab to doxorubicin demonstrated a statistically robust improvement in overall survival over doxorubicin alone. While the magnitude of the treatment effect is uncertain, the lower limit of the 95% confidence interval for the observed difference in median survival of 11.8 months includes a 3-month improvement in overall survival. Thus even if the observed magnitude of improvement is an over-estimate, based on this lower limit, a clinically important improvement in survival appears to present.

Recommendation: Priority Review

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
10/19/2016

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 # BLA 761038 / Lartruvo
Product Name:

PMR/PMC Description: Conduct and submit the results of a multicenter, randomized clinical trial confirming the clinical benefit of olaratumab in combination with doxorubicin in patients with soft tissue sarcoma that is not amenable to surgery or radiation

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	June 8, 2015
	Study/Trial Completion:	August 2019
	Final Report Submission:	January 2020
	Other: Interim Analysis Submission Date	June 2018

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

   Soft tissue sarcoma that is not amenable to surgery or radiation is a severe and life-threatening disease with few available treatment options.

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."

There is uncertainty regarding the magnitude of the clinical effect of olaratumab for patients with soft tissue sarcoma given the existing data, which consists of the results from a single small trial in a heterogeneous patient population. The goal of the clinical trial is to provide information from a larger randomized, controlled clinical trial to confirm the treatment effect in this patient population.

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.

Randomized and controlled clinical trial.

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.*

_____

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/s/

LEAH S HER
10/18/2016

MEREDITH K CHUK
10/18/2016

MARC R THEORET
10/18/2016

JEFFERY L SUMMERS
10/18/2016

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

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

Memorandum

Date: 9/23/2016

To: Leah S Her, MS
Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Olaratumab Injection of Intravenous Use
BLA 761038

Office of Prescription Drug Promotion comments on proposed carton container.

Office of Prescription Drug Promotion (OPDP) has reviewed the draft carton container for olaratumab injection for intravenous use as requested in consult from DOP2 dated March 8, 2016.

OPDP's review of the proposed carton container is based on the draft carton container dated July 8, 2016 (SDN50) accessed via the EDR link send via electronic mail on September 19, 2016 to OPDP (Nazia Fatima) from DOP2 (Leah Her). OPDP has reviewed the draft carton container and has no comments. OPDP's comments on the proposed draft PI for olaratumab were provided on September 15, 2016.

If you have any questions please feel free to contact me, Nazia Fatima at 240-402-5041 or at Nazia.Fatima@fda.hhs.gov. Thank you! OPDP appreciates the opportunity to provide comments on these materials

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/s/

NAZIA FATIMA
09/23/2016

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

****Pre-decisional Agency Information

Memorandum

Date: 09/15/2016

To: Leah S. Her, M.S
Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products

From: Nazia Fatima, Pharm.D, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: Olaratumab Injection for Intravenous Use
BLA 761038

Office of Prescription Drug Promotion Comments on proposed labeling (PI)

Office of Prescription Drug Promotion (OPDP) has reviewed the package insert (PI) for olaratumab injection for intravenous use as requested in consult from DOP2 dated March 8, 2016.

OPDP's review of the proposed PI is based on the substantially completed draft labeling titled, "Olaratumab – 072216 FDA comments to 050616 Lilly Proposed Label.docx" send via electronic mail on July 22, 2016 to OPDP (Nazia Fatima) from DOP2 (Leah Her). OPDP comments are provided directly on the attached draft substantially complete PI.

If you have any questions please feel free to contact me, Nazia Fatima at 240-402-5041 or at Nazia.Fatima@fda.hhs.gov. Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NAZIA FATIMA
09/15/2016

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 #	761038
Product Name:	Olaratumab
2878-6 PMC Description:	Conduct a study to re-assess drug substance and drug product specifications based on additional clinical experience with material manufactured using the commercial process and/or additional characterization data on product critical quality attributes. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided.

PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	December 2019
	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 PUBLICALY 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 DS and DP release and shelf-life specifications approved under BLA are sufficient to ensure safety and efficacy of olaratumab for the initial marketed product. Additional product characterization information or clinical experience gained with material that is representative of the commercial manufacturing process can generate improved specifications.

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

There is limited clinical experience using olaratumab manufactured with the commercial process. Clinical experience with commercial lots, along with additional product characterization data, will provide a more robust set of data for refining drug substance and drug product specifications.

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:

   Data from clinical trials using lots representative of the current commercial manufacturing process and/or additional process characterization studies will be used to evaluate drug substance and drug product specifications. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided.

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.*

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(signature line for BLAs only)

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/s/

CHIKAKO TORIGOE
09/08/2016

RASHMI RAWAT
09/08/2016

FINAL LABEL AND LABELING REVIEW

Date:	August 8, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products
Through:	Chikako Torigoe, PhD, Quality Reviewer Division of Biotechnology Review and Research II
Application:	BLA 761038/0
Product:	Lartruvo (olaratumab)
Applicant:	Eli Lilly and Company
Submission Dates:	January 27; July 8 2016

Executive Summary:

The container label and carton labeling for Lartruvo (olaratumab) 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 201.100 and United States Pharmacopeia (USP), [USP 39/NF 34 May 1, 2016 to July 31 2016]. Labeling deficiencies were identified and resolved. The container label and carton labeling submitted on July 8, 2016 is acceptable.

Background and Summary Description:

The Applicant submitted the final component of a rolling submission for BLA 761038 Lartruvo (olaratumab) on February 11, 2016. Table 1 lists the proposed characteristics of Lartruvo (olaratumab).

Table 1: Proposed Product Characteristics of Lartruvo (olaratumab).

Proprietary Name:	Lartruvo
Proper Name:	olaratumab
Indication:	platelet-derived growth factor receptor alpha (PDGFR-α) blocking antibody indicated, in combination with doxorubicin, for the treatment of patients with soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery and with a histologic subtype for which an antracycline-containing regimen is appropriate.
Dose:	15 mg/kg as an intravenous infusion over 60 minutes on Days 1 and 8 each 21-day cycle until disease progression or unacceptable toxicity.
Route of Administration:	Intravenous infusion
Dosage Form:	Injection
Strength and Container-Closure:	500 mg/50 mL single-dose vial
Storage and Handling:	Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton to protect from light. DO NOT FREEZE OR SHAKE the vial. Store the infusion solution under refrigeration for up to 24 hours at 2°C to 8°C (36°F to 46°F) and for up to an additional 4 hours at room temperature (below 25°C [77°F]). If refrigerated, allow the infusion solution to come to room temperature prior to administration. Storage times include the duration of infusion.

Materials Reviewed:

- Container Label (submitted January 27 2016)
- Carton Labeling (submitted January 27 2016)

(b) (4)

[redacted]

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

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 of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*.

(2) The name, address, and license number of manufacturer; *conforms*.

(3) The lot number or other lot identification; *conforms*.

(4) The expiration date; *conforms*.

(5) The recommended individual dose, for multiple dose containers.

(6) The statement: "'Rx only'" for prescription biologicals; *conforms*.

(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; *not applicable*.

(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; *not applicable*.

(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; *not applicable*.

(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 *not applicable*.

(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; *insufficient data submitted*.

OBP Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e). *The Applicant provided a photo showing the sufficient are for visual inspection*.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (ND) number is located at the top of the label. [See 21 CFR 207.35]; *conforms*.

C. 21 CFR 201.5 Drugs; adequate directions for use; *does not conform*.

(b) (4)

OBP Request: Delete the redundant statements (b) (4) Must dilute prior to use." on the side panel as this information is already communicated on the principal display panel (PDP) via the statement "Must Dilute Prior to Use". Deleting the redundant statements will also reduce clutter, thus improving the readability of the container label and carton labeling. Additionally, (b) (4) The instructions to dilute the product on the PDP are adequate for communicating what is required for safe use of the product (b) (4)

(b) (4)

D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *conforms*.

F. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

H. 21 CFR 201.25 Bar code; *conforms*.

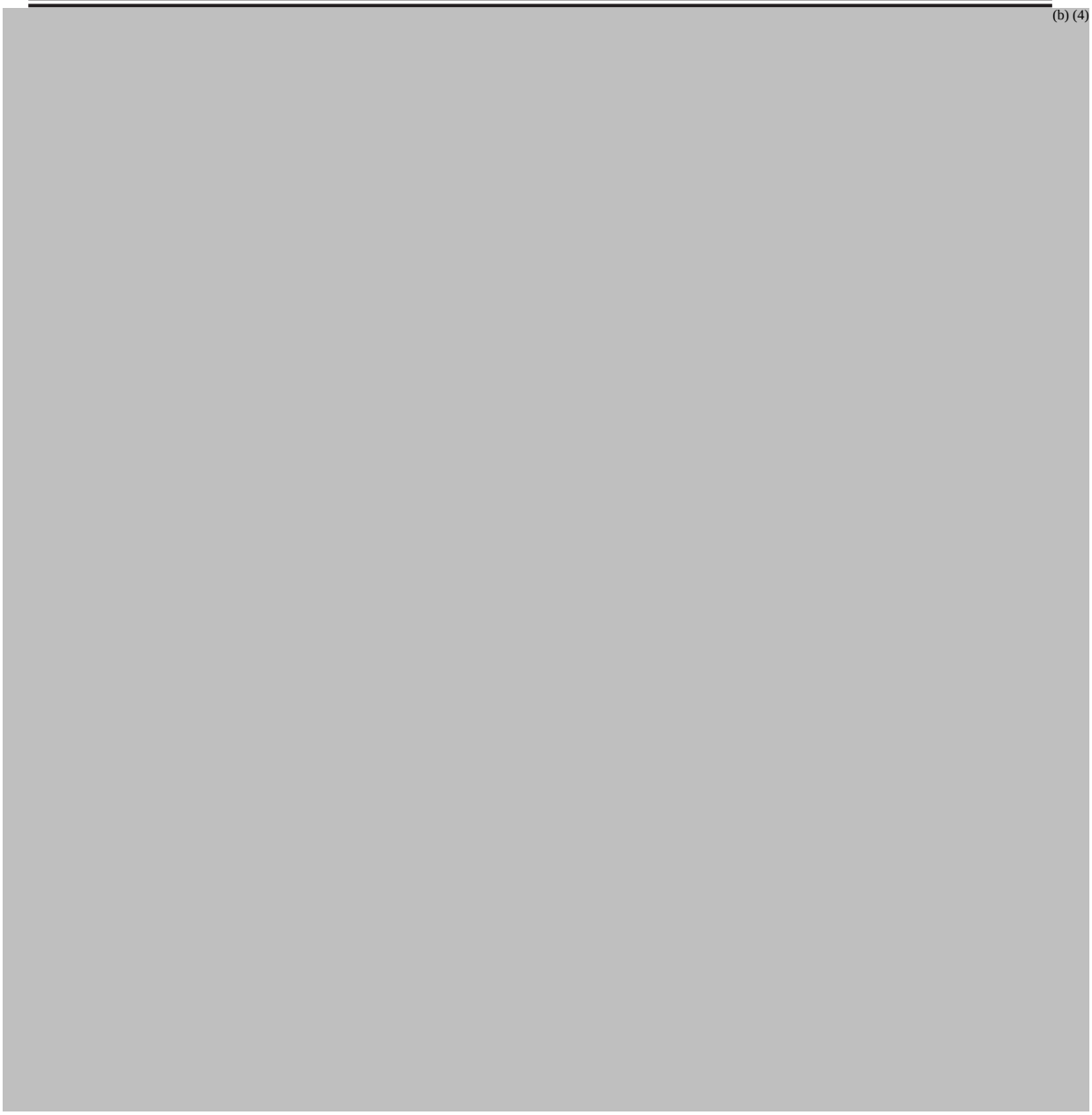
I. 21 CFR 201.50 Statement of identity; *conforms*.

J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

K. 21 CFR 201.55 Statement of dosage; *conforms*.

L. 21 CFR 201.100 Prescription drugs for human use; *conforms*.

(b) (4)



II. Carton

A. 21 CFR 610.61 Package Label:

a) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*.

b) The name, addresses, and license number of manufacturer; *conforms.*

c) The lot number or other lot identification; *conforms.*

d) The expiration date; *conforms.*

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"; *conforms*.

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; *conforms*.

h) The recommended storage temperature; *conforms*.

i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms.*

> However we concur with DMEPA's recommendation to revise the storage statement similar to the PI that reads, "Storage: Refrigerate at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE OR SHAKE. Keep the vial in the outer carton to protect from light." *Applicant revised as requested*.

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; *conforms*.

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; *not applicable*.

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"; *not applicable*.

s) The statement "Rx only" for prescription biologicals.

- 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.

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)]. *Lartruvo (olaratumab) is a monoclonal antibody, therefore exempt*.

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

D. 21 CFR 610.64 Name and address of distributor; *not applicable*.

E. 21 CFR 610.67 Bar code label requirements; *not applicable*.

Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (ND) number is located on top of the label [See 21 CFR 207.35]; *conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

(b) (4)

OBP Request: Delete the redundant statements (b) (4) Must dilute prior to use." on the side panel as this information is already communicated on the principal display panel (PDP) via the statement "Must Dilute Prior to Use". Deleting the redundant statements will also reduce clutter, thus improving the readability of the container label and carton labeling. Additionally, (b) (4) The instructions to dilute the product on the PDP are adequate for communicating what is required for safe use of the product (b) (4)

(b) (4)

Applicant revised as requested.

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *conforms*.

J. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

O. 21 CFR 201.55 Statement of dosage; *conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; *conforms*.

Additional Labeling Concerns

This section describes an additional labeling recommendation.

Confirm there is no text on the ferrule and cap overseal of the vials to comply with USP General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals. *The Applicant confirmed*.

Conclusions:

The container label and carton labeling for Lartruvo (olaratumab) 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 201.100 and United States Pharmacopeia (USP), [USP 39/NF 34 May 1, 2016 to July 31, 2016]. Labeling deficiencies were identified and resolved. The container label and carton labeling submitted on July 8, 2016 is acceptable (see below).

Container Label

(b) (4)

Carton Labeling

(b) (4)

Jibril Abdus-Samad

Digitally signed by Jibril Abdus-Samad
Date: 8/08/2016 03:26:53PM
GUID: 50814c7000007a3754a457f037f74915

Chikako Torigoe

Digitally signed by Chikako Torigoe
Date: 8/08/2016 03:30:28PM
GUID: 508da6d600026270ded10d59fae9886b

Clinical Inspection Summary

Date	July 29, 2016
From	Lauren Iacono-Connors, Reviewer
To	Ruth Maduro, Regulatory Project Manager Meredith Chuk, Clinical Reviewer Leslie Doros, Clinical Reviewer Division of Oncology Products 2
BLA #	761038
Applicant	Eli Lilly and Company
Drug	Lartruvo™ (olaratumab)
NME	Yes
Therapeutic Classification	Priority
Proposed Indication	Treatment of patients with advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery.
Consultation Request Date	March 3, 2016
Summary Goal Date	July 28, 2016
Action Goal Date	October 24, 2016
PDUFA Date	October 24, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study I5B-IE-JGDG (CP15-0806) was submitted to the Agency in support of BLA 761038. Three clinical sites, Dr. Edward Kim, M.D. (Site 15), Dr. William Tap, M.D. (Site 1), Dr. Brian Van Tine, M.D. (Site 12), the study sponsor, and one CRO (b) (4) who performed a retrospective independent radiology central review for Progression Free Survival (PFS), were selected for audit.

The primary efficacy endpoint, PFS, as reported in the application was verified with the source records generated at the inspected clinical sites and at the CRO for a sample of clinical sites. There were no significant deficiencies.

There were no significant inspectional findings for clinical investigators Dr. Edward Kim, M.D., Dr. William Tap, M.D., Dr. Brian Van Tine, M.D. the study sponsor Eli Lilly and Company, and CRO (b) (4) The data from Study I5B-IE-JGDG (CP15-0806) submitted to the Agency in support of BLA 761038, appear reliable based on available information.

II. BACKGROUND

Eli Lilly and Company [Lilly] seeks approval to market olaratumab for the treatment of patients with advanced soft tissue sarcoma. The key study supporting this application is I5B-IE-JGDG (CP15-0806). The study enrolled 15 subjects into the Phase 1b component of the study and 133 subjects into the Phase 2 component of the study (66 Investigational Arm, 67 Control Arm).

Study I5B-IE-JGDG (CP15-0806): "A Phase 1b/2 Randomized Phase 2 Study Evaluating the Efficacy of Doxorubicin With or Without a Human Anti-PDGFRα Monoclonal Antibody (IMC-3G3) in the Treatment of Advanced Soft Tissue Sarcoma."

Number of subjects: 133 subjects were enrolled into the Phase 2 component
Number of sites: 17
Number of countries where subjects were enrolled: 1 (United States)
Study Period:

Study start date: October 6, 2010
Primary outcome (progression-free survival [PFS]) data cutoff date: August 15, 2014
Date of last patient completed (final data cutoff): May 16, 2015
Primary efficacy endpoint:

(1) Progression Free Survival (PFS) per RECIST v1.1., determined by both investigator and Independent review facility (IRF).

Sponsor's interpretation of primary efficacy outcome: Time to event.

Objectives of Inspections:

a. Verify primary efficacy endpoint of PFS, as determined by the clinical investigator and the IRF, for a sample of enrolled subjects.
b. Verify key secondary efficacy endpoints for a sample of enrolled subjects:
    - Change in tumor size from baseline to best overall response (BOR)
    - Overall survival (OS)
c. Identification, documentation, and reporting of AEs for a sample of enrolled subjects.
d. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Edward Kim, M.D. Site Number: 15 825 Eastlake Avenue E. Seattle, WA 98109	Protocol: I5B-IE-JGDG (CP15-0806) Number of Subjects Enrolled: 18	April 11-22, 2016	Pending Interim classification: VAI
CI#2: Brian Van Tine, M.D., Ph.D. Site Number: 12 660 S Euclid Ave Saint Louis, MO 63110	Protocol: I5B-IE-JGDG (CP15-0806) Number of Subjects Enrolled: 24	March 21-28, 2016	NAI
Sponsor: Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana 46285	Protocol: I5B-IE-JGDG (CP15-0806)	May 9-13, 2016	Pending Interim classification: NAI
CRO: (b) (4) (Independent Radiology Review Facility) (b) (4)	Protocol: I5B-IE-JGDG (CP15-0806)	(b) (4)	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. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Edward Kim, M.D. (Site 15)

The inspection reviewed the conduct of one clinical study (I5B-IE-JGDG (CP15-0806)). The site screened 25 subjects and 18 were enrolled. At the time of this inspection, four subjects had completed the study. Study source documents/records of all enrolled subjects were compared to the eCRF and data listings submitted to BLA 761038, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, and efficacy endpoint verification, as determined by the site investigator. Assessment of study oversight and conduct by Dr. Kim included AE reporting practices, test article accountability, and general protocol compliance.

The inspection found no significant deficiencies. The efficacy endpoint, as determined by the investigator, and OS, was verifiable. There were several

inspectional observations related to AE reporting. For example, Subject 015-1008, had increased confusion and onset of falls that occurred on July 25, 2012. This AE was not reported to the sponsor. Also, one SAE was not reported to the sponsor within the protocol specified 24 hours of the site becoming aware of the event. Briefly, Subject 015-1021 was hospitalized due to hepatic hemorrhage (Grade 3) on May 12, 2013. The site became aware of the event on May 19, 2013, but did not report the SAE to the sponsor until June 14, 2013.

The inspectional observations summarized above represent exceptions to the overall conduct of the study at this site and should not importantly impact study outcomes, or have placed subjects at undue risk. The data from Site 15, associated with Study I5B-IE-JGDG (CP15-0806) appear reliable based on available information.

2. Dr. Brian Van Tine, M.D. (Site 12)

The inspection reviewed the conduct of one clinical study (I5B-IE-JGDG (CP15-0806)). The site screened 29 subjects and 24 were enrolled. At the time of this inspection, 22 subjects had died and the remaining subjects were off study. All subject records were audited. Study source documents/records of all subjects were compared to the eCRF and data listings submitted to BLA 761038, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, and efficacy endpoint verification, as determined by the site investigator. Assessment of study oversight and conduct by Dr. Van Tine included AE reporting practices, test article accountability, and general protocol compliance.

The inspection revealed no significant deficiencies. Primary efficacy endpoint data, PFS as determined by the site investigator, were verifiable. There was no evidence of under-reporting of AEs.

The data from Site 12, associated with Study I5B-IE-JGDG (CP15-0806) appear reliable based on available information.

3. Sponsor: Eli Lilly and Company [Lilly]

The inspection focused on the sponsor's control, oversight and management of Study I5B-IE-JGDG (CP15-0806). Monitoring records were reviewed from 5 clinical sites. Actions taken by the sponsor to bring non-compliant clinical sites into compliance were also assessed. Contract agreements and sponsor responsibility transfer agreements were reviewed as appropriate. Reporting practices for AEs and SAEs were also reviewed. The primary efficacy endpoint, PFS per RECIST1.1, as determined by the clinical investigators and AEs found in the EDC system were reconciled with the datalistings submitted to the application for 5 clinical sites. There were no major issues. Lilly maintained adequate oversight over the study. There was no evidence of under-reporting of AEs/SAEs.

The data from this sponsor submitted to the Agency associated with Study I5B-IE-JGDG (CP15-0806) appear reliable based on available information.

4. CRO: (b) (4) (Independent Radiology Review Vendor)

This inspection was issued to review the conduct of one clinical study (I5B-IE-JGDG (CP15-0806)), performed in support of BLA 761038. The inspection focused primarily on assessing the accuracy of the tumor response and disease progression source records as it pertains to the contractual obligations of the CRO. Subject source documents/records generated by the CRO for 79 subjects from four clinical sites were compared to the eCRF and data listings. Assessment of (b) (4) conduct of the Charter-Specified CRO responsibilities included training, education, and qualifications of radiologists, correspondence with clinical sites/sponsor, quality assurance, data collection and management, computer system validation and Independent Review Charter review and adherence.

All reviewed subjects' image readings performed by the CRO radiologists were verified against the data listings submitted to the application. There were no discrepancies. As of this inspection, there have been 148 subjects and 868 primary radiology endpoints from 17 clinical sites read by (b) (4). There was no evidence of CRO non-compliance with the Charter.

The data from this CRO, associated with Study I5B-IE-JGDG (CP15-0806) appear reliable based on available information.

The clinical investigator Dr. William Tap's inspection described below was conducted by the EMA and the results communicated to OSI.

5. Dr. William Tap, M.D. (Site 1)

This inspection was performed by European Medicines Agency (EMA) Inspectors as a routine data audit. The inspection reviewed the conduct of one clinical study (I5B-IE-JGDG (CP15-0806)). EMA considered overall study conduct, organization structure and study oversight and control. Study personnel qualifications and training, sponsor and IRB correspondence, data management, clinical monitoring, safety reporting and source data verification was also considered during the EMA inspection. The site screened 35 subjects and 32 were enrolled. Study source documents/records of all enrolled subjects were compared to the eCRF and data listings submitted to BLA 761038.

While there were inspectional observations at this site, the EMA Inspectors found no deficiencies that would affect data quality from this site or have placed subjects at undue risk.

The data from Site 1, associated with Study I5B-IE-JGDG (CP15-0806) appear reliable based on available information.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
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CONCURRENCE:

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CC:
Central Doc. Rm. BLA #761038
DOP2/Division Director/Patricia Keegan
DOP2/Clinical Team Leader/Marc Theoret
DOP2/Project Manager/Ruth Maduro
DOP2/Medical Officer/Leslie Doros
DOP2/Medical Officer/Meredith Chuk
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

LAUREN C IACONO-CONNORS
07/29/2016

SUSAN D THOMPSON
07/29/2016

KASSA AYALEW
07/29/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 7-21-2016

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S.
Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Oncology Products 2

Drug: Lartruvo (olaratumab) injection ; BLA 761038

Subject: Pregnancy and Lactation Labeling as part of original BLA

Applicant: Eli Lilly

Materials Reviewed:
- Applicant's proposed labeling
- Literature review

Consult Question: Please assist with Pregnancy and Lactation Labeling

INTRODUCTION

The applicant submitted a new molecular entity (NME) new biologic license application (BLA) on February 24, 2016, for Lartruvo (olaratumab), for the proposed indication of advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery, in combination with doxorubicin. This application was granted orphan and break through designation and a rolling review.

The Division of Oncology Products 2 (DOP 2) consulted the Division of Pediatric and Maternal Health (DPMH) on March 8, 2016 to assist with reviewing the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Product Background

Olaratumab is a recombinant human IgG1 monoclonal antibody that binds specifically to human platelet-derived growth factor receptor alpha (PDGFR-α). Platelet-derived growth factor receptor alpha is expressed on tumor and stromal cells and its signaling pathway is important in cancer cell proliferation, metastasis, and the tumor microenvironment.

The applicant did not conduct reproductive and developmental toxicity studies with olaratumab as cynomolgus monkeys are the only pharmacologically relevant species. Consistent with the alternative approach to providing information on the potential for reproductive toxicity described in ICH S6 (R1), the applicant provided a scientific literature review and assessment of the potential reproductive toxicity of olaratumab (primarily based on PDGFRα knockout mouse models) in conjunction with an embryo-fetal development study in mice using a chimeric surrogate antibody, IMC-1E10, instead of conducting a monkey study with olaratumab. DOP2 agreed to this approach in pre-BLA meetings. Literature submitted by the applicant based on PDGFR-α knockout mice suggest that inhibition of PDGFR-α signaling is teratogenic and may impair male fertility. An embryo-fetal development study in mice using a murine surrogate antibody at maternal exposures lower than the human olaratumab exposure at the recommended dose showed an increase in eye malformations and skeletal variations (additional ossification sites in the frontal/parietal skull).

Disease Background

Soft tissue sarcomas (STS) comprise a heterogeneous group of rare solid tumors originating from mesenchymal precursors.[1] STS occurs predominantly in those over 60 years of age. Although localized resected disease can often be cured, the prognosis of patients with metastatic STS is poor, with median survival of approximately one year.

The National Toxicology Program's review of the published literature on pregnancy outcomes following chemotherapy through May 2012 revealed 23 cases of sarcoma (type is not specified) out of a total of 1,247 cancer cases.[2]

[1] Chen C, Borker R, Ewing J, Tseng WY, Hackshaw MD, Saravanan S, Dhanda R, Nadler E. Epidemiology, treatment patterns, and outcomes of metastatic soft tissue sarcoma in a community-based oncology network. Sarcoma. 2014.

Pregnancy and Lactation Labeling Rule (PLLR)
The Pregnancy and Lactation Labeling Rule (PLLR) went into effect on June 30, 2015.[3] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a new subsection, 8.3 Females and Males of Reproductive Potential, under Use in Specific Populations (8). Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation.

Literature Review
A search of published literature was performed and no reports on the safety of olaratumab in pregnancy or lactation or on fertility effects were found.

DISCUSSION

Pregnancy
Olaratumab is an NME and there are no human pregnancy exposure data. Based on the drug's mechanism of action and on data from animal studies, olaratumab is likely teratogenic. The Risk Summary statements in Pregnancy labeling should reflect this information.

Lactation
Because olaratumab in combination with doxorubicin is associated with serious adverse reactions such as neutropenia and cardiac arrhythmias and dysfunction, DPMH and DOP2 agreed that women should be advised not to breastfeed. At a labeling meeting on 6-10-2016 DPMH suggested adding serious adverse reactions that occurred in adult clinical trials to Lactation in order to explain the rationale for advising women not to breastfeed. DOP2 preferred not to include this information because it is not clear if the serious adverse reactions occurred due to olaratumab or to doxorubicin.

Olaratumab has a long half-life of 11 days. Based on six half-lives, olaratumab should be cleared in 66 days. DPMH discussed that it would not be feasible to pump and discard for 66 days, and recommended not including a duration to not breastfeed. DOP2 preferred to include a recommendation to not breastfeed for a 3 month duration following treatment, in order to avoid giving the incorrect impression that women should never breastfeed following future pregnancies.

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[2] National Toxicology Program Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use during Pregnancy (May 2013).

[3] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

Females and Males of Reproductive Potential

Contraception

The applicant proposed the inclusion of recommendations to use contraception during treatment and for 3 months after treatment, under 8.3 Females and Males of Reproductive Potential. Based on the potential for fetal harm due to adverse developmental findings in animal studies at doses less than the recommended human dose and olaratumab' s mechanism of action, DPMH and DOP2 agreed for the need to add a contraception recommendation to 8.3 Females and Males of Reproductive Potential. Olaratumab' s half-life is 11 days. Based on six half-lives, olaratumab should be cleared in 66 days. Therefore, using a conservative approach, DPMH and DOP2 agreed to a duration of 3 months to continue contraception after the final dose.

Infertility

Nonclinical studies suggested a potential for reduced fertility in males, therefore a statement regarding possible impaired fertility was added to 8.3 Females and Males of Reproductive Potential.

CONCLUSION

The Pregnancy and Lactation subsections of labeling were structured to be consistent with PLLR, as follows:

- 8.1 Pregnancy
  - The "Pregnancy" subsection of Lartruvo labeling was formatted in the PLLR format to include "Risk Summary" and "Data" sections.
- 8.2 Lactation
  - The "Lactation" subsection of Lartruvo labeling was formatted in the PLLR format to include the "Risk Summary" section.
- 8.3 Females and Males of Reproductive Potential
  - The "Females and Males of Reproductive Potential" subsection of Lartruvo labeling was formatted in the PLLR format to include the "Contraception" heading for females and the "Infertility" heading for males.

DPMH LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 8.3 of the Lartruvo labeling for compliance with PLLR. DPMH discussed labeling recommendations with DOP2 at labeling meetings. DPMH recommendations are below.

See final labeling for all of the labeling revisions negotiated with the applicant.

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS

- Embryo-Fetal Toxicity: Can cause fetal harm (b) (4). Advise females (b) (4) of the potential risk to a fetus and to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose (5.3, 8.1, 8.3).

USE IN SPECIFIC POPULATIONS
Lactation: Advise women not to breastfeed (8.2)

WARNINGS AND PRECAUTIONS
5.3 Embryo-Fetal Toxicity
Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis caused malformations and skeletal variations. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose *[see Use in Specific Populations (8.1 and 8.3)* (b) (4)

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm *[see Clinical Pharmacology (12.1)]*. There are no available data on LARTRUVO use in pregnant women. No animal studies using olaratumab have been conducted to evaluate its effect on female reproduction and embryo-fetal development. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis at exposures less than the exposure at the maximum recommended human dose caused malformations and skeletal variations *[see Data]*. (b) (4)

(b) (4) In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data
No animal studies have been conducted using olaratumab to evaluate the effect of blocking PDGFRα signaling on reproduction and embryo-fetal development. In PDGFR-α knockout mice, disruption of PDGFR-α signaling resulted in embryo-fetal lethality and teratogenicity, including cleft face and spina bifida. Intravenous administration of an anti-murine PDGFR-α antibody once every 3 days to pregnant mice during organogenesis at 50 and 150 mg/kg resulted in increased malformations (abnormal eyelid development) and skeletal variations (additional ossification sites in the frontal/parietal skull). Increased post-implantation loss occurred at a dose of 5 mg/kg. The effects on fetal development in mice administered this antibody occurred at exposures less than the AUC exposure at the maximum recommended human dose of 15 mg/kg LARTRUVO.

8.2 Lactation

Risk Summary

There is no data on the presence of olaratumab in human milk, or its effects on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions in breastfed infants from olaratumab, advise women not to breastfeed during treatment with LARTRUVO and for 3 months following the last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Based on (b) (4) its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)* (b) (4) . Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose.

Infertility

Males

Based on animal models, LATRUVO may impair male fertility *[see Nonclinical Toxicology (13.1)]*.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with LARTRUVO and for 3 months after the (b) (4) dose (b) (4) to inform their healthcare provider of a known or suspected pregnancy.

Lactation

Advise women not to breastfeed during treatment with LARTRUVO and for 3 months after the last dose *[see Use in Specific Populations (8.2)]*.

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/s/

LEYLA SAHIN
07/21/2016

TAMARA N JOHNSON
07/22/2016

LYNNE P YAO
07/25/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 12, 2016
Requesting Office or Division:	Division of Oncology Products II (DOP2)
Application Type and Number:	BLA 761038
Product Name and Strength:	Lartruvo (Olaratumab) Injection, 500 mg/50 mL (10 mg/mL)
Submission Date:	July 8, 2016
Applicant/Sponsor Name:	Eli Lilly and Company
OSE RCM #:	2016-585-1
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Oncology Products II (DOP2) requested that we review the revised container label and carton labeling for Lartruvo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSION

Eli Lilly and Company incorporated our recommendations from the previous review[1], and after review of the revised label and labeling, we find them acceptable from a medication error perspective. We have no further recommendations at this time.

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

[1] Thomas S. Label and Labeling Review for Lartruvo (BLA 761038). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JUNE 01. 10 p. OSE RCM No.: 2016-585.

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/s/

SARAH E THOMAS
07/12/2016

CHI-MING TU
07/12/2016

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

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 761038

Application Type: original BLA

Drug Name(s)/Dosage Form(s): Lartruvo (olaratumab) injection, for intravenous use / 500 mg/50 mL (10 mg/mL)

Applicant: Eli Lilly and Company

Receipt Date: February 24, 2016

Goal Date: October 24, 2016

1. Regulatory History and Applicant's Main Proposals

Eli Lilly and Company (Lilly) submitted BLA 761038 on February 24, 2016 via rolling submissions for olaratumab in combination with doxorubicin for the treatment of patients with advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery. The clinical development of olaratumab (b) (4) IND 121500 on February 21, 2014. Lilly was granted Fast Track on August 21, 2014, Orphan Drug Designation for soft tissue sarcoma on October 9, 2014, and Breakthrough Therapy Designation on February 20, 2015.

Lilly met with FDA on March 4, 2015, (Type B/EOP2), June 9, 2015, (Type B/CMC), June 18, 2015, (Type B/Advisory; meeting cancelled due to acceptance of preliminary meeting comments), August 18, 2015, (Type B/Administrative; teleconference cancelled due to acceptance of preliminary meeting comments), October 6, 2015, (Type A/CMC), and October 16, 2015, (Type B/Pre-BLA).

FDA conditionally accepted the proposed proprietary name (b) (4) on July 19, 2015, and withdrew the conditional acceptance on March 7, 2016 as per Lilly's February 25, 2016, request. Lilly submitted a new propriety name request on February 24, 2016 for LARTRUVO.

As agreed to during the October 16, 2015, pre-BLA meeting, Lilly submitted the draft embryo-fetal development (EFD) study report on March 23, 2016, after the submission of the original BLA on February 24, 2016 as a minor component. An Applicant orientation meeting with Lilly was held on March 14, 2016, and the post-mid-cycle teleconference with Lilly is scheduled for June 1, 2016. Based upon preliminary review, the application will be reviewed under an 8-month priority review, with Advisory Committee review (ODAC) tentatively scheduled to occur September 14 and 15, 2016.

Clinical imaging sites will be inspected (CRO: (b) (4) BLA 761038 has been targeted for ongoing pilot study multidisciplinary review within the Office of Hematology and Oncology Products, Division of Oncology Products 2.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 7, 2016. The resubmitted PI will be used for further labeling review

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

NO

5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

   Comment: *Remove the white spacing between 1) HL Heading and HL Limitation Statement, and 2) Product Title and Initial U.S. Approval.*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

   Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	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 five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES

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

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(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, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Selected Requirements of Prescribing Information

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** 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 in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

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 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
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:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "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 practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), 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:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *Currently no approved patient labeling for LARTRUVO*

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *Currently no approved patient labeling for LARTRUVO*

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

LEAH S HER
06/06/2016
Due to RPM transition, this review was initiated by R. Maduro and uploaded by L. Her

MELANIE B PIERCE
06/07/2016

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]

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>BLA# 761038</td><td>BLA Supplement #: S- N/A</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Animal Rule Confirmatory Study (SE10)</td></tr>
<tr><td colspan="3">Proprietary Name: Lartruvo (conditional approval)
Established/Proper Name: olaratumab
Dosage Form: Injection, Solution for Intravenous Infusion
Strengths: 10 mg/mL</td></tr>
<tr><td colspan="3">Applicant: Eli Lilly and Company
Agent for Applicant (if applicable): N/A</td></tr>
<tr><td colspan="3">Date of Application: February 24, 2016
Date of Receipt: February 24, 2016
Date clock started after UN: NA</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: October 24, 2016</td><td>Action Goal Date (if different): NA</td></tr>
<tr><td colspan="2">Filing Date: April 24, 2016</td><td>Date of Filing Meeting: March 23, 2016</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s): Proposed as “LARTRUVO is a platelet-derived growth factor receptor alpha (PDGFR-α) antagonist indicated in combination with doxorubicin for the treatment of advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery”..</td></tr>
<tr><td colspan="2">Type of Original NDA: N/A
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☐ 505(b)(1)
☐ 505(b)(2)

☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☒ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☒ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): INDs (b) (4) 121500	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***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.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***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*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☐	X	

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• 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)].**	☐	☐		
• 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)]?** ***If you answered yes to any of the above bulleted 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 for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug 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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☐	☒	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ 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).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
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 (3397/3792), 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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
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)?	☐	☐	☒	
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)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☐	☒		Not submitted in the BLA, but requested in the acknowledgement letter.

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***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…"*	☒	☐	☐	
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? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☐	☒		Orphan designation was granted for STS on 10/9/14

[2]

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), 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 reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Orphan designation was granted for STS on 10/9/14
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Orphan designation was granted for STS on 10/9/14
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	The proprietary name was submitted on February 24, 2016 for review
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**

http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** 1.OSI – uploaded in DARRTS on 3/3/16 2. DMPP – uploaded in DARRTS on 4/6/16 3. QT/IRT – uploaded in DARRTS on 3/8/16 4. DPMH – uploaded in DARRTS on 3/9/16	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** March 4, 2015 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** October 16, 2015 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 23, 2016

BACKGROUND: Eli Lilly and Company (Lilly) submitted BLA 761038 on February 24, 2016 via rolling submissions for olaratumab in combination with doxorubicin for the treatment of patients with advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery. The clinical development of olaratumab was initiated under (b) (4) IND 121500 on February 21, 2014. Lilly was granted Fast Track on August 21, 2014, Orphan Drug Designation for soft tissue sarcoma on October 9, 2014, and Breakthrough Therapy Designation on February 20, 2015.

Lilly met with FDA on March 4, 2015 (Type B/EOP2), June 9, 2015 (Type B/CMC), June 18, 2015 (Type B/Advisory; meeting cancelled due to acceptance of preliminary meeting comments), August 18, 2015 (Type B/Administrative; teleconference cancelled due to acceptance of preliminary meeting comments), October 6, 2015 (Type A/CMC), and October 16, 2015 (Type B/Pre-BLA).

FDA conditionally accepted the proposed proprietary name (b) (4) on July 19, 2015, and withdrew the conditional acceptance on March 7, 2016 as per Lilly's February 25, 2016, request. Lilly submitted a new propriety name request on February 24, 2016 for LARTRUVO.

As agreed, Lilly submitted the minor Draft EFD study report on March 23, 2016, after the submission of the original BLA on February 24, 2016. An Applicant Orientation Meeting with Lilly was held on March 14, 2016, and the post-mid-cycle teleconference with Lilly is scheduled for June 1, 2016. Based upon preliminary review, the application will be reviewed under an 8-month priority review, with Advisory Committee review (ODAC) tentatively scheduled to occur September 14 and 15, 2016.

Clinical imaging sites will be inspected (CRO: (b) (4)). BLA 761038 has been targeted for ongoing pilot study multidisciplinary review within the Office of Hematology and Oncology Products, Division of Oncology Products 2.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ruth Maduro	Y
	CPMS/TL:	Melanie Pierce	N
Cross-Discipline Team Leader (CDTL)	Marc Theoret		N
Division Director	Patricia Keegan		Y
Office Director	Richard Pazdur		N
Clinical	Reviewer:	Meredith Chuk (efficacy)/ Leslie Doros (safety)	Y
	TL:	Marc Theoret	N
Clinical Pharmacology	Reviewer:	Ruby Leong	Y
	TL:	Hong Zhao	Y
• Pharmacometrics	Reviewer:	Fang Li	Y
	TL:	Jingyu (Jerry) Yu	Y
Biostatistics	Reviewer:	Huanyu (Jade) Chen	Y
	TL:	Kun He	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Emily Wearne	Y
	TL:	Whitney Helms	Y
Product Quality (CMC) Review Team:	Reviewer:	Chikako Torigoe	Y
	ATL:	Rashmi Rawat	Y
	RBPM:	Melinda Bauerlien	N
• Microbiology	Reviewer:	Monica Markovski (DS)/Natalia Pripuzova (DP)	Y
	TL:	Colleen Thomas/Patricia Hughes	Y
• Facility	Reviewer:	Ruth Moore	Y
	TL:	Peter Qiu	N
• Labeling (BLAs only)	Reviewer:	Jabril Abdus-Samad	Y
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Sharon Mills	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Nazia Fatima	N
	TL:	Jessica Cleck Derenick, Olga Salis	N
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Sarah Thomas	N
	TL:	Chi-Ming Tu (Alice)	N
OSE/DRISK (REMS)	Reviewer:	Mei-Yean Chen	Y
	TL:	Naomi Redd	Y
Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	N
	TL:	Susan Thompson	N
Other reviewers/disciplines			
• Maternal Health	Reviewer:	Leyla Sahin	Y
	TL:	Tamara Johnson	Y
Other Attendees	Lori Gorski		Y

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: Rolling submission Nonclinical 12-10-2015 CMC 12-17-2015 CMC, Nonclinical, Clinical 1-18-2016 CMC 1-27-2016 CMC, Clinical 2-22-2016 CMC 2-24-2016	☐ Not Applicable ☐ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☒ YES Date if known: 9/13/16-9/14/16 ☐ NO ☐ To be determined Reason:
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	NA; this is an original BLA ☐ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**: No review issues were identified	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • 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?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	NA
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, M.D. **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): May 20, 2016 **Comments**: Refer to the Background section.	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

LEAH S HER
06/06/2016
Due to RPM transition, this review was initiated by R. Maduro and uploaded by L. Her

MELANIE B PIERCE
06/06/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 1, 2016
Requesting Office or Division:	Division of Oncology Products II (DOP2)
Application Type and Number:	BLA 761038
Product Name and Strength:	Lartruvo (Olaratumab) Injection, 500 mg/50 mL (10 mg/mL)
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Eli Lilly and Company
Submission Dates:	January 27, 2016 and May 6, 2016
OSE RCM #:	2016-585
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the BLA review process for Lartruvo (Olaratumab) injection, the Division of Oncology Products II (DOP2) requested that we review the proposed container label and carton labeling, and prescribing information (PI) for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed container label, carton labeling, and PI to identify deficiencies that may lead to medication errors and areas for improvement.

After careful review of the proposed container label, carton labeling, and PI we found that they can be improved to promote the safe use of this product. We note that there is some inconsistency in the provision of storage information related to refrigeration and photosensitivity across the proposed container label, carton labeling, and PI. As for the PI, we note that the route is not specifically stated in some instances in the dosage and administration sections of the Highlights and Full PI. Also, information to facilitate identification of the parenteral dosage form is not provided in section 16. Thus, we provide recommendations in section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, container label, and carton labeling can be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on our review, we recommend the changes to the PI, which are presented in tracked changes in Appendix H, be implemented prior to the approval of this BLA.

4.2 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

We recommend the following changes to the container label and carton labeling be implemented prior to approval of this BLA:

A. General Recommendations (container label and carton labeling)
   1. Revise the statement [redacted] (b) (4) to read "Usual Dose: See prescribing information. "
   2. Delete the redundant statements [redacted] (b) (4) Must dilute prior to use." on the side panel as this information is already communicated on the principal display panel (PDP) via the statement "Must Dilute Prior to Use". Deleting the redundant statements will also reduce clutter, thus improving the readability of the container label and carton labeling.
   3. We note that the PI recommends to "Keep the vial in the outer carton to protect from light," and that this statement is not included on the container label or carton labeling. Therefore, revise the storage information to include information on storing the vial in its outer carton, as follows: "Storage: Refrigerate at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE OR SHAKE. Keep the vial in the outer carton to protect from light."

B. Container Label
   1. Add the statement "Keep refrigerated" to the PDP underneath the statement "Discard unused portion," similar to what is presented on the carton labeling PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lartruvo (Olaratumab) Injection that Eli Lilly and Company submitted on January 27, 2016.

Table 2. Relevant Product Information for Lartruvo (Olaratumab) Injection	
Initial Approval Date	N/A
Active Ingredient	Olaratumab
Indication	Recombinant human mAb of IgG1 that specifically binds to PDGFRa. Proposed indication is for use in combination with doxorubicin to treat patients with advanced or metastatic soft tissue sarcoma that is not amenable to curative treatment with radiotherapy or surgery.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	500 mg/50 mL (10 mg/mL)
Dose and Frequency	The expected approved dosing regimen is 15 mg/kg administered on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. For the first 8 cycles, Lartruvo is co-administered with doxorubicin, which is given on day 1 of each cycle following the Lartruvo infusion.
How Supplied	Available in single-dose, 50 mL glass vials, which are individually packaged in cartons.
Storage	Refrigerate at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton to protect from light. Do not freeze or shake the vial.
Container Closure	Type I tubing glass vial with a (b) (4) stopper (b) (4) The stopper is further sealed in place with an aluminum seal; two piece flip-top design.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 2, 2016, we searched the L:drive and AIMS using the terms Lartruvo, Olaratumab, and BLA 761038 to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two prior proprietary name reviews[1,2] in the L:Drive search, but the reviews are not applicable to this label and labeling review.

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

[1]Townsend, O. Proprietary Name Review for (b) (4) (Olaratumab) Injection (IND 121500). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 JULY 17. 20 p. RCM 2015-368195.

[2]Thomas, S. Proprietary Name Review for Lartruvo (Olaratumab) Injection (BLA 761038). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 APRIL 22. 23 p. RCM 2016-2879900.

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

/s/

SARAH E THOMAS
06/01/2016

CHI-MING TU
06/01/2016

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

BLA	761038
Brand Name	LARTRUVO
Generic Name	Olaratumab (LY3012207)
Sponsor	Eli Lilly and Company
Indication	Treatment of advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery
Dosage Form	Injection: 500 mg/50 mL (10 mg/mL) solution, single-dose vial
Drug Class	Platelet-derived growth factor receptor alpha (PDGFR-α) antagonist
Therapeutic Dosing Regimen	15 mg/kg on days 1 and 8 of each 3 week cycle until disease progression or unacceptable toxicity
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	No maximum tolerated dose was identified during the clinical development
Submission Number and Date	SDN 0002; 01/18/2016
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

In this open-label, Phase 1 study, a total of 25 patients were administrated olaratumab alone and in combination with doxorubicin. Overall summary of findings is presented in Table 1. There is no evidence from clinical data to suggest that olaratumab has the potential to delay ventricular repolarization.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds of Olaratumab 15 mg/kg and in combination with Doxorubicin 75 mg/m^2 (FDA Analysis)

Treatment	Cycle	Time (h)	Mean	Std Dev	90% CI (ms)
Doxorubicin -75 mg/m^2	Cycle 1 Day 1	0	2.3	5.7	(0.3, 4.2)
Olaratumab - 15 mg/kg	Cycle 1 Day 10	0.1	4.4	7.4	(1.5, 7.2)
	Cycle 2 Day 8	4	6.8	8.6	(2.9, 10.7)
Olaratumab - 15 mg/kg +Doxorubicin - 75 mg/m^2	Cycle 2 Day 1	0	1.7	7.8	(-1.3, 4.7)

There was no statistically significant relationship between olaratumab concentrations and ΔQTcF. The 15 mg/kg dose selected for this QT study is the therapeutic dose as proposed in the label. Since the olaratumab is a monoclonal antibody with elimination primarily by IgG breakdown, it is not anticipated to be affected by renal or hepatic impairment and the Applicant's population pharmacokinetic (PopPK) analysis showed no effect of age, sex, race or concomitant monotherapies. Furthermore, the Applicant stated that the PopPK simulations indicated that at 15 mg/kg administered on day 1 and day 8 of a 21-day cycle, the accumulation was marginal with an accumulation ratio of 1.19 for C_{max}. The C_{max} results from limited data in this study showed approximately 33% higher C_{max} with third dose compared to the first dose (refer to Figure 5). Since the olaratumab concentration data were collected in Cycle 2 (after the third dose), the study evaluated the effect on ΔQTcF with this accumulated higher concentrations. The study showed no effect of olaratumab on the PK of doxorubicin with ratio of geometric LS means (Doxorubicin + Olaratumab: Doxorubicin) being 1.05 and 0.984 for $AUC_{0\text{-}inf}$ and C_{max}.

2 PROPOSED LABEL

The Applicant proposed following labeling language:

12.2 Pharmacodynamics

(b) (4)

[redacted]

QT-IRT's proposed labeling language is stated below and is a suggestion only. We defer final labeling decisions to the Division.

(b) (4)

[redacted]

3 BACKGROUND

3.1 PRODUCT INFORMATION

Olaratumab is a fully humanized monoclonal antibody of the immunoglobulin G class 1 that specifically binds to platelet-derived growth factor (PDGF) receptor (PDGFR)α and has demonstrated activity in both in vitro and in vivo cancer models known to be driven by a PDGF-PDGFRα autocrine loop.

3.2 MARKET APPROVAL STATUS

Olaratumab is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

See Appendix 6.1.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1.

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under BLA 761038. The sponsor submitted the study report I5B-EW-JGDI for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.1 TQT STUDY

4.1.1 Title

An Open-Label Study to Evaluate the Pharmacokinetics of Doxorubicin following the Concomitant Intravenous Administration of Olaratumab (IMC-3G3) to Patients with Advanced Soft Tissue Sarcoma

4.1.2 Protocol Number

I5B-EW-JGDI

4.1.3 Study Dates

Date of first patient enrolled: 22 January 2015
Data cutoff date : 20 May 2015

4.1.4 Objectives

The primary objective of this study was to evaluate the effect of olaratumab on the PK of doxorubicin.

The secondary objectives of this study were:

- to evaluate the PK of olaratumab alone and in combination with doxorubicin
- to evaluate the safety profile of olaratumab alone and in combination with doxorubicin
- to evaluate the immunogenicity (IK) of olaratumab
- to document any antitumor activity observed with olaratumab in combination with doxorubicin.

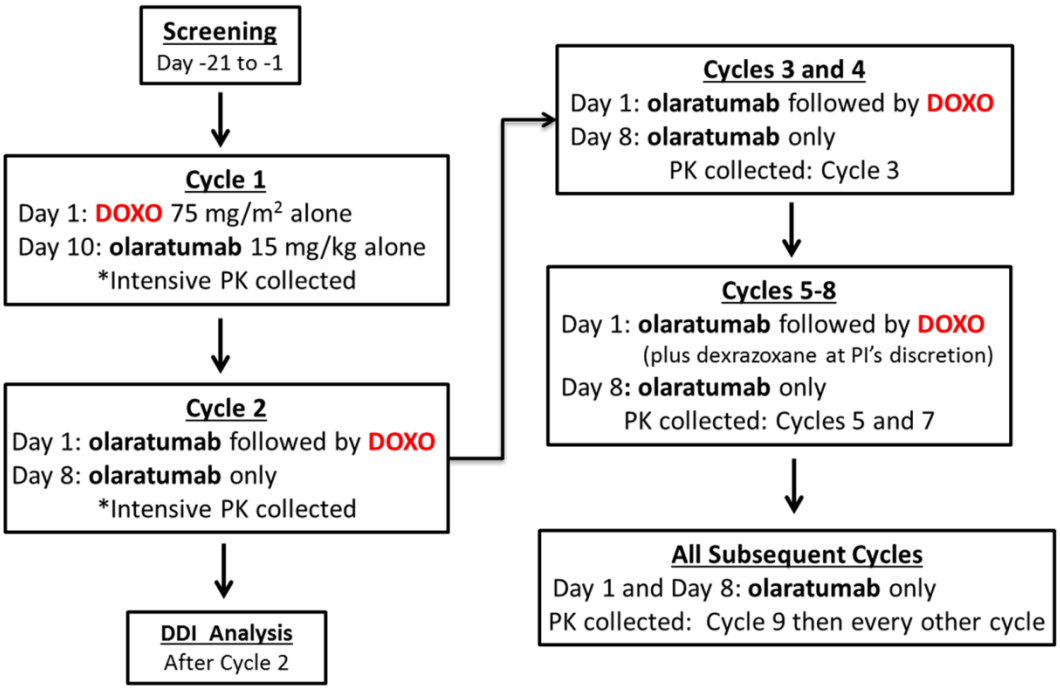
The exploratory objective of this study was to evaluate the effect of olaratumab on cardiac repolarization when given alone or in combination with doxorubicin.

4.1.5 Study Description

4.1.5.1 Design

This was a multicenter, nonrandomized, open-label, Phase 1 study in male and female patients with metastatic or locally advanced STS not amenable to treatment with surgery or curative radiotherapy. Patients were required to be aged ≥18 years, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and an echocardiogram (ECHO) or multigated acquisition (MUGA) scan with an actual left ventricular ejection fraction ≥50%. Figure 1 presented the study design.

Figure 1: Applicant's Study Design



*Cycles 1 and 2 PK Sampling Times:
Cycle 1 (doxorubicin PK): 0 (post-infusion, Day 1); 0.5, 1, 2, 4, 8, 24, 48, 72, and 96 hours post-infusion (Days 1-5); pre-infusion (Day 10)
Cycle 1 (olaratumab PK): pre-infusion (Day 1); 0 (post-infusion, Day 10); 1, 4, 24, 48, 72, and 96 hours post-infusion (Days 10-14)
Cycle 2 (doxorubicin PK): 0 (post-infusion, Day 1); 0.5, 1, 2, 4, 8, 24, 48, 72, and 96 hours post-infusion (Days 1-5)
Cycle 2 (olaratumab PK): pre-infusion (Day 1); 0 (post-infusion, Day 1); 1, 4 , 24, 48, 72, and 96 hours post-infusion (Days 1-5); pre-infusion (Day 8); 0 (post-infusion, Day 8); 1 and 4 hours post-infusion (Day 8)

Abbreviations: DDI = drug-drug interaction; DOXO = doxorubicin; PI = principal investigator; PK = pharmacokinetic(s).

A treatment cycle was defined as 21 days. For Cycles 1 through 8, the administration of each doxorubicin infusion defined Day 1. Patients were to receive the combination treatment (olaratumab + doxorubicin) for up to 8 cycles, as long as they continued to receive clinical benefit and did not develop unacceptable toxicity. From Cycle 9 onwards, patients were to receive olaratumab only. The planned duration of treatment was not fixed; patients were to remain on study until they fulfilled one of the criteria for study discontinuation. Cycles 1 to 2 represented the DDI phase of the study, during which intensive PK sampling occurred.

4.1.5.2 Controls

The Applicant did not include placebo and positive (moxifloxacin) controls.

4.1.5.3 Blinding

The study was conducted in an open-label manner.

4.1.6 Treatment Regimen

4.1.6.1 Treatment Arms

- Olaratumab was administered at 15 mg/kg as an IV infusion over 60 minutes
- Doxorubicin was administered at 75 mg/m^2 as an IV infusion over 15 minutes

4.1.6.2 Sponsor's Justification for Doses

On Cycle 1, Day 1, patients received 75 mg/m^2 doxorubicin via an approximately 15 minute IV infusion. On Cycle 1, Day 10, patients received 15 mg/kg olaratumab administered via an approximately 60-minute IV infusion.

For Cycle 2 onwards, patients received 15 mg/kg of olaratumab on Days 1 and 8 of each 21-day cycle, administered via IV infusion. On Day 1 of Cycles 2 to 8, 75 mg/m^2 of doxorubicin was to be administered via an approximately 15-minute IV infusion immediately following the completion of the olaratumab infusion.

To mitigate adverse cardiac effects due to doxorubicin, the use of dexrazoxane was allowed at the discretion of the investigator during Cycles 5 through 8 for patients who exceeded the cumulative dose of 300 mg/m^2 doxorubicin. Dexrazoxane was administered at a 10:1 ratio with the doxorubicin dose. If dexrazoxane was indicated, administration was to be performed immediately following completion of olaratumab infusion on Day 1 of each 21-day cycle. Doxorubicin was to be given within 30 minutes after beginning the infusion with dexrazoxane.

Expected high clinical scenario: Olaratumab elimination is not expected to depend on CYP-mediated metabolism or to be impacted by either renal or hepatic status. Study JGDI showed no DDI between olaratumab and doxorubicin, and PopPK analyses did not show a difference in olaratumab PK when combined with other chemotherapies (carboplatin/paclitaxel). It is thus not expected that olaratumab serum exposure would depart from expected values.

PopPK showed no effect of hepatic or renal function on either CL or V1. There were no patients with severe hepatic or renal impairment in the dataset; however, since olaratumab is a biological agent, it is not expected that its disposition is affected by renal or hepatic status.

Reviewer's Comment: No detailed justification was provided by the Applicant for the dose. The 15 mg/kg dose selected for this QT study is the therapeutic dose as proposed in the label. Since the drug is a monoclonal antibody with elimination primarily by IgG breakdown, it is not anticipated to be affected by renal or hepatic impairment and the Applicant's PopPK analysis showed no effect of age, sex, race or concomitant monotherapies. Further, the Applicant stated that the PopPK simulations indicated that at 15 mg/kg administered on day 1 and day 8 of a 21-day cycle, the accumulation was marginal with an accumulation ratio of 1.19 for C_{max}. The C_{max} results from limited data in this study showed approximately 33% higher C_{max} with third dose compared to the first dose (refer to Figure 5). Since the olaratumab concentration data was collected in Cycle 2 (after the third dose), the study could evaluate the effect on ΔQTcF with this accumulated higher concentrations. So a supratherapeutic dose may not be warranted to

explore further high exposure scenario. The combination treatment proposed for the indication involves doxorubicin which is known to induce cardiomyopathy. But the study showed no effect of olaratumab on the PK of doxorubicin with ratio of geometric LS means (Doxorubicin + Olaratumab: Doxorubicin) being 1.05 and 0.984 for $AUC_{0\text{-}inf}$ and C_{max}.

4.1.6.3 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 IV infusion.

4.1.6.4 ECG and PK Assessments

Appendix 6.2 includes the ECG and PK assessment timings.

Briefly, ECG collections were as follows:

- single point ECG at screening
- ECGs in triplicate at baseline (-2, -1.5, -1, and -0.5 hour and predose relative to study drug administration) on Cycle 1, Days 1 and 10 and Cycle 2- Days 1 and 8
- serial ECGs in triplicate for Cycle 1, Day 10 immediately post-infusion and then at 1, 4, 24, 48, 72 and 96 hour post infusion and Cycle 2- Day 8 immediately post-infusion and then at 1, and 4 hour post infusion

During Cycles 1 and 2, PK samples were taken predose on each visit and serial postdose collections that matched the nominal time of ECG collections above. ECGs were planned to be collected within 10 minutes prior to any blood draws scheduled at the same time point. Additionally, PK samples were also collected in Cycle2-Day 1 immediately post-infusion and then at 1, 4, 24, 48, 72 and 96 hour post infusion, in presence of concomitant administration of doxorubicin, although no ECGs were collected at these time points.

Reviewer's Comment: The T_{max} for the drug is approximately at 2 hours, i.e. at 1 hour post infusion in Cycle 1-Day 10 in the absence of doxorubicin and at 1.8 hours post infusion in Cycle 2-Day 1 in presence of doxorubicin. Mean olaratumab C_{max} in Cycle 1-Day 10 in the absence of doxorubicin and in absence of accumulation effect was 293 µg/mL and mean olaratumab C_{max} in Cycle 2- Day 1 in the presence of doxorubicin and with accumulation effect due to repeat dosing was 393 µg/mL. Thus, the proposed sampling for ECGs and PK are appropriate from the perspective of capturing potential effects near T_{max} and delayed effects over 96 hours post-infusion after Cycle 1-Day 10 dosing, but no ECG was collected after Cycle 2-Day 1 dosing to capture data at a higher C_{max} of olaratumab (although there could be a confounding effect at this dosing event because of presence of doxorubicin which is known to induce cardiomyopathy).

4.1.6.5 Baseline

Baseline was defined as the average of pre-infusion QTc values on Day 1.

4.1.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.1.8 Sponsor's Results

4.1.8.1 Study Subjects

A total of 25 patients, 10 male and 15 female, between the ages of 27 and 83 years with metastatic or locally advanced soft tissue sarcoma (STS) participated in this study received at least 1 dose of study drug. As of the data cutoff date, a total of 6 patients had been withdrawn from the study and 19 patients were still on study.

4.1.8.2 Statistical Analyses

4.1.8.2.1 Central Tendency Analysis

Not Provided.

Reviewer's Comments: We provided our independent analysis result in Section 5.2.

4.1.8.2.2 Assay Sensitivity

No assay sensitivity analysis performed because no positive control included in the study.

4.1.8.2.3 Categorical Analysis

4.1.8.3 Safety Analysis

No deaths had occurred during this study.

A total of 8 distinct treatment-emergent serious adverse events (SAEs) were reported for 4 patients. Of these, 6 SAEs in 4 patients (hypersensitivity, thrombocytopenia, vomiting, nausea, and 2 SAEs of neutropenia) were considered by the investigator to be related to study treatment; however, 4 out of 6 treatment-related SAEs (thrombocytopenia, vomiting, and 2 SAEs of neutropenia) occurred in Cycle 1 prior to the first dose of olaratumab and thus were considered related to doxorubicin. Four of the 6 treatment-related SAEs were Common Terminology Criteria (CTC) Grade 3 and the other 2 were Grade 4.

Most treatment-related SAEs had resolved by the time of database lock for this report (with or without concomitant medication), but 1 patient had Grade 3 SAEs of vomiting and nausea that were not recovered or resolved at the time of database lock. One patient was withdrawn from the study due to an SAE of Grade 4 hypersensitivity that was considered by the investigator to be related to olaratumab.

All 25 patients reported at least 1 AE prior to the data cutoff date. A total of treatment-emergent AEs (TEAEs) 207 were reported as of the data cutoff date, of which 120 were considered by the investigator to be related to study treatment. More than 50% of all TEAEs reported up to the cutoff date were reported during Cycle 1, with approximately two thirds of these occurring before the first dose of olaratumab.

Cardiac arrhythmia is a relatively rare but reported toxicity associated with doxorubicin and has been identified as an AESI for doxorubicin and the combination of olaratumab + doxorubicin. A predefined list of preferred terms (cardiac arrhythmias SMQ version 17.1) was used to identify all potential AEs constituting cardiac arrhythmias (Table JGDI.11.1). Based on this analysis, 4 of 25 patients (16.0%) experienced a cardiac arrhythmia;

however, 2 of these patients (Patients 8001 and 8002) had events that were preexisting (Table JGDI.8.5). None of the cardiac arrhythmias were Grade ≥3. One patient reported a Grade 2 syncope, considered by the investigator as related to doxorubicin, which resolved within 24 hours (source: prd/ly3012207/integrations/idb/programs_nonsdd/tfl_output/lissasof.r1 [Olaratumab Clinical Safety Summary analyses]). The investigator considered that the syncope was likely due to dehydration (secondary to vomiting) and not to cardiac arrhythmia.

Table 2: Applicant's Adverse Events of Special Interest of Cardiac Arrhythmias

AESI Category Preferred Term	Number of Patients with Adverse Event (%) Overall (N = 25) Any Grade	 Grade ≥3
Cardiac Arrhythmias	4 (16.0)[b]	0
Atrioventricular Block First Degree[a]	1 (4.0)	0
Bundle Branch Block Left[a]	1 (4.0)	0
Bundle Branch Block Right[a]	1 (4.0)	0
Defect Conduction Intraventricular[a]	1 (4.0)	0
Electrocardiogram PR Prolongation[a]	2 (8.0)	0
Palpitations	1 (4.0)	0
Syncope	1 (4.0)	0

Abbreviations: AESI = adverse event (AE) of special interest; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients studied.

Note: MedDRA version 17.1 was used in this analysis.

Note: Only those preferred terms that were observed are listed in table. Refer to Table JGDI.11.1 for the full list of preferred terms included in the AESI. Some patients had recorded AEs for more than 1 preferred term.

[a] The start times of these 6 AEs, which occurred on Cycle 1, Day 1, were not recorded in the database in error; therefore, they were treated as treatment emergent for the purposes of this analysis. However, the investigator has confirmed the AEs began before administration of any study treatment.

[b] 2 (8.0%) patients with the AEs in footnote [a] excluded.

Source: prd/ly3012207/integrations/idb/programs_nonsdd/tfl_output/sissaesi.r4 (Olaratumab Clinical Safety Summary analyses).

Source: Figure JGDI.8.5 in sponsor's study report, pg 44

In summary:

- The most common TEAEs reported during the study were nausea (48%) and fatigue (44%).
- Most of the gastrointestinal disorders reported were consistent with toxicities known to be associated with doxorubicin; they were monitorable and predominantly Grade ≤2.
- Three patients had Grade 4 neutropenia, but this was not associated with serious infections or febrile neutropenia.
- As with other monoclonal antibodies, infusion-related/hypersensitivity reactions were reported with olaratumab. The rate of IRR was 8% (2 patients) in this study.
- The incidence of treatment-emergent cardiac arrhythmias was 8% and the overall incidence of cardiac dysfunction was 4%. These rates were similar to what is expected with doxorubicin alone.
- The combination of olaratumab and doxorubicin has an acceptable, monitorable safety profile.
- There were no ADA positive samples in this small study, thus any impact on safety or concentration profiles could not be evaluated.

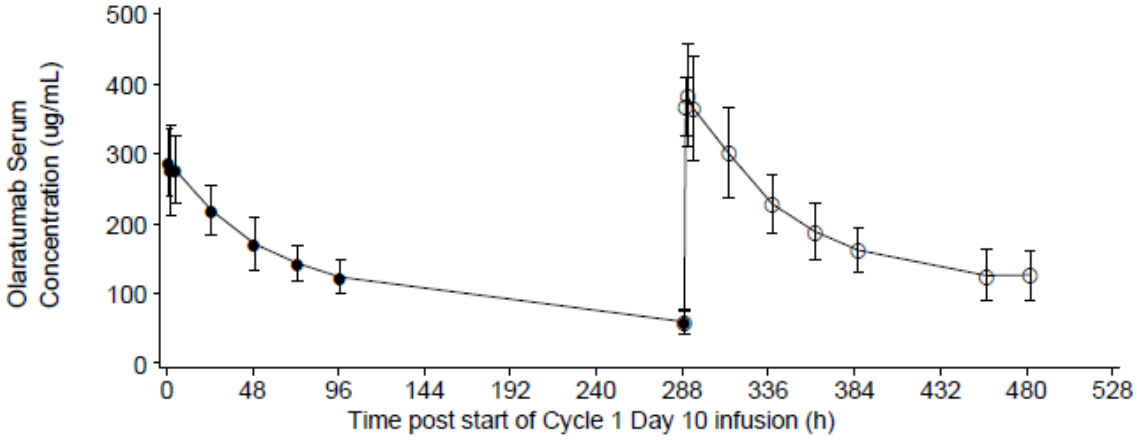
- There was no evidence of QT prolongation following administration of olaratumab in patients with metastatic or locally advanced STS.

4.1.8.4 Clinical Pharmacology

4.1.8.4.1 Pharmacokinetic Analysis

Sponsor's mean serum concentration-time profile for olaratumab following intravenous administration of therapeutic dose of olaratumab with or without doxorubicin is shown in Figure 2. The corresponding PK results are presented in Table 3.

Figure 2: Applicant's Arithmetic Mean (±Standard Deviation) Serum Concentration Profiles for Olaratumab Following Intravenous Administration of Olaratumab with or without Doxorubicin



Note: Due to variability in the actual timing of the Cycle 2, Day 1 preinfusion sample, this sample has been assigned a nominal sampling time of 288 hours for the purposes of presenting the mean data.

Source: Figure JGDI.7.3 in sponsor's study report, pg 34

Table 3: Applicant's Results for Pharmacokinetic Parameters of Olaratumab Following Intravenous Administration of Olaratumab with or without Doxorubicin

	Geometric Mean (CV%)	
Parameter	Olaratumab Only (Cycle 1, Day 10) (N = 14)	Olaratumab + Doxorubicin (Cycle 2, Day 1) (N = 15)
AUC(0-t_{last}) (µg·h/mL)	32900 (18)	33100 (19)
AUC(0-∞) (µg·h/mL)	42600 (23)[a]	56100 (29)[b]
%AUC(t_{last}-∞)	27.7 (26)	39.7 (21)
C_{max} (µg/mL)	293 (16)	393 (16)
CL (L/h)	0.0259 (31)	0.0218 (32)
$t_{1/2}$ (h)[c]	157 (112 – 211)[d]	131 (92.3 – 195)[e]
t_{max} (h)[f]	2.00 (1.00 – 23.17)	2.83 (1.80 – 6.43)
V_z (L)	5.85 (24)	4.12 (28)
V_{ss} (L)	5.63 (23)	4.00 (26)

Source: Table JGDI.7.3 in sponsor's study report, pg 35

4.1.8.4.2 Exposure-Response Analysis

The relationship between serum concentrations of olaratumab and time-matched QT interval corrected for heart rate (QTc) using Fridericia's formula (ΔQTcF; defined as QTcF at each time point minus the baseline [baseline was defined as the average of all Day 1 preinfusion readings] for each patient) was explored graphically using a double y-axis plot of time-matched ΔQTcF and mean drug concentration versus time since dosing. The plot included data from Cycle 1 only.

In addition, a linear mixed-effects model was constructed that assessed the effect of olaratumab concentrations on ΔQTcF. The response variable was the time-matched ΔQTcF value and the independent variable was the time-matched olaratumab drug concentrations at each time point.

The following linear mixed-effects model was employed to analyze the data:

ΔQTcF = Intercept + Slope * Concentrations + Random Patient + Residual Error

Based upon this relationship, the predicted ΔQTcF and its corresponding 90% 2-sided CI was computed at the geometric mean steady-state Cmax observed in the study.

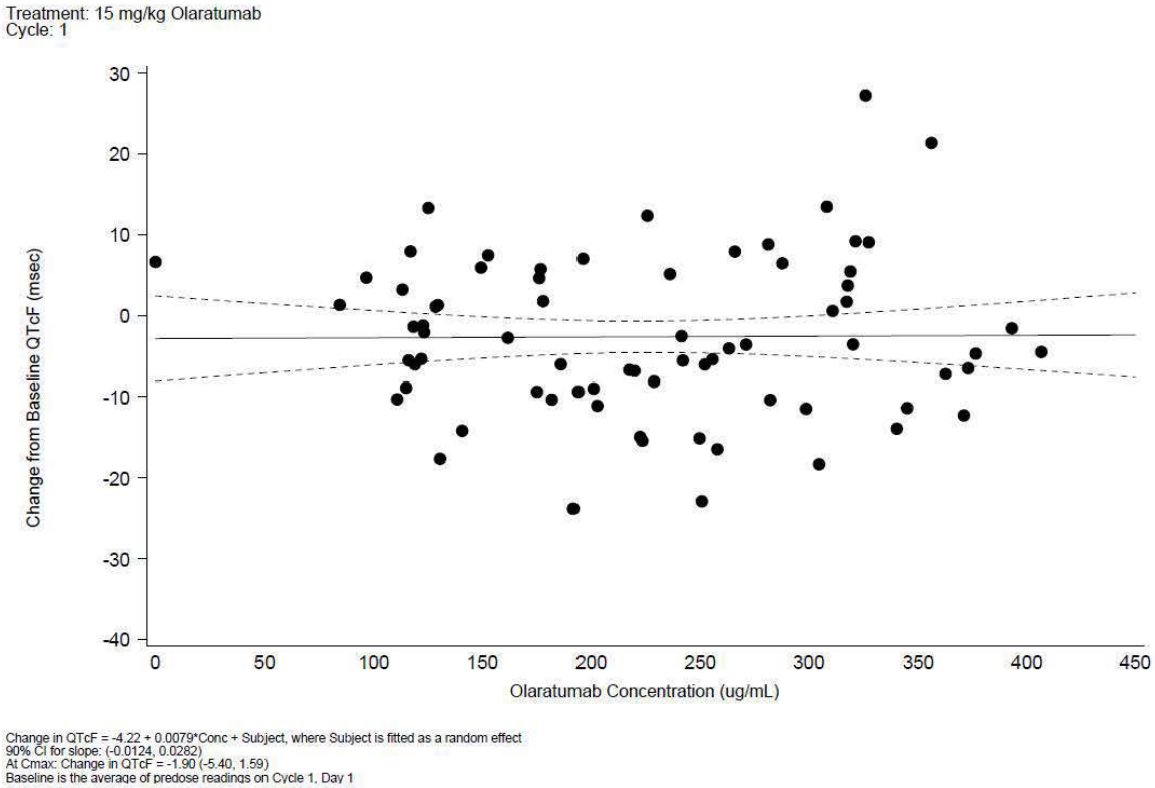
In addition, a scatter plot of ΔQTcF versus olaratumab concentrations was presented along with the fitted lines.

The same analysis was repeated with data from both Cycles 1 and 2 combined. For Cycle 2, baseline was defined as the average of all Day 1 preinfusion readings.

The 90% CI for the slope of the regression line contained zero, and the upper limit of the 90% CI at Cmax excluded 10 ms, indicating lack of a concentration-QT effect.

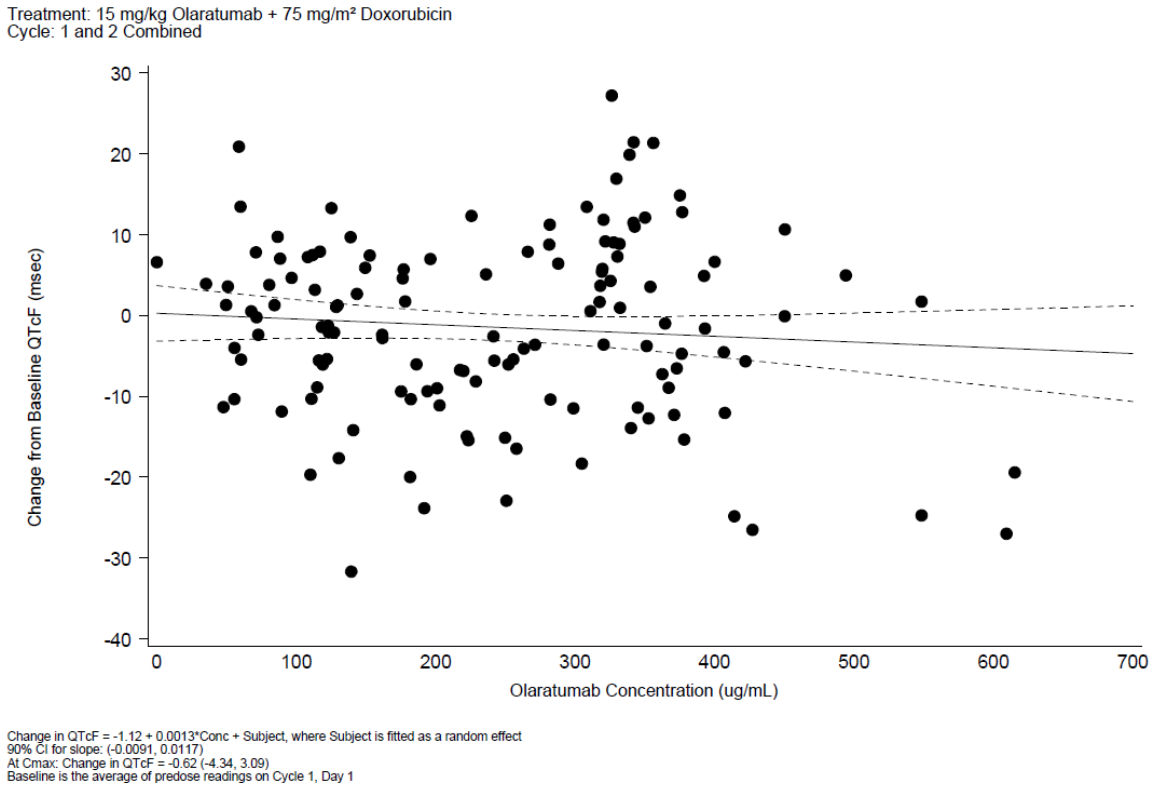
Figure 3: Applicant's Scatterplot of Changes from Baseline (Cycle 1, Day 1 Predose) in QTcF Values versus Serum Concentrations of Olaratumab

A.



Change in QTcF = -4.22 + 0.0079*Conc + Subject, where Subject is fitted as a random effect
90% CI for slope: (-0.0124, 0.0282)
At Cmax: Change in QTcF = -1.90 (-5.40, 1.59)
Baseline is the average of predose readings on Cycle 1, Day 1

B.



Source: Figures in Section 11.4.2 in sponsor's study report, pg 1151-1152

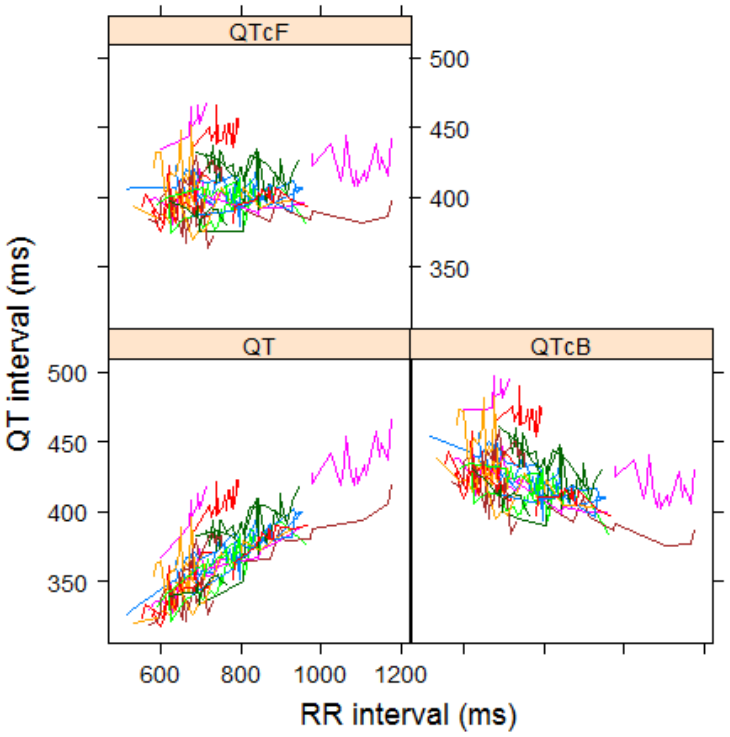
Reviewer's Analysis: A plot of ΔQTcF vs. olaratumab concentrations is presented in Figure 6.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

This review did not evaluate QT/RR correction method because the sponsor provided QTcB and QTcF correction intervals. The relationship between different correction methods and RR is presented in Figure 4.

Figure 4: 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 Olaratumab

The primary endpoint is the change from baseline of QTcF. Table 4 presents the summary statistics (mean and standard deviation) and the 90% confidence interval for the mean stratified by after a 60-minute IV infusion of 15 mg/kg olaratumab or after a 60-minute IV infusion of 15 mg/kg olaratumab followed by a 15-minute IV infusion of 75 mg/m^2 doxorubicin.

Table 4: Descriptive Statistics Results of ΔQTcF following Intravenous Administration of Olaratumab with or without Doxorubicin

Treatment	Cycle	Day	Time (h)	N	Mean	Std Dev	90% CI for Mean
Doxorubicin-75mg/m^2	Cycle 1	1	-2	25	-1.8	5.2	(-3.5, 0.0)
			-1.5	23	-1.4	3.6	(-2.7, -0.1)
			-1	25	-0.3	5.2	(-2.1, 1.5)

Treatment	Cycle	Day	Time (h)	N	Mean	Std Dev	90% CI for Mean
			-0.5	24	1.1	4.3	(-0.4, 2.6)
			0	25	2.3	5.7	(0.3, 4.2)
Olaratumab - 15 mg/kg	Cycle 1	10	-2	19	-5.6	11.1	(-10.0, -1.2)
			-1.5	20	-1.5	8.8	(-4.9, 2.0)
			-1	19	-0.4	9.1	(-4.1, 3.2)
			-0.5	20	0.6	11.5	(-3.8, 5.1)
			0	21	1.4	10.7	(-2.7, 5.4)
			0.1	20	1.8	12.1	(-2.8, 6.5)
			1	20	2.1	12.8	(-2.8, 7.1)
			4	18	-0.4	11.8	(-5.2, 4.5)
			24	17	-4.9	10.1	(-9.1, -0.6)
			48	17	-1.6	11.5	(-6.5, 3.2)
			72	16	-2.9	10.3	(-7.5, 1.6)
			96	17	-3.9	10.0	(-8.1, 0.4)
	Cycle 2	8	0	18	-0.7	13.0	(-6.0, 4.7)
			0.1	18	4.9	13.1	(-0.5, 10.3)
			1	17	1.5	12.7	(-3.8, 6.9)
			4	15	5.7	13.8	(-0.5, 12.0)
Olaratumab -15mg/kg+Doxorubicin-75mg/m^2	Cycle 2	1	0	20	4.1	12.5	(-0.7, 9.0)

5.2.1.1 Assay Sensitivity Analysis

Not applicable because no positive control arm was included.

5.2.1.2 Categorical Analysis

Table 5 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms between 480 ms and 500 ms and >500. No subject's QTcF is above 480 ms.

Table 5: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500
Olaratumab - 15 mg/kg	23	22 (95.7%)	1 (4.3%)	0 (0.0%)	0 (0.0%)

Table 6 lists the categorical analysis results for ΔQTcF. No subject's change from baseline is above 60 ms.

Table 6: Categorical Analysis of ΔQTcF

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms	60 ms<Value<=90 ms	Value>90 ms
Olaratumab -15mg/kg	23	22 (95.7%)	1 (4.3%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The primary endpoint is the change from baseline of HR. Table 7 presents the summary statistics (mean and standard deviation) and the 90% confidence interval for the mean stratified by after a 60-minute IV infusion of 15 mg/kg olaratumab or after a 60-minute IV infusion of 15 mg/kg olaratumab followed by a 15-minute IV infusion of 75 mg/m^2 doxorubicin. Table 8 presents the categorical analysis of HR. Six subjects who experienced HR intervals greater than 100 bpm are in olaratumab group.

Table 7: Descriptive Statistics Results of ΔHR Following Intravenous Administration of Olaratumab with or without Doxorubicin

Treatment	Cycle	Day	Time (h)	N	Mean	Std Dev	90% CI for Mean
Doxorubicin-75mg/m^2	Cycle 1	1	-2	25	1.5	4.8	(-0.1, 3.2)
			-1.5	23	1.2	2.1	(0.4, 1.9)
			-1	25	-0.3	3.3	(-1.4, 0.8)
			-0.5	24	-1.1	2.8	(-2.1, -0.1)
			0	25	-1.2	3.8	(-2.5, 0.1)
Olaratumab -15mg/kg	Cycle 1	10	-2	19	3.0	8.7	(-0.5, 6.5)
			-1.5	20	3.2	8.4	(-0.0, 6.5)
			-1	19	1.2	7.9	(-1.9, 4.4)
			-0.5	20	1.9	6.6	(-0.7, 4.4)
			0	21	3.7	7.8	(0.8, 6.6)
			0.1	20	4.4	7.4	(1.5, 7.2)
			1	20	4.8	6.5	(2.3, 7.3)
			4	18	8.1	9.1	(4.3, 11.8)
			24	17	3.0	7.3	(-0.0, 6.1)
			48	17	-0.5	6.9	(-3.5, 2.4)
			72	16	1.8	6.1	(-0.9, 4.4)
			96	17	5.2	8.1	(1.8, 8.6)
	Cycle 2	8	0	18	5.7	7.9	(2.4, 8.9)
			0.1	18	6.8	8.6	(3.3, 10.3)

Treatment	Cycle	Day	Time (h)	N	Mean	Std Dev	90% CI for Mean
			1	17	9.6	9.8	(5.5, 13.8)
			4	15	6.8	8.6	(2.9, 10.7)
Olaratumab - 15mg/kg+Doxorubicin-75mg/m^2	Cycle 2	1	0	20	1.7	7.8	(-1.3, 4.7)

Table 8: The Category Analysis of HR

Treatment Group	Total N	HR <= 100 bpm	HR >100 bpm
Olaratumab -15mg/kg	23	17 (73.9%)	6 (26.1%)

5.2.3 PR Analysis

The primary endpoint is the change from baseline of PR. Table 9 presents the summary statistics (mean and standard deviation) and the 90% confidence interval for the mean stratified by after a 60-minute IV infusion of 15 mg/kg olaratumab or after a 60-minute IV infusion of 15 mg/kg olaratumab followed by a 15-minute IV infusion of 75 mg/m^2 doxorubicin. Table 10 presents the categorical analysis of PR. Two subjects who experienced PR intervals greater than 200 ms are in olaratumab group.

Table 9: Descriptive Statistics Results of ΔPR Following Intravenous Administration of Olaratumab with or without Doxorubicin

Treatment	Cycle	Day	Time(h)	N	Mean	Std Dev	90% CI for Mean
Doxorubicin-75mg/m^2	Cycle 1	1	-2	24	-3.4	7.0	(-5.9, -1.0)
			-1.5	22	-0.5	4.2	(-2.0, 1.0)
			-1	24	0.6	6.9	(-1.9, 3.0)
			-0.5	22	1.8	8.2	(-1.3, 4.8)
			0	24	1.7	5.3	(-0.1, 3.6)
Olaratumab -15mg/kg	Cycle 1	10	0	20	-4.2	9.2	(-7.8, -0.7)
			0.1	19	-3.2	10.3	(-7.3, 0.9)
			1	19	-5.3	12.7	(-10.3, -0.2)
			4	17	-8.0	12.1	(-13.1, -2.8)
			24	16	-8.7	14.3	(-15.0, -2.4)
			48	16	-9.3	14.3	(-15.6, -3.1)
			72	15	-9.6	12.6	(-15.3, -3.8)
			96	16	-8.6	16.1	(-15.6, -1.5)

Treatment	Cycle	Day	Time(h)	N	Mean	Std Dev	90% CI for Mean
	Cycle 2	8	0	17	-9.3	18.7	(-17.2, -1.3)
			0.1	17	-2.5	13.2	(-8.1, 3.1)
			1	16	-6.8	11.8	(-12.0, -1.6)
			4	14	-5.4	14.2	(-12.1, 1.3)
Olaratumab -15mg/kg+Doxorubicin-75mg/m^2	Cycle 2	1	0	19	-5.0	10.3	(-9.2, -0.9)

Table 10: Categorical Analysis for PR

Treatment Group	Total N	PR <= 200 ms	PR >200 ms
Olaratumab -15mg/kg	22	20 (90.9%)	2 (9.1%)

5.2.4 QRS Analysis

The primary endpoint is the change from baseline of QRS. Table 11 presents the summary statistics (mean and standard deviation) and the 90% confidence interval for the mean stratified by after a 60-minute IV infusion of 15 mg/kg olaratumab or after a 60-minute IV infusion of 15 mg/kg olaratumab followed by a 15-minute IV infusion of 75 mg/m^2 doxorubicin. Table 12 presents the categorical analysis of QRS. Three subjects who experienced QRS intervals greater than 110 ms are in olaratumab group.

Table 11: Descriptive Statistics Results of ΔQRS Following Intravenous Administration of Olaratumab with or without Doxorubicin

Treatment	Cycle	Day	Time(h)	N	Mean	Std Dev	90% CI for Mean
Doxorubicin-75mg/m^2	Cycle 1	1	-2	25	0.8	5.1	(-0.9, 2.6)
			-1.5	23	1.0	2.9	(-0.1, 2.0)
			-1	25	-0.8	5.0	(-2.5, 0.9)
			-0.5	23	-0.3	3.3	(-1.5, 0.9)
			0	25	-0.6	4.2	(-2.1, 0.8)
Olaratumab -15mg/kg	Cycle 1	10	-2	19	-4.0	5.6	(-6.2, -1.7)
			-1.5	20	-1.9	3.7	(-3.4, -0.5)
			-1	19	-2.6	5.3	(-4.7, -0.5)
			-0.5	20	-1.8	6.6	(-4.3, 0.8)
			0	21	-1.1	6.5	(-3.6, 1.3)
			0.1	20	-3.1	6.1	(-5.5, -0.8)
			1	20	-2.3	5.5	(-4.4, -0.1)
			4	18	-3.3	3.3	(-4.7, -2.0)

Treatment	Cycle	Day	Time(h)	N	Mean	Std Dev	90% CI for Mean
			24	17	-0.9	6.5	(-3.7, 1.9)
			48	17	-0.5	4.5	(-2.4, 1.4)
			72	16	-0.8	5.5	(-3.2, 1.7)
			96	17	-0.6	4.8	(-2.6, 1.5)
	Cycle 2	8	0	18	-2.6	5.3	(-4.8, -0.4)
			0.1	18	-0.4	5.7	(-2.8, 1.9)
			1	17	-1.0	7.0	(-4.0, 1.9)
			4	15	-1.0	5.9	(-3.7, 1.7)
Olaratumab -15mg/kg+Doxorubicin-75mg/m^2	Cycle 2	1	0	20	-0.0	5.7	(-2.2, 2.2)

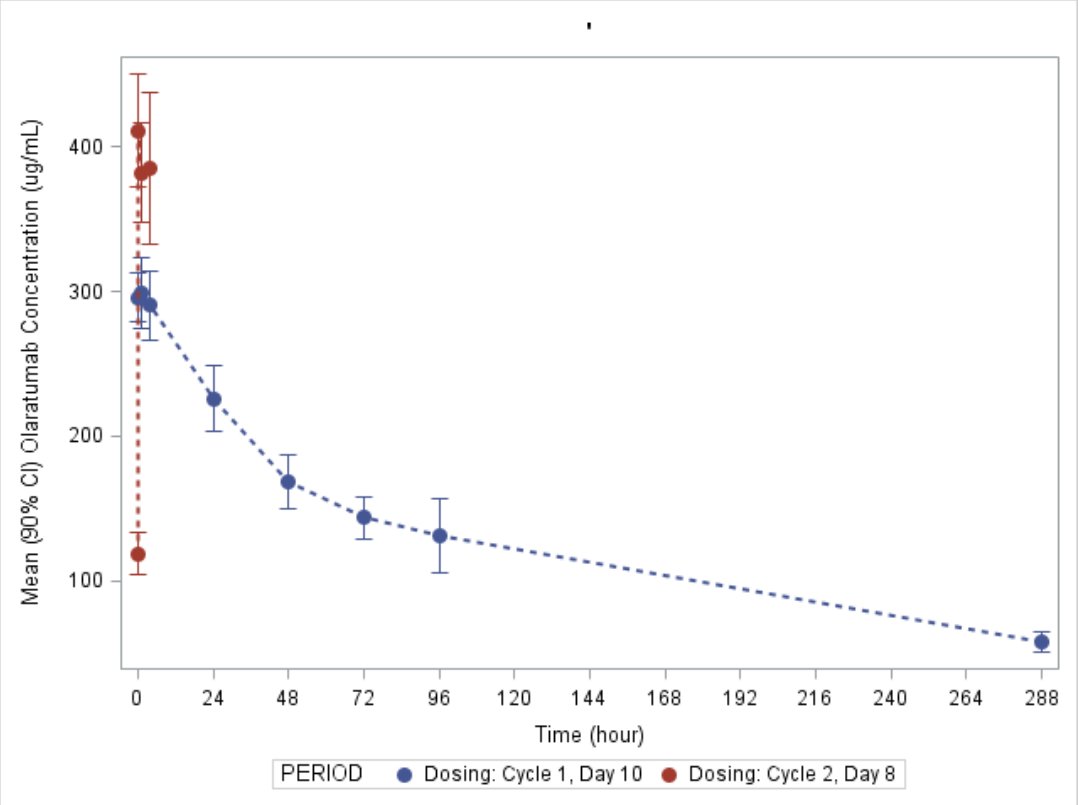
Table 12: Categorical Analysis for QRS

Treatment Group	Total N	QRS <= 110 ms	QRS > 110 ms
Olaratumab -15mg/kg	23	20 (87.0%)	3 (13.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

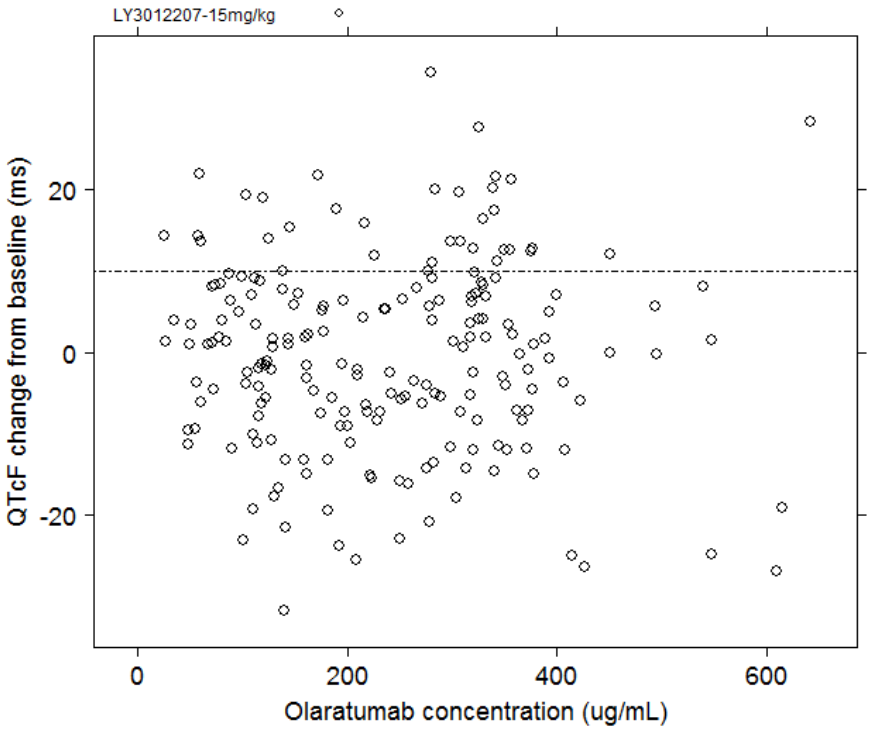
The mean drug concentration-time profile is illustrated in Figure 5.

Figure 5: Mean Olaratumab Concentration-time Profiles after 15 mg/kg Dosing on Day 10 in Cycle 1 (Blue Line) and Day 8 in Cycle 2 (Red Line) in 21 Day Cycle



The relationship between ΔQTcF and olaratumab concentrations was investigated by linear mixed-effects modeling and the slope of this relationship was not statistically significant. The relationship between ΔQTcF and olaratumab concentrations is visualized in Figure 6 with no evident exposure-response relationship.

Figure 6: ΔQTcF vs. Olaratumab Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Cardiac safety assessments

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

One patient reported a Grade 2 syncope, considered by the investigator as related to doxorubicin, which resolved within 24 hours. The investigator considered that the syncope was likely due to dehydration (secondary to vomiting) and not to cardiac arrhythmia.

There is an increase in heart rate after administration of olaratumab in Cycles 1 and 2, which peaked at approximately 8 to 10 bpm above baseline (predose on Cycle 1, Day 1) and persisted until approximately 24 hours postinfusion. Six subjects experienced heart rates greater than 100 bpm.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Although there were no mean increases in the PR and QRS intervals, 2 patients reported prolonged PR intervals on day 1 of cycle 1. It's not known if these AEs are related to study drug because the start times of the AEs were not recorded, but the investigator confirmed that the AEs began prior to dosing.

- Patient 8001 experienced AEs of Grade 1 ECG PR prolongation and atrioventricular block first degree on Day 1 of Cycle 1 that were ongoing at study cutoff.
- Patient 8002 experienced AEs of Grade 1 left and right bundle branch block, defect conduction intraventricular, ECG PR prolongation, and ECG ST-T change on Day 1 of Cycle 1 that were ongoing at study cutoff.

6 APPENDICES

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	The maximum proposed clinical dosing regimen is 15 mg/kg administered as a 1-hour infusion on Days 1 and 8 of a 21-day cycle. The following mean (%CV) C_{max} and AUC at steady state with the maximum proposed clinical dosing regimen were estimated by PopPK modeling: • C_{max} = 423 (17.7% CV) ug/mL • $AUC_{0\text{-}504hr}$ = 100800 (29.9% CV) ug.hr/mL
Maximum tolerated dose	• No maximum tolerated dose was identified during the clinical development of olaratumab. • In the 39-week monkey study the no-observed-adverse-effect-level was 75 mg/kg.
Principal adverse events	The most common adverse events in Study JGDG and Study JGDI are summarized in the appended tables (see SCS Section 2.7.4A and 2.7.4B). In Phase 2 portion of Study JGDG (appended tables), the most common TEAEs observed in the Investigational Arm (olaratumab plus doxorubicin) were: • Nausea, n=47 (73.4%); • Fatigue (consolidated term including fatigue and asthenia), n=44 (68.8%); • Musculoskeletal pain (consolidated terms including arthralgia, back pain, bone pain, flank pain, groin pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity), n=41 (64.1%); • Neutropenia (consolidated terms including leukopenia, neutropenia, decreased neutrophil count, and decreased white blood cell count), n=38 (59.4%); • Mucositis (consolidated terms including stomatitis, mucosal inflammation, and oropharyngeal pain), n=34 (53.1%); and • Alopecia, n=33 (51.6%). In the Control Arm (doxorubicin alone), the most common TEAEs observed were: • Fatigue (consolidated term, see above), n=45 (69.2%); • Nausea, n=34 (52.3%); • Alopecia, n=26 (40.0%); • Neutropenia (consolidated term, see above), n=25 (38.5%); • Anemia (consolidated terms including anemia and hemoglobin decreased), n=24 (36.9%);

	• Mucositis (consolidated terms, see above), n=23 (35.4%); and • Constipation, n=21 (32.3%). As shown in the appended tables, in Study JGDG (Phase 1b) the most frequently reported TEAEs considered related to study therapy were: • Anemia, n=11 (73.3%); • Neutropenia, n=9 (60.0%); • Nausea and fatigue, n=8 (53.3%) for each. In Study JGDI, the most frequently reported TEAEs considered related to study therapy were: • Nausea, n=12 (48.0%); • Fatigue, n=10 (40.0%); and • Neutropenia, n=7 (28.0%). As shown in the appended tables, the most frequently reported Grade ≥3TEAEs were neutropenia (n=5 [33.3%]) and anemia (n=4 [26.7%]) in Study JGDG (Phase 1b) and neutropenia (n=6 [24.0%]) in Study JGDI. In the Phase 1 and 2 studies, olaratumab monotherapy was well tolerated, with no dose-limiting toxicities (DLTs) observed across a wide variety of doses and schedules. For additional information, please see Sections 2.7.4B and 2.7.4C of the Summary of Clinical Safety (SCS). No DLTs were reported in the Phase 1b portion of Study JGDG, where olaratumab was given in combination with doxorubicin.

Maximum dose tested	Single Dose	Not applicable
	Multiple Dose	In Study JGDC, the maximum dose tested was a total dose of approximately 60-65 mg/kg over a 6-week period, administered according to one of two different regimens: • 16 mg/kg administered on D1, D8, D15, and D22 of a 42-day cycle • 20 mg/kg administered every 14 days
Exposures Achieved at Maximum Tested Dose	Single Dose	Non Applicable
	Multiple Dose	Simulations performed with the PopPK model (on file and available upon request) indicate that the following serum exposures are reached at the maximum tested doses: <u>At 16 mg/kg administered D1, D8, D15, and D22 of a 42-day cycle</u> $C_{max,ss}$ = 480 (18.1% CV) ug/mL $AUC_{0\text{-}1008hr,ss}$ = 208920 (29.3% CV) ug.hr/mL <u>At 20 mg/kg on Day 1 of a 14-day cycle</u> $C_{max,ss}$ = 481 (16.0% CV) ug/mL $AUC_{0\text{-}336hr,ss}$ = 68162 (30.1% CV) ug.hr/mL
Range of linear PK	Like most biologics, olaratumab has nonlinear PK due to target-mediated drug disposition. PK data available with the validated assay have made it possible to establish that the PK of olaratumab is linear at the following doses: • 15 mg/kg on D1, D8 of a 21-day cycle • 20 mg/kg on D1 of a 14-day cycle	
Accumulation at steady state	PopPK simulations indicate that at 15 mg/kg administered on D1 and D8 of a 21-day cycle, R_{Cmax} = 1.19 and $R_{AUC0\text{-}504hr}$ = 1.43.	
Metabolites	Not Applicable	
Absorption	Absolute/Relative Bioavailability	Not Applicable
	T_{max}	Not Applicable
Distribution	V_d/F or V_d	Population PK (PopPK) analyses yielded the following estimates for olaratumab volume of distribution: Central Compartment: V1 = 4.16 L (15.6% CV) Peripheral Compartment: V2 = 3.58 L

	% bound	Non Applicable
Elimination	Route	Olaratumab linear PK at the doses studied in STS patients suggest that the elimination of olaratumab is primarily driven by IgG breakdown
	Terminal t½	PopPK estimate = 11.3 days
	CL/F or CL	PopPK estimate for CL = 0.0233 L/hr (33.3% CV)
Intrinsic Factors	Age	PopPK showed no effect of age on either CL or V1
	Sex	PopPK showed no effect of sex on either CL or V1
	Race	PopPK showed no effect of race on either CL or V1
	Hepatic & Renal Impairment	PopPK showed no effect of hepatic or renal function on either CL or V1. There were no patients with severe hepatic or renal impairment in the dataset; however, since olaratumab is a biological agent, it is not expected that its disposition is affected by renal or hepatic status.
Extrinsic Factors	Drug interactions	Study JGDI (effect of olaratumab on the PK of doxorubicin) Ratio of Geometric LS Means (Doxorubicin + Olaratumab:Doxorubicin) (90% confidence interval [CI]) indicate no effect of olaratumab on the PK of doxorubicin: $AUC_{(0-\infty)}$ (ng·h/mL): 1.05 (0.948, 1.17) $AUC_{(0-tlast)}$ (ng·h/mL): 1.06 (0.939, 1.19) C_{max} (ng/mL): 0.984 (0.755, 1.28) PopPK Analyses (effect of concomitant chemotherapies on the PK of olaratumab) There was no apparent change in olaratumab CL when combined with either doxorubicin or carboplatin/paclitaxel
	Food Effects	Non Applicable
Expected High Clinical Exposure Scenario	Olaratumab elimination is not expected to depend on CYP-mediated metabolism or to be impacted by either renal or hepatic status. Study JGDI showed no DDI between olaratumab and doxorubicin, and PopPK analyses did not show a difference in olaratumab PK when combined with other chemotherapies (carboplatin/paclitaxel). It is thus not expected that olaratumab	

	serum exposure would depart from expected values.
Preclinical Cardiac Safety	A thorough evaluation was done in all repeat-dose studies up to 39 weeks, in which olaratumab was administered by weekly intravenous infusion to monkeys at doses up to 75 mg/kg. Electrocardiogram (ECG) and measurements of heart rate and blood pressure were performed during acclimation, on designated treatment days, and in the recovery period. No treatment-related effects were evident upon on assessments of blood pressure, heart rate, and ECG.
Clinical Cardiac Safety	The effect of olaratumab on cardiac repolarization was studied in Study JGDI, in which a total of 133 mean QTc observations were available from 15 patients who had received olaratumab at a dose of 15 mg/kg in the absence of doxorubicin. The total range of olaratumab serum concentrations corresponding to these QTc observations was 0 to 615.207 µg/mL. Visual inspection revealed no relationship between ΔQTcF values and olaratumab concentrations. In addition, the 90% CI for the slope of the regression line contained zero, and the upper limit of the 90% CI at C_{max} excluded 10 ms, indicating lack of a concentration-QT effect.

6.2 TABLE OF PK AND ECG ASSESSMENTS

Pharmacokinetic/Pharmacodynamic Sampling Schedule for Cycle 1

Cycle	Day	Dosing[a]		Sampling Time (hour)[b]	Pharmacokinetic Assessments		Electrocardiogram	Immunogenicity[e,f]
		Doxorubicin	Olaratumab		Doxorubicin[c]	Olaratumab[c]		
1	1			Pre-infusion		X	X[d]	X
		X						
				Immediately postinfusion	X			
				0.5	X			
				1	X			
				2	X			
				4 ± 0.5	X			
				8 ± 0.5	X			
	2			24 ± 3	X			
	3			48 ± 3	X			
	4			72 ± 3	X			
	5			96 ± 3	X			
	10			Pre-infusion	X		X[d]	
			X					
				Immediately postinfusion		X	X	
				1		X	X	
				4 ± 0.5		X	X	
	11			24 ± 3		X	X	
	12			48 ± 3		X	X	
	13			72 ± 3		X	X	
	14			96 ± 3		X	X	

[a] Olaratumab 15 mg/kg and doxorubicin 75 mg/m^2 will be administered as a 60-minute and 15-minute infusions, respectively.
[b] Time 0 is defined as end of infusion.
[c] Samples of approximately 3 mL of whole blood will be drawn into tubes. For the olaratumab samples, olaratumab serum PK measurements will be performed. For the doxorubicin samples, doxorubicin plasma PK measurements will be performed.
[d] Triplicate ECGs to be performed: -2, -1.5, -1, and -0.5 hour and predose (relative to study drug administration). ECGs should be collected within 10 minutes prior to any blood draws scheduled at the same time point.
[e] Samples of approximately 4 mL will be collected.
[f] In addition to the scheduled immunogenicity sampling, in the event of an infusion-related reaction, samples are to be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event.

Pharmacokinetic/Pharmacodynamic Sampling Schedule for Cycle 2

Cycle	Day	Dosing[a]		Sampling Time (hour)[b]	PK Assessments		ECG[d]	Immunogenicity[e,f]
		Doxorubicin	Olaratumab		Doxorubicin[c]	Olaratumab[c]		
2	1			Pre-infusion		X	X	X
			X					
		X						
				Immediately postinfusion	X	X		
				0.5	X			
				1	X	X		
				2	X			
				4 ± 0.5	X	X		
				8 ± 0.5	X			
	2			24 ± 3	X	X		
	3			48 ± 3	X	X		
	4			72 ± 3	X	X		
	5			96 ± 3	X	X		
	8			Pre-infusion		X	X	
			X					
				Immediately postinfusion		X	X	
				1		X	X	
				4 ± 0.5		X	X	

Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic(s).

[a] Olaratumab 15 mg/kg and doxorubicin 75 mg/m^2 will be administered as a 60-minute and 15-minute infusions, respectively.

[b] Time 0 is defined as the end of doxorubicin infusion on Day 1 and olaratumab infusion on Day 8.

[c] Samples of approximately 3 mL of whole blood will be drawn into tubes. For the olaratumab samples, olaratumab serum PK measurements will be performed. For the doxorubicin samples, doxorubicin plasma PK measurements will be performed.

[d] ECGs should be collected within 10 minutes prior to any blood draws scheduled at the same time point.

[e] Samples of approximately 4 mL will be collected.

[f] In addition to the scheduled immunogenicity sampling, in the event of an infusion-related reaction, samples are to be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event.

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CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Oncology Products 2
Office of Hematology and Oncology Products
February 13, 2015

Summary Box

1. IND Number: 121500
2. Company name: Eli Lilly
3. Drug name: Olaratumab
4. Indication: treatment of locally advanced, unresectable, and/or metastatic soft tissue sarcomas.
5. The drug is intended for use in combination with doxorubicin to treat a serious or life-threatening disease or condition.
6. The preliminary clinical evidence suggests substantial improvement on a clinically significant endpoint over available therapies.

Division: Oncology Products 2 (DOP2)
Clinical Reviewer: Jennie Chang, PharmD
Clinical Team Leader: Marc Theoret, MD

I. Brief description of the drug

Olaratumab is a human, immunoglobulin G, class 1 (IgG1) monoclonal antibody, IMC-3G3, that targets PDGFRα. IMC-3G3 possesses high affinity for PDGFRα (Kd = 0.04 nM) and is an antagonist of PDGF-AA, -BB, -CC ligand binding. In addition to blocking ligand-induced cell mitogenesis and receptor autophosphorylation, olaratumab inhibits phosphorylation of the downstream signaling molecules Akt and mitogen-activated protein kinase. According to the Sponsor, this inhibition is seen in both a porcine aortic endothelial cell line transfected with PDGFRα and tumor cell lines expressing PDGFRα. IMC-3G3 inhibited the proliferation of U118 glioblastoma, SKLMS-1 leiomyosarcoma, and KHOS/NP osteosarcoma human tumor xenografts grown in athymic mice. In the leiomyosarcoma and osteosarcoma xenografts models, IMC-3G3 showed an enhanced antitumor effect when combined with doxorubicin.

II. Brief description of the disease and intended population

Soft tissue sarcomas (STS) comprise a heterogeneous group of solid tumors that arise from a common mesenchymal precursor that differentiates into many various tissue lineages. They comprise a group of relatively uncommon tumors that possess distinct histological and morphological characteristics. Sarcomas have traditionally been divided into two major categories: bone sarcomas and STS. Soft tissue sarcomas occur more frequently and represent approximately 1% of all malignancies in adults. These tumors

may arise in a variety of sites that include soft tissues, skin, muscle, and internal organs, with differentiation patterns similar to smooth muscle, adipocyte, striated muscle, endothelium or fibrocyte, all mesenchymal in origin. Examples of sarcomas include liposarcoma, synovial sarcoma, leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma, and angiosarcoma. The most common STS are undifferentiated/unclassified soft tissue sarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor. Based on histologic subtype, some STS are more chemosensitive than others.

In 2014, it is estimated that there will be 12,020 new soft tissue sarcoma cases and 4,740 deaths from soft tissue sarcoma in the United States.[1] The five-year survival rates were 90%, 70%, 50%, and 10-20% for Stage I, II, III, and IV disease, respectively.[2]

III. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

The endpoint used by the Sponsor in the clinical data submitted to support the request for breakthrough designation is overall survival (OS). Eli Lilly also provided data on progression-free survival (PFS).

Pazopanib was approved by FDA in 2012 for treatment of patients with metastatic STS who had received prior chemotherapy based on demonstration of an improvement in PFS, as shown in Table 1.

IV. Brief description of available therapies

Prognosis depends on a variety of factors most importantly patient age and tumor size, histologic grade, mitotic activity and stage. Surgical resection is the standard of care for all soft tissue sarcomas. For patients with advanced disease, prognosis is poor and treatment consists of judicious use of chemotherapy to minimize symptoms and delay disease progression. Although the role for chemotherapy in advanced disease is unclear, doxorubicin with or without ifosfamide is generally considered the standard therapy for advanced, unresectable disease; however, a recently published phase 3 study showed that addition of ifosfamide to doxorubicin in the first-line treatment of patients with advanced or metastatic soft tissue sarcoma did not prolong overall survival compared with single-agent doxorubicin.[3] Many agents are used in refractory disease, including dacarbazine, gemcitabine and docetaxel, ifosfamide, but none have been shown to improve survival. Pazopanib was recently approved for use in patients with advanced soft tissue sarcomas who have received prior therapy but did not prolong overall survival. There are no FDA-

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[1] Siegel R, Ma, J, Zhaohui Z, et al. Cancer statistics, 2014. CA Cancer J Clin. 2014; 64:9-29.

[2] Nedea EA, DeLaney TF. Sarcoma and skin radiation oncology. Hematol Oncol Clin North Am. 2006;20(2):401–429.

[3] Judson I1, Verweij J2, Gelderblom H3, et al; European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014;15:415-23.

approved therapies that have demonstrated improved in overall survival in patients with unresectable or metastatic STS.

Table 1 summarizes the FDA-approved systemic therapies for the STS indication:

Table 1. FDA-approved Therapy for Soft-Tissue Sarcomas

Drug Approval Year	Indication	Clinical Benefit/Effect
Doxorubicin	Metastatic STS	ORR of 10 to 25%
Pazopanib 2012	Advanced STS who have received prior chemo	mPFS: 4.6 vs. 1.6 months HR (95% CI): 0.35 (0.26, 0.48) BORR: 4% vs. 0% mDOR (95% CI): 9.0 months (3.9, 9.2)

Abbreviations in table: BORR, best overall response rate; HR, hazard ratio; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; BORR, best overall response rate; OS, overall survival.

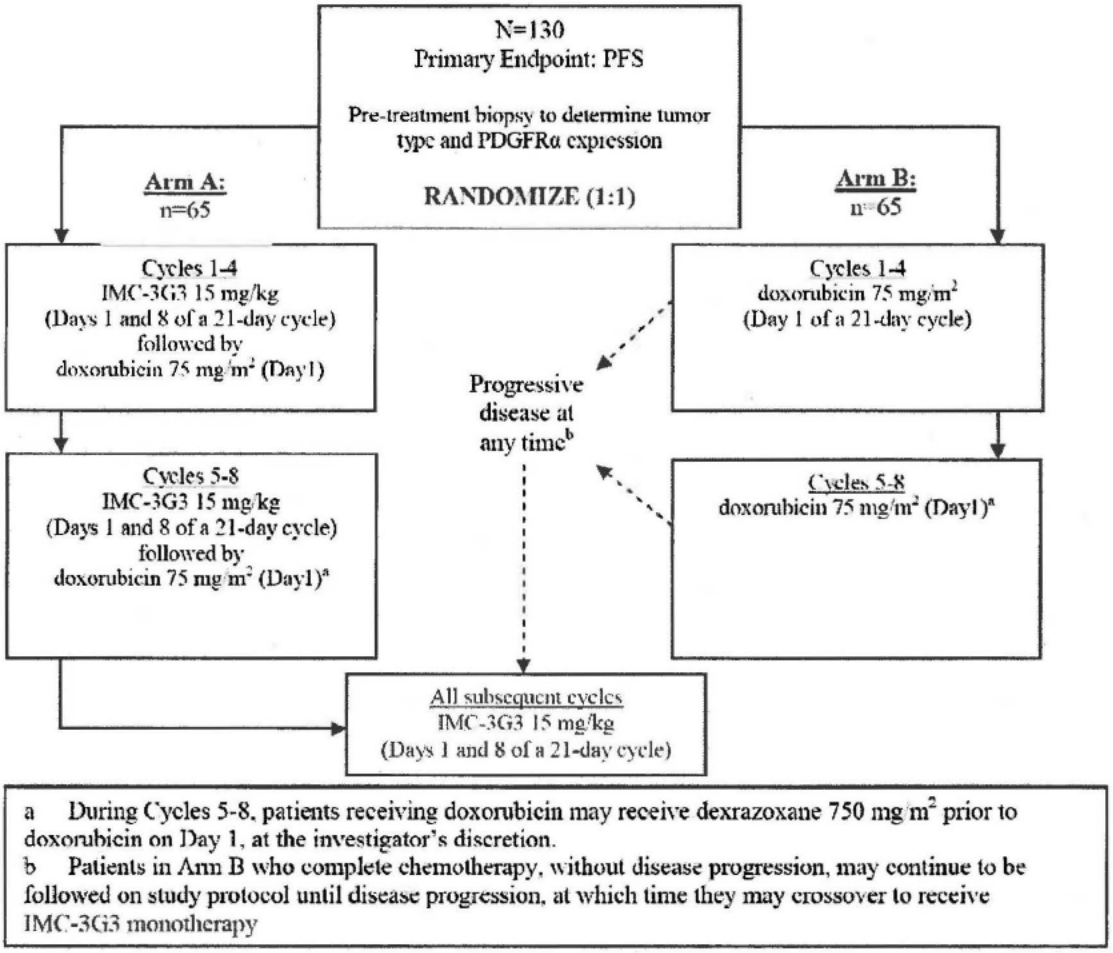
IV. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation.

No drug has received breakthrough therapy designation for STS.

VII. Description of preliminary clinical evidence

The clinical data for the breakthrough designation request is from an open-label, multicenter, randomized, activity-estimating study entitled, "A Phase 1b/2 Randomized Phase 2 Study Evaluating the Efficacy of Doxorubicin With or Without a Human Anti-PDGFR α Monoclonal Antibody (IMC-3G3) in the Treatment of Advanced Soft Tissue Sarcoma (Lilly I5B-IE-JGDG)". The objective of the Phase 1b portion was to characterize the safety profile of olaratumab when administered in combination with doxorubicin. In the Phase 2 portion of the study, 133 patients with advanced STS with documented disease progression, and not amenable to treatment with surgery or radiotherapy, were randomized (129 treated) in a 1:1 ratio to receive doxorubicin plus olaratumab for up to 8 cycles followed by single-agent olaratumab vs. doxorubicin for eight cycles. Randomization was stratified according to PDGFR α expression (positive vs. negative), number of previous lines of treatment (0 vs. 1+ lines), histological tumor type (i.e., leiomyosarcoma vs. synovial sarcoma vs. other tumor type), and ECOG performance status (0-1 vs. 2). Patients randomized to single-agent doxorubicin arm were permitted to receive single-agent olaratumab at the time of disease progression. Tumor response was assessed every 6 weeks. Figure 1 summarizes the study design and the treatment plan.

Figure 1. Study Design



a During Cycles 5-8, patients receiving doxorubicin may receive dexrazoxane 750 mg/m² prior to doxorubicin on Day 1, at the investigator's discretion.
b Patients in Arm B who complete chemotherapy, without disease progression, may continue to be followed on study protocol until disease progression, at which time they may crossover to receive IMC-3G3 monotherapy

The primary endpoint is PFS as assessed by the investigator per RECIST v1.1. PFS was defined as the interval from date of registration to the earliest date of documented evidence of recurrent or progressive disease, or date of death due to any cause, per protocol in patients who received at least one dose of study drug and had at least one post-baseline tumor assessment.

A planned sample size of 130 patients for the Phase 2 portion of the study was based on the assumption of a 50% improvement in PFS (HR = 0.67) for olaratumab plus doxorubicin, with 80% statistical power using a two-sided 0.20 significance level. A planned interim analysis of the primary endpoint of PFS was performed applying a nominal alpha spending of 0.0001.

Therefore, the final nominal alpha level was adjusted to 0.1999 (two-sided); p-values presented in this document are all two-sided, unadjusted nominal values. The primary analysis was originally planned to be performed when at least 110 PFS events were observed; however, protocol-defined censoring rules for PFS required that PFS be censored at the last radiographic assessment if death or disease progression was observed after two consecutive missed visits after last assessment. Similarly, any patient beginning

a new systemic anticancer therapy prior to progression was also censored for PFS at the time of last assessment. Among the 129 randomized and treated patients, 20 were censored for one of these 2 reasons, such that 110 PFS events could not be attained for the primary analysis. Therefore, the statistical analysis plan (SAP) and protocol were amended to define the data cutoff date of August 15, 2014 for the (final) primary analysis of PFS, by which time it was projected that at least 100 PFS events would be observed. Following data validation, it was confirmed that 103 investigator-determined PFS events had occurred prior to this cutoff date.

Secondary endpoints are to compare overall survival and objective response rates between the study arms as well as to measure the maximum change in tumor size from baseline (waterfall plot). A hierarchical procedure to test for multiplicity in the secondary endpoints was not pre-specified in the protocol.

- Overall survival is defined as the time from the date of randomization to the date of death from any cause, OS will be censored on the last date the patient is known to be alive. OS will be evaluated by the Kaplan-Meier method and a 90% CI will be provided for the median OS. The hazard ratio and 90% CI for OS will be estimated from the Cox regression model, taking the stratification factors as covariates. The final analysis for OS will be conducted using a data cut-off date of 2 years after the last patient started treatment or after reaching approximately 91 deaths (i.e., about 70% of the modified intent-to-treat (mITT) population), whichever occurs later. The final OS analysis is estimated to occur in the first half of 2015.

  The protocol specified that an interim analysis for OS will be performed at the time of the final PFS analysis. To account for this interim analysis, the alpha-spending approach of Lan-DeMets (1983) will be applied using an error-spending function to approximate the standard O'Brien-Fleming boundaries assuming 91 deaths at final OS analysis.
- Objective response rate is defined as the proportion of patients achieving a best overall response of partial response (PR) or CR (complete response) according to RECIST v1.1. The ORR in each treatment group will be compared using Fisher's exact test. Exact confidence bounds (90% CI) will be determined. The duration of response for responders only is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that the criteria for progressive disease (PD) are met, or death. Duration of response will be estimated with the Kaplan-Meier method; a 90% CI will be provided for the median duration of response. DOR is censored at the day of the last objective tumor assessment for patients who do not relapse.

Exploratory endpoints include analyses of the association between tumor PDGFR expression and clinical outcomes, such as PFS and ORR.

Summary of clinical data

Of the one hundred thirty-three patients (age range 33 to 97 years) with advanced STS randomized in the trial, 64 patients received the assigned protocol regimen in Arm A (olaratumab plus doxorubicin) and 65 patients received the assigned protocol regimen in

Arm B (single-agent doxorubicin). In response to FDA's information request, dated January 30, 2015, Eli Lilly stated that 132 patients had Stage IV disease at randomization, and one patient who did not receive any study drug, did not have any baseline radiologic assessment.

Patient demographics and prior anticancer treatment are summarized by treatment arm in Tables 2 and 3, respectively, with additional demographic information on sarcoma subtypes presented in Appendix 1 (Tables 7, 8, and 9):

Table 2. Baseline Patient Demographics and Characteristics

Variable	Arm A Olaratumab + Doxorubicin N = 64	Arm B Doxorubicin N = 65
Sex n (%)		
Male	26 (40.6)	32 (49.2)
Female	38 (59.4)	33 (50.8)
Age (years)		
Median age (range)	57.5 (22-76)	58.0 (29-86)
Age group n (%)		
Age < 65 years	47 (73.4)	41 (63.1)
Age ≥ 65 years	17 (26.6)	24 (36.9)
Race n (%)		
White	53 (82.8)	59 (90.8)
Black	6 (9.4)	4 (6.2)
Asian	2 (3.1)	2 (3.1)
Native Hawaiian or other Pacific Islander	1 (1.6)	0
Other	2 (3.1)	0
Ethnicity n (%)		
Hispanic or Latino	6 (9.4)	2 (3.1)
Not Hispanic or Latino	58 (90.6)	62 (95.4)
Missing	0	1 (1.5)
ECOG PS n (%)		
0	36 (56.3)	37 (56.9)
1	25 (39.1)	25 (38.5)
2	3 (4.7)	3 (4.6)
Randomization Strata (IVRS)		
PDGFRα Positive	56 (87.5)	58 (89.2)
PDGFRα Negative	8 (12.5)	7 (10.8)
Histological Type		
Leiomyosarcoma	24 (37.5)	25 (38.5)
Synovial Sarcoma	1 (1.6)	2 (3.1)
Other	39 (60.9)	38 (58.5)
ECOG PS		
0-1	61 (95.3)	61 (93.8)
2	3 (4.7)	4 (6.2)
Number of previous treatments		
0	26 (40.6)	30 (46.2)
>1	38 (59.4)	35 (53.8)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IVRS = interactive voice response system; mITT = modified intent to treat; N = number of randomized patients; n = number of patients in category; PDGFR = platelet-derived growth factor receptor.

Data cut-off date: 15 August 2014.

Table 3. Prior Anticancer Treatment

	Olaratumab + Doxorubicin N = 66	Doxorubicin N = 67
Any Systemic Treatment, n (%)	37 (56.1)	38 (56.7)
Neoadjuvant, n (%)	3 (4.5)	10 (14.9)
Adjuvant, n (%)	14 (21.2)	7 (10.4)
First-Line, n (%)	26 (39.4)	23 (34.3)
Second-Line, n (%)	13 (19.7)	7 (10.4)
Third-Line, n (%)	4 (6.1)	1 (1.5)
Fourth-Line, n (%)	2 (3.0)	0
Prior Surgery, n (%)	56 (84.8)	57 (85.1)
Prior Radiotherapy, n (%)	31 (47.0)	32 (47.8)

Abbreviations: ITT = intent to treat; N = number of randomized patients; n = number of patients in category.

Thirty (45%) patients in the doxorubicin arm crossed over to receive single-agent olaratumab at the time of disease progression. Two (7%) patients continued to receive olaratumab as of August 15, 2014, and 28 had discontinued, with 22 (73%) due to disease progression or symptomatic deterioration.

Patient disposition is summarized in Table 4 below. The most common reason for treatment discontinuation was radiographic disease progression, 64% in the olaratumab plus doxorubicin arm, and 39% in the doxorubicin arm. Treatment discontinuation for adverse event was 8% in the olaratumab plus doxorubicin arm, and 21% in the doxorubicin arm.

Table 4. Patient Disposition

	Number of Patients (%)	
	Olaratumab + Doxorubicin	Doxorubicin
Randomized	66	67
Treated	64 (97.0)	65 (97.0)
On-Treatment	1 (1.5)	0
Off-Treatment	63 (95.5)	65 (97.0)
Reasons for Discontinuation from Study Therapy		
Adverse Event	5 (7.6)	14 (20.9)
Death	2 (3.0)	1 (1.5)
Progressive Disease - Radiographically Documented	42 (63.6)	26 (38.8)
Progressive Disease - Symptomatic Deterioration	3 (4.5)	6 (9.0)
Withdrawal of Consent (Follow-Up Permitted)	4 (6.1)	5 (7.5)
Withdrawal of Consent (Follow-Up Not Permitted)	1 (1.5)	1 (1.5)
Other	6 (9.1)	6 (9.0)
Completed Treatment	NA	6 (9.0)

Abbreviation: NA = not applicable.
Data cut-off date: 15 August 2014.

Efficacy

According to the study protocol, the primary statistical analysis was to use the mITT population, defined as patients who were enrolled and received any dose of study medication. Although not provided herein, the results based on mITT are consistent with the results based on the ITT. The analyses presented below are based on the ITT population.

Progression-free Survival

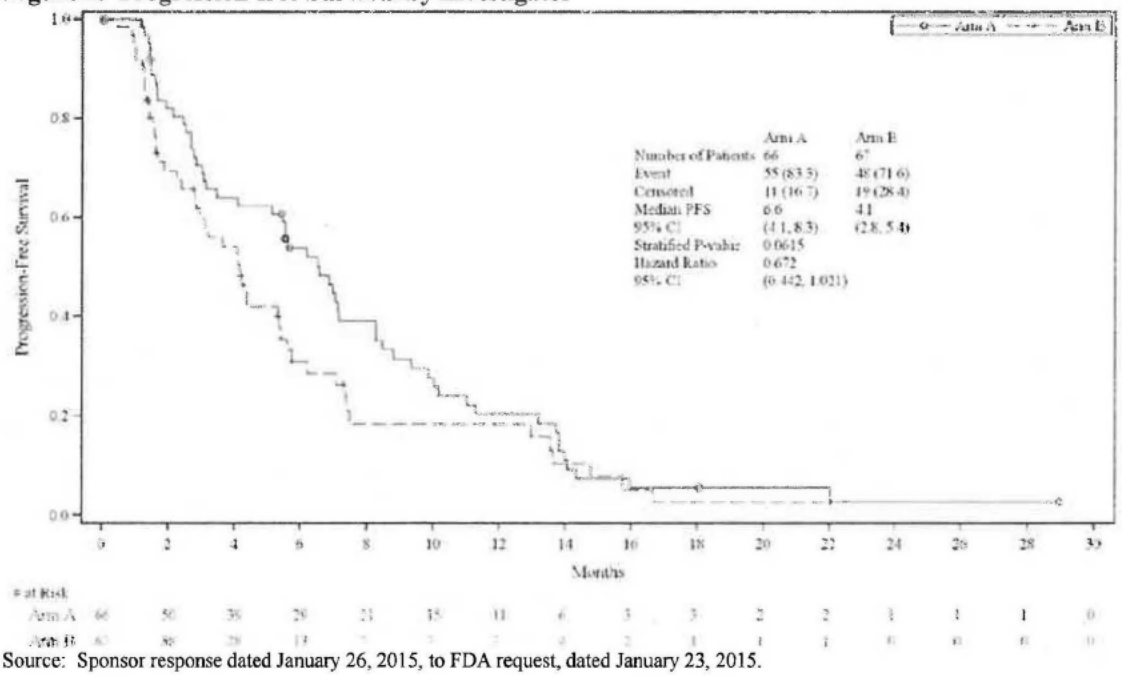
According to the Sponsor, the study met the protocol-defined final significance level for PFS (i.e., two-sided alpha 0.1999), thereby demonstrating a statistically significant improvement in PFS in the olaratumab plus doxorubicin arm compared to the doxorubicin arm, with a median of 6.6 months versus 4.1 months, respectively, and a hazard ratio (HR) of 0.67 (95% CI: 0.44, 1.02; p=0.062). Table 5 summarizes the results and Figure 2 illustrates the Kaplan-Meier (K-M) curves of PFS as assessed by the investigator in the intent-to-treat (ITT) population.

Table 5. Progression-Free Survival per Investigator Assessment

	Olaratumab + Doxorubicin N=66 (%)	**Doxorubicin N=67**
Events	55 (83)	50 (75)
Censored	11 (17)	19 (28)
No baseline tumor assessment	1 (2)	2 (3)
No post-baseline tumor assessments	2 (3)	2 (3)
Death or progression after ≥2 missed visits	1 (2)	3 (5)
Start of new anti-cancer therapy	5 (8)	5 (8)
No documented progression	2 (3)	6 (9)
Withdraw consent	0	1 (2)
Median PFS in months (95% CI)	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
Hazard Ratio (95% CI)	0.67 (0.44, 1.02)	
p-value (stratified log-rank)	0.06	

Source: Sponsor response dated January 26, 2015, to FDA request, dated January 23, 2015.

Figure 2. Progression-free Survival by Investigator



Source: Sponsor response dated January 26, 2015, to FDA request, dated January 23, 2015.

A blinded independent radiologic review (BCIR) was also conducted. The results of the PFS analysis, as summarized in Appendix 2 (Figure 4), demonstrate an increase in median PFS in the olaratumab plus doxorubicin arm compared to the doxorubicin arm, 8.2 months versus 4.4 months, respectively, with a hazard ratio (HR) of 0.74 (95% CI: 0.47, 1.2, p=0.12).

Exploratory analyses of PFS were consistent with the investigator-assessed PFS results and across multiple subgroups, including histologic subtype (leiomyosarcoma vs. non-leiomyosarcoma) PDGFRα status, number of previous lines of treatment, ECOG performance status, gender, race, and ethnicity (Appendix 2, Figure 5 and Appendix 3, Table 10).

Overall Survival

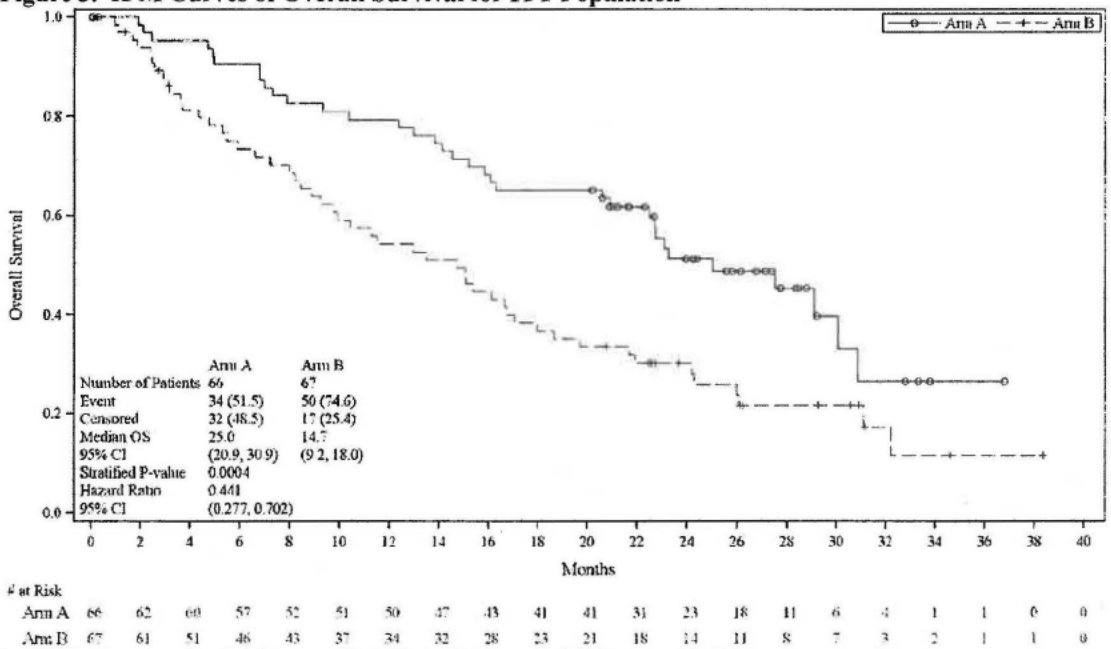
An interim analysis of OS was pre-planned to occur at the time of the final PFS analysis. At the August 15, 2014, cutoff date, 84 events were reported (49% censoring); however, 91 events (7 more) required to conduct the pre-planned final analysis of OS (30% censoring). In analyses based on the ITT population, the median survival on the olaratumab plus doxorubicin arm was 25 months and on the single-agent doxorubicin arm was 14.7 months, with a HR 0.44 (95% CI: 0.28, 0.70; p=0.0004). The final OS analysis is projected to occur in the first half of 2015. Table 6 summarizes the OS results, and Figure 3 illustrates the K-M curves of OS.

Table 6. Overall Survival for ITT Population

	Olaratumab + Doxorubicin N=66 (%)	Doxorubicin N=67 (%)
Events*	34 (52)	50 (75)
Censored Alive Lost to follow-up Withdrawal of consent	32 (49) 29 (44) 1 (2) 2 (3)	17 (25) 14 (21) 1 (2) 2 (3)
Median OS in months (95% CI)	25 (20.9, 30.9)	14.7 (9.2, 18)
Hazard Ratio (95% CI)	0.44 (0.28, 0.70)	
p-value (stratified log-rank)	0.0004	

Source: Sponsor response dated January 26, 2015, to FDA request, dated January 23, 2015.
* Per Sponsor's response dated Feb. 6th, "All patients randomized to the control arm were analyzed as a part of the control arm regardless of whether they crossed over

Figure 3. K-M Curves of Overall Survival for ITT Population



Source: Sponsor response dated January 26, 2015, to FDA request, dated January 23, 2015.

Eli Lilly also presented subgroup analyses of OS according to histological subtype of STS, leiomyosarcoma or non-leiomyosarcoma, in Appendix 3 (Table 10) and Appendix 4 (Figures 6 and 7). Additional exploratory analyses of OS demonstrate a consistent effect with the HR favoring the olaratumab plus doxorubicin arm across multiple subgroups including PDGFRα status, number of previous lines of treatment, ECOG performance status, gender, race, and ethnicity (Appendix 4, Figure 8).

Objective Response Rate

For analyses of the secondary endpoint of ORR, the protocol did not require the patient to have a repeat tumor response evaluation that confirmed an objective tumor response in order to consider a patient a responder. The unconfirmed ORR was 18% in the investigational arm, and 12% in the control arm. Unconfirmed complete responses were observed in two patients (3%) in the olaratumab plus doxorubicin arm, and one patient (2%) in the doxorubicin arm. Unconfirmed partial responses were observed in 10 patients (15%) in the olaratumab plus doxorubicin arm, and 7 patients (10%) in the doxorubicin arm.

Safety

Distribution of adverse events were reported similarly between both arms, 98% in the olaratumab plus doxorubicin arm and 99% in the doxorubicin arm; however, slightly more serious adverse events, ≥ Grade 3 were reported in the olaratumab arm compared to the doxorubicin arm. Discontinuation of any study drug and adverse events with death as an outcome were observed more in the doxorubicin arm, compared to the olaratumab + doxorubicin arm.

Types of adverse events that were reported (1) in ≥15% of patients in the investigational, and (2) at a higher rate (≥5% difference) in the olaratumab + doxorubicin arm compared to the doxorubicin arm, included nausea, neutropenia, mucositis, alopecia, vomiting, anemia, diarrhea, decreased appetite, pyrexia, pain in extremity, headache, back pain, and infusion-related reaction.

Grade 3 and 4 events that were reported at a higher rate (≥5% difference) in the olaratumab + doxorubicin arm compared to the doxorubicin arm included neutropenia, anemia, and fatigue.

Patients were evaluated for cardiac function via echocardiogram and MUGA pre-study and prior to cycles 5 and 7 for potential cardiac toxicity for olaratumab and doxorubicin. In the treatment arm, an increase in treatment emergent adverse events in the System Organ Class of Cardiac Disorders was observed, 14% in the olaratumab + doxorubicin arm and 2% in the doxorubicin monotherapy arm. One patient in the olaratumab + doxorubicin arm experienced Grade 3 congestive cardiac failure. Changes in left ventricular dysfunction were similar between the two arms. One patient in the treatment arm and four patients in the control arm discontinued treatment due to decreased ejection fraction.

Refer to Appendix 5 (Tables 11 through 15) for additional details of the safety analyses provided by the Sponsor.

VIII. Division's recommendation and rationale

The Division of Oncology Products 2 recommends granting the request for breakthrough designation of olaratumab in combination with doxorubicin for treatment of patients with locally advanced, unresectable, and/or metastatic soft tissue sarcomas.

The proposed indication is a serious and life-threatening disease with a high unmet medical need—there are few effective therapies for this advanced sarcoma population and none have demonstrated an improvement in overall survival. In addition, the preliminary clinical data based on the Sponsor results reported for Trial I5B-IE-JGDG, while not definitive, may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

Specifically, Eli Lilly observed an increase in overall survival of a large magnitude with the addition of olaratumab to standard doxorubicin (i.e., an increase in median OS of approximately 10 months, from 14.7 months on the single-agent doxorubicin arm to 25 months on the olaratumab plus doxorubicin arm with a HR 0.44 [95% CI: 0.28, 0.70]), an effect that consistent across all subgroups in exploratory analyses. It is likely that the final OS results will be consistent with those observed at the interim given the maturity of the interim OS data (83 of the required 91 events for the final OS analysis were observed), the interim OS nominal p-value of 0.0004, and the large magnitude of increased OS. In addition, Eli Lilly reported numerical increases in analyses of the primary endpoint PFS (although not meeting statistical significance) and ORR, a secondary endpoint, with the addition of olaratumab to standard doxorubicin.

IX. Division's next steps and Sponsor's plan for future development

Eli Lilly has submitted an EOP2 meeting request on January 5, 2015, (1) to determine whether the final analysis of Trial 15B-IE-JGDG if consistent with the interim OS results presented herein could serve as primary data to support registration and (2) to discuss plans for a registration study for olaratumab in combination with doxorubicin in patients with advanced or metastatic STS. The proposed design for the trial submitted in the EOP2 meeting request is a global, multicenter, randomized (1:1), double-blind, placebo-controlled trial to compare the safety and efficacy of olaratumab plus doxorubicin to doxorubicin plus placebo in approximately 460 patients with advanced or metastatic STS not amenable to surgery or radiotherapy with curative intent. The proposed primary endpoint of the trial is overall survival.

Appendix 1

Table 7. Sarcoma Subtypes

Subtype, n (%)	Olaratumab + Doxorubicin N = 66	Doxorubicin N = 67
Predefined Subtypes		
Angiosarcoma	4 (6.1)	3 (4.5)
Fibrosarcoma	1 (1.5)	0
Leiomyosarcoma	24 (36.4)	26 (38.8)
Liposarcoma	8 (12.1)	11 (16.4)
Malignant Fibrous Histiocytoma	2 (3.0)	1 (1.5)
Neurofibrosarcoma	1 (1.5)	0
Synovial Sarcoma	1 (1.5)	2 (3.0)
Subtypes Entered Manually on CRF		
Alveolar Soft Part Sarcoma	1 (1.5)	0
Chondroblastic Osteosarcoma	0	1 (1.5)
Chondrosarcoma	0	2 (3.0)
Clear Cell Sarcoma	1 (1.5)	0
Endometrial Stromal Sarcoma	1 (1.5)	0
Epithelial Sarcoma	1 (1.5)	0
Epithelioid	1 (1.5)	0
Extraskeletal Myxoid Chondrosarcoma	1 (1.5)	0
Fibromyxoid Sarcoma	1 (1.5)	1 (1.5)
Fibrosarcomatous Transformation in a Recurrent Dermatofibrosarcoma	1 (1.5)	0
Hemangiopericytoma	1 (1.5)	1 (1.5)
High Grade Spindle and Pleomorphic Sarcoma	1 (1.5)	1 (1.5)
High Grade Undifferentiated Sarcoma	0	1 (1.5)
High-Grade Pleomorphic Undifferentiated Sarcoma	0	1 (1.5)
Malignant Glomus Tumor	1 (1.5)	0
Malignant Peripheral Nerve Sheath Tumor	1 (1.5)	0
Malignant Solitary Fibrous Tumor	1 (1.5)	0
Malignant Spindle Cell Sarcoma	0	1 (1.5)
Malignant Spindle Cell Tumor with Rhabdoid Features	0	1 (1.5)
Myxofibrosarcoma	1 (1.5)	0
Myxoid Chondrosarcoma	1 (1.5)	0
Myxoid Liposarcoma	0	3 (4.5)
Myxoid Sarcoma	0	1 (1.5)
Not Otherwise Specified	2 (3.0)	2 (3.0)
Pleiomorphic Sarcoma	3 (4.5)	3 (4.5)
Pleomorphic Liposarcoma	0	1 (1.5)
Poorly Differentiated	1 (1.5)	0
Round Cell Sarcoma	1 (1.5)	0
Severe High Grade	1 (1.5)	0
Smooth Muscle Tumor	0	1 (1.5)
Spindle Cell Sarcoma	0	2 (3.0)
Undifferentiated Sarcoma	1 (1.5)	1 (1.5)
Undifferentiated Uterine Sarcoma	1 (1.5)	0

Abbreviations: ITT = intent to treat; N = number of randomized patients; n = number of patients in category.

Table 8. Prior Anticancer Therapy for Leiomyosarcoma Patients

	Olaratumab + Doxorubicin N = 25	Doxorubicin N = 26
Any Systemic Treatment, n (%)	21 (84.0)	22 (84.6)
Neoadjuvant, n (%)	1 (4.0)	5 (19.2)
Adjuvant, n (%)	10 (40.0)	5 (19.2)
First-Line, n (%)	13 (52.0)	13 (50.0)
Second-Line, n (%)	6 (24.0)	4 (15.4)
Third-Line, n (%)	3 (12.0)	1 (3.8)
Fourth-Line, n (%)	2 (8.0)	0
Prior Surgery, n (%)	20 (80.0)	23 (88.5)
Prior Radiotherapy, n (%)	9 (36.0)	15 (57.7)

Abbreviations: N = number of randomized patients; n = number of patients in category.

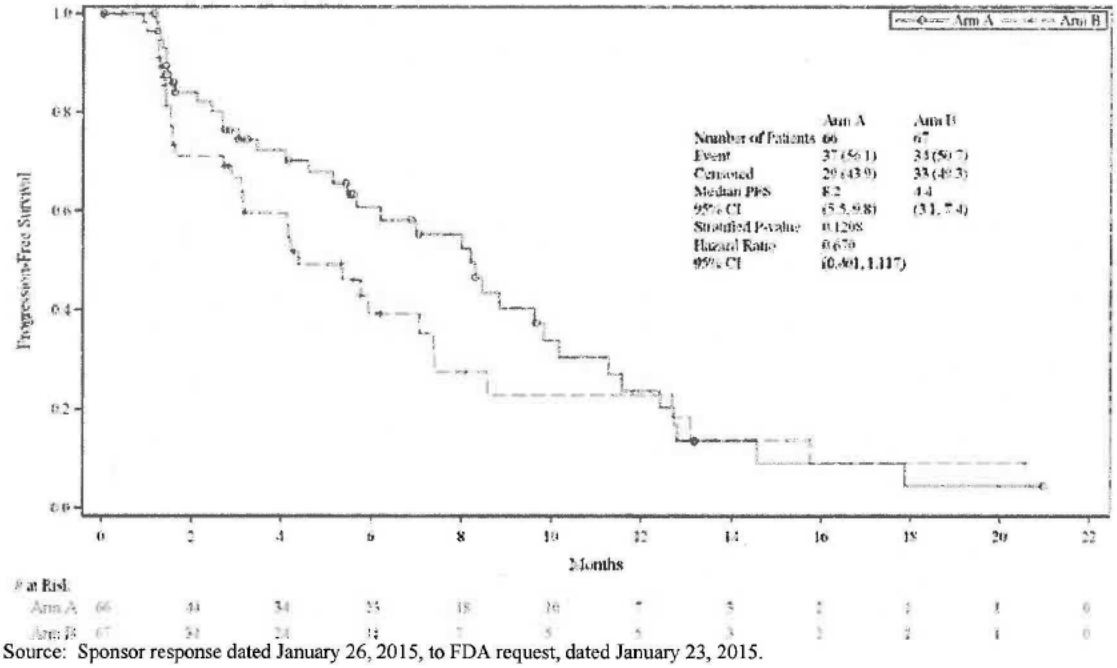
Table 9. Prior Anticancer Therapy for Non-Leiomyosarcoma Patients

	Olaratumab + Doxorubicin N = 41	Doxorubicin N = 41
Any Systemic Treatment, n (%)	16 (39.0)	16 (39.0)
Neoadjuvant, n (%)	2 (4.9)	5 (12.2)
Adjuvant, n (%)	4 (9.8)	2 (4.9)
First-Line, n (%)	13 (31.7)	10 (24.4)
Second-Line, n (%)	7 (17.1)	3 (7.3)
Third-Line, n (%)	1 (2.4)	0
Prior Surgery, n (%)	36 (87.8)	34 (82.9)
Prior Radiotherapy, n (%)	22 (53.7)	17 (41.5)

Abbreviations: N = number of randomized patients; n = number of patients in category.

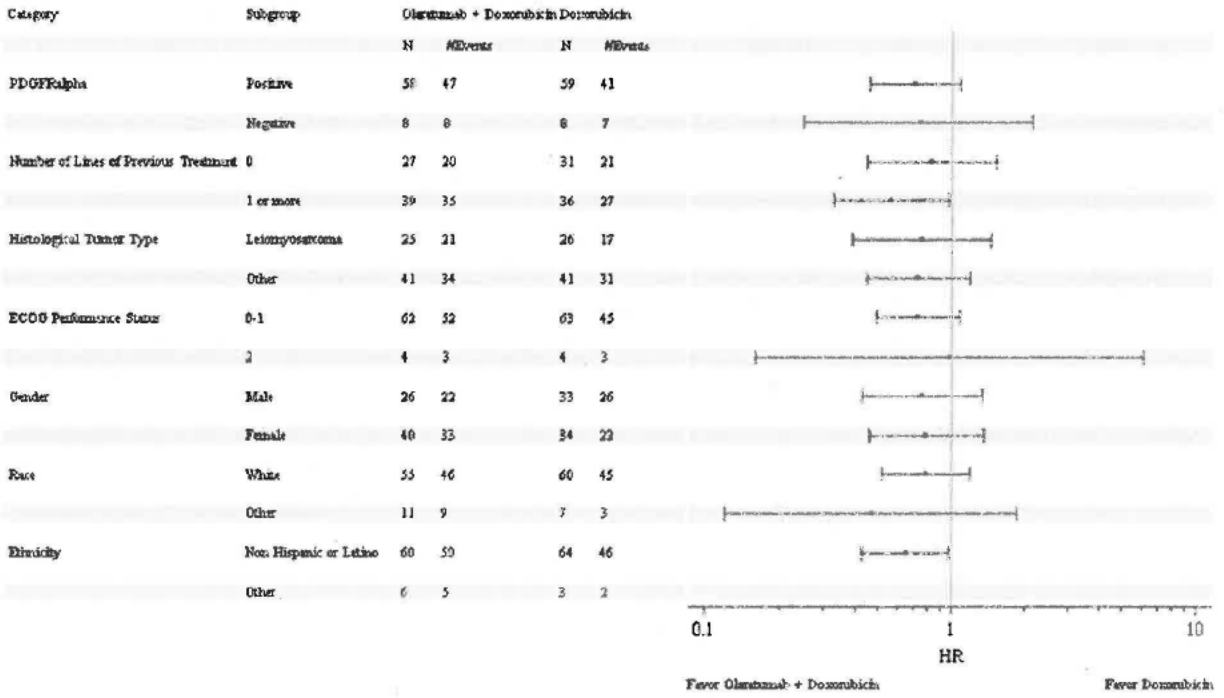
Appendix 2

Figure 4. Progression-free Survival by BCIR



Source: Sponsor response dated January 26, 2015, to FDA request, dated January 23, 2015.

Figure 5. Forest Plot of Hazard Ratios and 95% CIs for PFS by Subgroup for ITT Population



Source: January 26, 2015 response to FDA information request on January 23, 2015.

Appendix 3

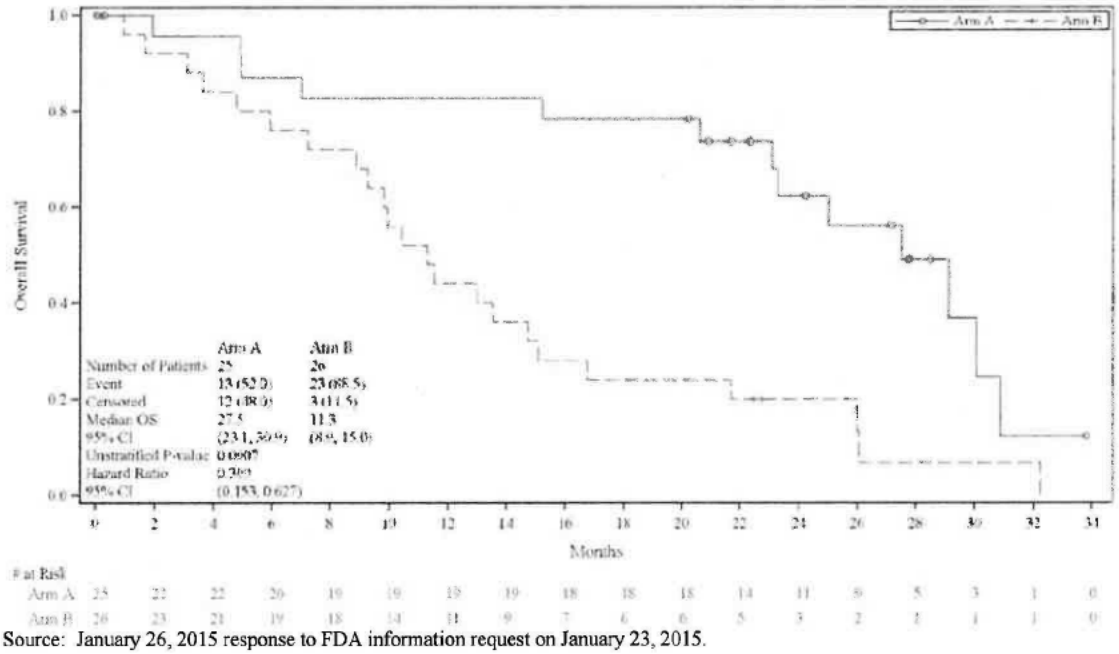
Table 10. Progression-free Survival and Overall Survival According to Histological Subtype of Sarcoma by BCIR

Histological subtype	Olaratumab + Doxorubicin	Doxorubicin
Leiomyosarcoma	N=25	N=26
PFS		
Events	21 (84)	17 (65)
Median PFS, months (95% CI)	6.5 (3.0, 9.8)	3.6 (1.6, 7.4)
Hazard Ratio (95% CI)	0.75 (0.39-1.47)	
p-value	0.4	
OS		
Events	13 (52)	23 (89)
Median OS, months (90% CI)	28 (23.1, 30.9)	11.3 (8.9, 15.0)
Hazard Ratio (95% CI)	0.31 (0.15-0.63)	
p-value	0.0007	
Other sarcoma subtypes	N=41	N=41
PFS		
Events	34 (83)	31 (76)
Median PFS, months (95% CI)	6.6 (2.8, 8.4)	4.4 (2.2, 5.6)
Hazard Ratio (95% CI)	0.73 (0.45, 1.19)	
p-value	0.2	
OS		
Events	21 (51)	27 (66)
Median OS, months (95% CI)	23 (14.5, NE)	17.1 (8, 24.2)
Hazard Ratio (95% CI)	0.64 (0.36, 1.13)	
p-value	0.12	

Source: January 26, 2015 response to FDA information request on January 23, 2015.

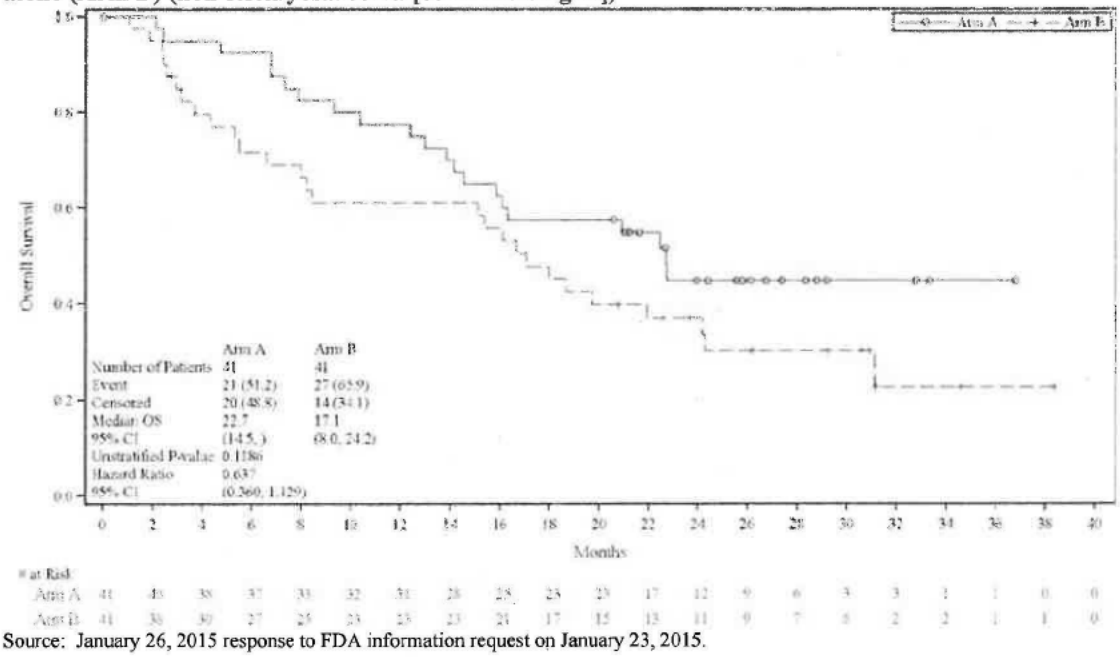
Appendix 4

Figure 6. Kaplan-Meier curves for OS for olaratumab plus doxorubicin (Arm A) versus doxorubicin alone (Arm B) (leiomyosarcoma)



Source: January 26, 2015 response to FDA information request on January 23, 2015.

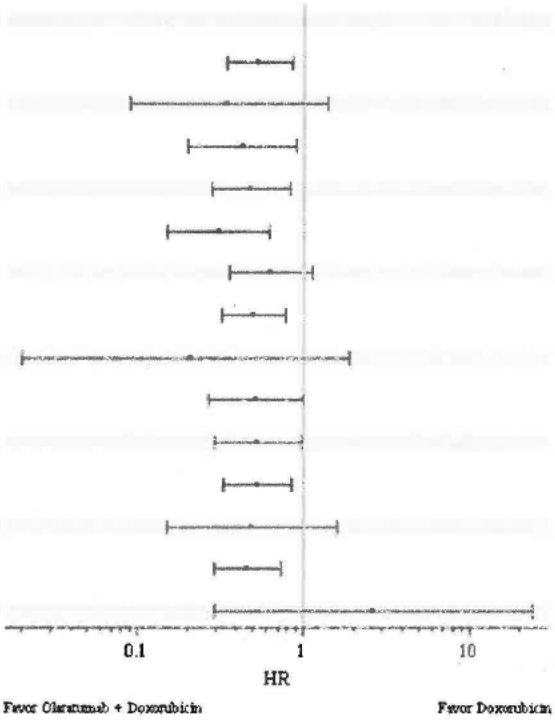
Figure 7. Kaplan-Meier curves for OS for olaratumab plus doxorubicin (Arm A) versus doxorubicin alone (Arm B) (non-leiomyosarcoma [other histologies])



Source: January 26, 2015 response to FDA information request on January 23, 2015.

Figure 8. Forest Plot of Hazard Ratios and 95% CIs for OS by Subgroup for ITT Population

Category	Subgroup	Olaratumab + Doxorubicin		Doxorubicin	
		N	#Events	N	#Events
PDGFRalpha	Positive	58	31	59	44
	Negative	8	3	8	6
Number of Lines of Previous Treatment	0	27	10	31	20
	1 or more	39	24	36	30
Histological Tumor Type	Leiomyosarcoma	25	13	26	23
	Other	41	21	41	27
ECOG Performance Status	0-1	62	31	63	46
	2	4	3	4	4
Gender	Male	26	14	33	28
	Female	40	20	34	22
Race	White	55	28	60	45
	Other	11	6	7	5
Ethnicity	Non Hispanic or Latino	60	30	64	49
	Other	6	4	3	1



Source: January 26, 2015 response to FDA information request on January 23, 2015

Appendix 5

Table 11. Treatment –Emergent Adverse Events

	Olaratumab + Doxorubicin N = 64	Doxorubicin N = 65
Any Adverse Event	63 (98.4)	64 (98.5)
Related to any Study Drug	62 (96.9)	63 (96.9)
Related to Olaratumab Study Drug	55 (85.9)	NA
Related to Ctx Study Drug	61 (95.3)	63 (96.9)
Any Serious Adverse Event	27 (42.2)	25 (38.5)
Related to any Study Drug	14 (21.9)	17 (26.2)
Related to Olaratumab Study Drug	10 (15.6)	NA
Related to Ctx Study Drug	12 (18.8)	17 (26.2)
Any Grade ≥ 3 Adverse Event	49 (76.6)	43 (66.2)
Related to any Study Drug	41 (64.1)	35 (53.8)
Related to Olaratumab Study Drug	28 (43.8)	NA
Related to Ctx Study Drug	37 (57.8)	35 (53.8)
Any AE Leading to Discontinuation of any Study Drug	8 (12.5)	14 (21.5)
Any AE Leading to Discontinuation of Olaratumab	5 (7.8)	NA
Any AE Leading to Discontinuation of Ctx	6 (9.4)	14 (21.5)
Any Adverse Event with Outcome of Death	0	5 (7.7)
Related to any Study Drug	0	2 (3.1)
Related to Olaratumab Study Drug	0	NA
Related to Ctx Study Drug	0	2 (3.1)

Abbreviations: AE = adverse event; Ctx = chemotherapy; N = number of randomized patients: NA = not applicable.

Data cut-off date: 15 August 2014.

Note 1: Adverse event with missing or unknown relationship to study drug is counted as 'related'.

Note 2: This table summarizes all the treatment-emergent adverse events.

Table 12. Summary of Common Adverse Events (All Grades) Occurring in ≥15% of Patients in the Investigational Arm

Preferred Term	Olaratumab + Doxorubicin N = 64 n (%) Median no. of doxorubicin infusions=7	Doxorubicin N = 65 n (%) Median no. of doxorubicin infusions=4
	Any Grade	Any Grade
Patients with any AE	**63 (98.4)**	**64 (98.5)**
Nausea	47 (73.4)	34 (52.3)
Fatigue	44 (68.8)	45 (69.2)
Neutropenia[a]	36 (56.3)	25 (38.5)
Mucositis[b]	34 (53.1)	23 (35.4)
Alopecia	32 (50.0)	24 (36.9)
Vomiting	29 (45.3)	12 (18.5)
Infections and Infestations[c]	26 (40.6)	27 (41.5)
Anemia[d]	26 (40.6)	22 (33.8)
Constipation	22 (34.4)	23 (35.4)
Diarrhea	22 (34.4)	15 (23.1)
Decreased Appetite	21 (32.8)	13 (20.0)
Pyrexia	15 (23.4)	12 (18.5)
Pain In Extremity	14 (21.9)	1 (1.5)
Thrombocytopenia	13 (20.3)	11 (16.9)
Headache	13 (20.3)	6 (9.2)
Cough	13 (20.3)	13 (20.0)
Dyspnea	11 (17.2)	12 (18.5)
Back Pain	11 (17.2)	5 (7.7)
Febrile Neutropenia[f]	8 (12.5)	9 (13.8)
Infusion-Related Reaction[e,f]	7 (10.9)	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of randomized patients; n = number of patients with given event.

Data cut-off date: 15 August 2014.

a. Consolidated term comprising the following preferred terms: leukopenia, neutropenia, neutrophil count decreased, white blood cell count decreased.
b. Consolidated term comprising the following preferred terms: mucosal inflammation, oropharyngeal pain, stomatitis.
c. Includes all preferred terms within the MedDRA system organ class of Infections and Infestations.
d. Consolidated term comprising the following preferred terms: anaemia, haemoglobin decreased.
e. Consolidated term comprising the following preferred terms: hypersensitivity, infusion-related reaction.
f. Included as these AEs were associated in Grade ≥3 events and considered clinically important.

Table 13. Grade 3 and ≥Grade 4 Adverse Events

Preferred Term	Olaratumab + Doxorubicin N = 64 n (%) Median no. of doxorubicin infusions=7		Doxorubicin N = 65 n (%) Median no. of doxorubicin infusions=4	
	Grade 3	Grade ≥ 4	Grade 3	Grade ≥ 4
Patients with any AE	**22 (34.4)**	**27 (42.2)**	**24 (36.9)**	**19 (29.2)**
Neutropenia[a]	10 (15.6)	23 (35.9)	6 (9.2)	16 (24.6)
Anemia[d]	8 (12.5)	0	5 (7.7)	0
Febrile Neutropenia	7 (10.9)	1 (1.6)	9 (13.8)	0
Fatigue	6 (9.4)	0	2 (3.1)	0
Thrombocytopenia	4 (6.3)	2 (3.1)	3 (4.6)	2 (3.1)
Infections and Infestations[c]	4 (6.3)	0	4 (6.2)	3 (4.6)
Mucositis[b]	2 (3.1)	0	3 (4.6)	0
Diarrhea	2 (3.1)	0	0	0
Pain In Extremity	2 (3.1)	0	0	0
Back Pain	2 (3.1)	0	0	0
Infusion-Related Reaction[e]	0	2 (3.1)	0	0
Nausea	1 (1.6)	0	2 (3.1)	0
Decreased Appetite	1 (1.6)	0	0	0
Constipation	0	0	1 (1.5)	0
Dyspnea	0	0	1 (1.5)	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of randomized patients; n = number of patients with given event.

Data cut-off date: 15 August 2014.

a. Consolidated term comprising the following preferred terms: leukopenia, neutropenia, neutrophil count decreased, white blood cell count decreased.
b. Consolidated term comprising the following preferred terms: mucosal inflammation, oropharyngeal pain, stomatitis.
c. Includes all preferred terms within the MedDRA system organ class of Infections and Infestations.
d. Consolidated term comprising the following preferred terms: anaemia, haemoglobin decreased.
e. Consolidated term comprising the following preferred terms: hypersensitivity, infusion-related reaction, infusion site erythema, injection site pain.

Table 14. Treatment-Emergent Adverse Events in the SOC of Cardiac Disorders

SOC and PT	Olaratumab + Doxorubicin Median no. of doxorubicin infusions=7			Doxorubicin Median no. of doxorubicin infusions=4		
	Any grade	Grade 3	Grade ≥4	Any grade	Grade 3	Grade ≥4
Cardiac Disorders	***9 (14.1)***	***1 (1.6)***	***0***	***6 (9.2)***	***0***	***0***
Sinus Tachycardia	0	0	0	2 (3.1)	0	0
Tachycardia	4 (6.3)	0	0	3 (4.6)	0	0
Bradycardia	1 (1.6)	0	0	0	0	0
Cardiac failure congestive	1 (1.6)	1 (1.6)	0	0	0	0
Cyanosis	1 (1.6)	0	0	0	0	0
Left Ventricular Dysfunction	1 (1.6)	0	0	0	0	0
Myocardial Infarction	1 (1.6)	0	0	0	0	0
Sinus Arrhythmia	1 (1.6)	0	0	0	0	0
Sinus Bradycardia	1 (1.6)	0	0	0	0	0
Supraventricular Tachycardia	0	0	0	1 (1.5)	0	0

Abbreviations: PT = preferred term; SOC = system organ class.

Data cut-off date: 15 August 2014.

Table 15. Results of Abnormal LVEF Results

	Olaratumab + Doxorubicin N = 64	Doxorubicin N = 65
End of Treatment		
n	33	12
≤50%	6 (18.2)	2 (16.7)
Decrease from baseline ≥10%	8 (24.2)	3 (25.0)
Lowest Post-Baseline		
n	51	32
≤50%	10 (19.6)	4 (12.5)
Decrease from baseline ≥10%	14 (27.5)	8 (25.0)

Abbreviations: LVEF = left ventricular ejection fraction; N = number of randomized patients; n = number of patients in given category.

Data cut-off date: 15 August 2014.

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/s/

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03/13/2015

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