

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761038Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 761038 Supplement Number: NA NDA Supplement Type (e.g. SE5): _____

Division Name: DOP2 PDUFA Goal Date: 10/24/16 Stamp Date: 2/24/2016

Proprietary Name: Lartruvo (proposed)

Established/Generic Name: olaratumab

Dosage Form: solution for intravenous use

Applicant/Sponsor: Eli Lilly and Company

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) NA

(2) _____

(3) _____

(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: 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."

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)
- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
☐ Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

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pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)
- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
☐ Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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
09/20/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA # 761038	BLA Supplement # NA	If NDA, Efficacy Supplement Type: NA <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Lartruvo Established/Proper Name: Olaratumab Dosage Form: Solution for intravenous injection		Applicant: Eli Lilly and Company Agent for Applicant (if applicable): NA
RPM: Leah Her		Division: DOP2
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☒ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> NA Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>October 24, 2016</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☒ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☒ Fast Track	☐ Rx-to-OTC full switch
☒ Rolling Review	☐ Rx-to-OTC partial switch
☒ Orphan drug designation	☐ Direct-to-OTC
☒ Breakthrough Therapy designation	

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	☒ Yes ☐ No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No Notified on 9/21/16
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other ASCO Burst and Information Advisory
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) October 19, 2016
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included version dated October 14, 2016
Original applicant-proposed labeling	☒ Included version dated January 19, 2016
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☐ Included
Original applicant-proposed labeling	☐ Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
Most-recent draft labeling	☒ Included version dated July 8, 2016
❖ Proprietary Name	
- Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> - Review(s) <i>(indicate date(s))</i>	4/28/16 Conditional Approval 4/22/16 Final Review / 4/22/16 TL Concur
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: ☐ None 6/6/16 Final Review / 6/7/16 CPMS Concur DMEPA: ☐ None 7/12/16 Additional Review / 7/12/16 TL Concur 6/1/16 Initial Review / 6/1/16 TL Concur DMPP/PLT (DRISK): ☐ None See Risk Management section of this checklist OPDP: ☐ None 9/23/16 Review (carton and container) 9/15/16 Review (package insert) SEALD: ☒ None CSS: ☒ None Product Quality ☐ None 8/8/16 Final Review / CMC Reviewer Concur 8/8/16 Other: ☐ None DPMH Review 7/21/16 Final Review / 7/22/16 TL Concur / 7/25/16 DD Concur

Administrative / Regulatory Documents	
❖ RPM Filing Review⁴/Memo of Filing Meeting (<i>indicate date of each review</i>) ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	6/6/16 Final Review / 6/6/16 CPMS Concur ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	☐ Included NA; this is a BLA
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm • Applicant is on the AIP • This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>This drug has orphan designation therefore, exempt from PREA</u>	9/20/16 Final Pediatric Page Uploaded
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	2/20/15 Breakthrough Designation Granted
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	3/13/15 Generated / 3/16/15 DD Concur
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	NA
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	10/14/16 – Labeling (final comments) – uploaded 10/18/16 10/12/16 – Labeling IR (3 rd round) 10/12/16 – Tcon Labeling (uploaded on 10/18/16) 10/6/16 – PMC/PMR (uploaded 10/12/16) 10/3/16 – Labeling IR (2 nd round) 9/23/16 – Clinical IR 9/19/16 – Clinical IR 8/31/16 – Late Cycle background package 8/15/16 – CMC IR 7/22/16 – PMC/PMR 7/22/16 – Labeling IR (1 st round) 7/20/16 - CMC IR 7/18/16 – Clinical IR 7/15/16 – Clinical IR 7/14/16 – CMC IR

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

	7/11/16 – Clinical IR 7/5/16 – CMC IR 7/1/16 – Labeling IR (carton & container) 6/23/16 – CMC IR 6/16/16 – CMC IR 6/13/16 – Clinical IR 6/8/16 – CMC IR 6/2/16 – Clinical IR 5/27/16 – Clinical Pharmacology IR 5/27/16 – Post Mid-Cycle communication agenda 5/23/16 - Stats IR 5/18/16 – CMC IR 5/17/16 – Clinical IR 5/18/16 – Tcon (uploaded on 9/20/16) 5/13/16 – Clinical IR 5/10/16 – Clinical IR 5/6/16 – Clarification to 5/5/16 Clinical IR (uploaded 5/24/16) 5/5/16 (2) – Clinical IR 5/2/16 – CMC IR 4/29/16 – Tcon (uploaded 5/25/16) 4/29/16 – Clinical IR 4/28/16 – CMC IR 4/27/16 – Clinical IR 4/22/16 – No Filing Issues 4/18/16 – Clinical IR 4/11/16 – QT/IRT IR (uploaded 4/12/16) 4/8/16 – Clinical IR 4/6/16 – Clinical IR (uploaded 4/8/16) 3/25/16 – Stats IR 3/15/16 – Clin Pharm IR (uploaded 3/24/16) 3/7/16 – Acknowledge BLA submission 3/2/16 – Clinical IR 2/26/16 – Clinical IR 2/1/16 – Acknowledge presubmission 1/29/16 – Acknowledge presubmission 12/22/15 (2) – Acknowledge presubmission <u>Correspondence issued under the IND:</u> 2/3/16 – AI on 120 day safety update 12/9/15 – Grant Rolling Review 8/21/14 – Grant Fast Track 8/21/14 – AI on Trial JGDG
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g.,	9/26/16 Division Director Priority Review Designation Memo –

Regulatory Briefing minutes, Medical Policy Council meeting minutes)	uploaded 10/19/16 9/23/16 SGE Tcon – uploaded 10/18/16 9/23/16 Wrap Up Meeting Summary – uploaded 9/29/16 9/21/16 SGE Tcon – uploaded 10/18/16 9/16/16 SGE Tcon – uploaded 10/18/16 8/29/16 Internal Pre-Late Cycle and Team Meeting Summary – uploaded 9/23/16 7/18/16 Team Meeting Summary – uploaded 9/20/16 6/16/16 Team Meeting Summary – uploaded 9/20/16 5/20/16 Internal Mid-Cycle Meeting Summary – uploaded 9/22/16 4/11/16 Team Meeting Summary – uploaded 10/4/16 3/4/16 Planning Meeting Summary – uploaded 10/4/16
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 10/16/15 (uploaded 11/6/15)
EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg 3/4/15 (uploaded 3/16/16)
Mid-cycle Communication (<i>indicate date of mtg</i>)	☐ N/A 6/1/16 (uploaded 7/1/16)
Late-cycle Meeting (<i>indicate date of mtg</i>)	☐ N/A 9/7/16 (uploaded 10/11/16)
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	NA

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	NA
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None 10/19/16 Final Review Concur – see Multidisciplinary Review
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 10/19/16 Final Review Concur – see Section 17 of Multidisciplinary Review 10/19/16 summary of final assessment and reference to Multidisciplinary Review for final review
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 10/19/16 Final Review Concur – see Executive Summary section of Multidisciplinary Review 10/17/16 summary of final assessment and reference to Multidisciplinary Review for final review
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 1 CMC PMC 9/8/16 / TL Concur 9/8/16 1 Clinical PMR 10/18/16 / TL Concur 10/18/16 / DDS Concur 10/18/16
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review 10/19/16 Final Review Concur – see Clinical/Statistics section of Multidisciplinary Review 7/29/16 Final Assessment Concur – See Memorandum 3/23/16 Filing Review Concur– See Clinical Review
• Clinical review(s) (<i>indicate date for each review</i>)	10/19/16 Final Review – see Clinical section of Multidisciplinary Review 7/29/16 Memorandum – summary of final assessment and reference to Multidisciplinary Review for final review 3/22/16 & 3/23/16 Filing Review
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See page 177 of the Multi-disciplinary Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	NA NA ☐ None 7/28/16 Final Review / 7/28/16 TL Concur
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☐ None requested 7/29/16 Final Review / 7/29/16 TL Concur / 7/29/16 BC Concur 9/13/16 OSI Letter to Eli Lilly 9/9/16 OSI Letter to Edward Kim, M.D. 8/11/16 OSI Letter to (b) (4) 6/7/16 OSI Letter to Brian Van Tine, M.D.
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review 10/19/16 Final Review Concur – see Statistical section of Multidisciplinary Review 7/29/16 Final Assessment Concur – See Memorandum
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review 10/19/16 Final Review Concur – see Statistical section of Multidisciplinary Review 7/29/16 Final Assessment Concur – See Memorandum 4/7/16 Filing Review Concur – See Statistical Review
	☐ None 10/19/16 Final Review – see

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

	Statistical section of Multidisciplinary Review 7/29/16 Memorandum – summary of final assessment and reference to Multidisciplinary Review for final review 4/5/16 Filing Review
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review 10/19/16 Final Review Concur – see Clinical Pharmacology section of Multidisciplinary Review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review 10/19/16 Final Review Concur – see Clinical Pharmacology section of Multidisciplinary Review 7/28/16 Final Assessment Concur – See Memorandum 4/19/16 Filing Review Concur– See Clinical Pharmacology Review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	☐ None 10/19/16 Final Review – see Clinical Pharmacology section of Multidisciplinary Review 7/28/16 Memorandum – summary of final assessment and reference to Multidisciplinary Review for final review 5/16/16 QT/IRT Final Review 4/19/16 Filing Review
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ No separate review 10/19/16 Final Review Concur – see Nonclinical section of Multidisciplinary Review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☒ No separate review 10/19/16 Final Review Concur – see Nonclinical section of Multidisciplinary Review 7/20/16 Final Assessment Concur – See Memorandum 3/29/16 Filing Review Concur – See Pharm/Tox Review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 10/19/16 Final Review – see Nonclinical section of Multidisciplinary Review 7/18/16 Memorandum – summary of final assessment and reference to Multidisciplinary Review for final review 3/29/16 Filing Review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	☐ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☒ None 9/28/16 Addendum Concur - see Integrated Quality Assessment Review 7/29/16 Final Review Concur - see Integrated Quality Assessment Review
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	☐ None Addendum to Integrated Quality Assessment Review: • 9/28/16 CMC TL • 9/28/16 Microbiology Reviewer / TL Concur Integrated Quality Assessment Review: • 7/29/16 CMC TL • 7/29/16 Microbiology TL Concur • 7/31/16 Facilities TL Concur 7/28/16 CMC Final Review / 7/28/16 TL Concur 4/5/16 CMC Filing Review / 4/5/16 TL Concur
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☐ None 9/26/16 Microbiology (drug product) Addendum to Final Review / 9/26/16 TL Concur 7/28/16 Microbiology (drug substance/drug product) Final Review / 7/28/16 TL Concur
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See page 6 Summary of Quality Assessments section of the Integrated Quality Assessment Review
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
☐ Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable 6/16/16 Inspection Waiver Memorandum / 6/23/16 TL Concur / 6/16/16 CMC Reviewer & TL Concur / 6/16/16 CMC (micro) Reviewer & TL Concur / 6/22/16 DD Concur 6/13/16 Final Review / 6/13/16 TL Concur Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes NA ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☐ Done NA
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☒ Done completed 10/19/16 (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> • Notify the Division of Online Communications, Office of Communications	☐ Done NA
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done completed 10/19/16
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done completed 10/19/16
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done verified 10/19/16
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done completed 10/19/16

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
10/24/2016



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

Memorandum

Date: October 12, 2016
From: Leah Her, Regulatory Health Project Manager - CDER/OHOP/DOP2
Subject: **BLA 761038 – Eli Lilly and Company**
Labeling

Date and Time of Teleconference: October 12, 2016, approximately 12:00 - 1:00 PM (EST)

FDA Participants:

Patricia Keegan	Director, DOP2
Marc Theoret	Clinical Team Lead, DOP2
Meredith Chuk	Clinical Reviewer, DOP2
Leah Her	Regulatory Health Project Manager, DOP2
Kun He	Statistical Team Lead, DBV
Linda Park	Regulatory Officer, OPDP

Sponsor Participants:

Jody Roth	Director, Global Regulatory Affairs – Oncology
Allen S Melemed	Sr. Director, Global Regulatory Affairs – Oncology
(b) (4)	Consultant-Regulatory Affairs-Oncology
Lawrence Carl Starke	Associate Vice President Regulatory
(b) (4)	Consultant-Regulatory Global Labeling
Robert Metcalf	Vice President- Regulatory Affairs North America
Raffael Kurek	Sr. Director Global Patient Safety Medical and Benefit-
Risk Ashwin Shahir	Medical Advisor, Global Patient Safety
Robert L Ilaria	Sr. Medical Director, Oncology
Samuel Cowan Ramage	Research Scientist-Clinical
Olaratumab Gary Mo	Research Scientist-Pharmacometrics
Patrick M Peterson	Research Advisor Statistics-Oncology
Chirag Jani	Manager-Statistical Programming Global Statistics
YangPing Wang	Sr. Director, Statistics
Vijayapal R Reddy	Sr. Research Advisor, Non-clinical Safety Assessment
Symantha Ann Melemed	Product Team Leader, Olaratumab
Richard Brian Gaynor	Sr. VP, Product and Clinical Development, Oncology
Stephanie Roberson	Consultant-Clinical Project Management-Oncology

This was an FDA-initiated meeting to discuss the proposed package insert provided by electronic (email) communication on October 7, 2016, in support of the pending Biologics License Application (BLA) 761038 received on February 24, 2016, for the proposed use of 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. In advance of this meeting on October 12, 2016, FDA provided initial and updated counter-proposed labeling for discussion during the meeting.

Summary of the TCON:

Following introductions by all participants, FDA noted that the goal of the meeting was to discuss the proposed labeling for olaratumab. FDA reminded Eli Lilly that the Highlights section will be reviewed after agreement on the Full Prescribing Information has been reached.

The following labeling sections were discussed:

- Section 2.2. Premedication
- Section 6 Adverse Reactions
- Section 14 Clinical Studies

Eli Lilly agreed with all FDA-proposed revisions to the above sections. Regarding Table 3 in Section 14, Eli Lilly requested clarification on the reasoning for [REDACTED]^{(b) (4)} the results based on independent review in the updated label as [REDACTED]^{(b) (4)}

[REDACTED] FDA stated that use of the independent review is consistent with the pre-BLA submission advice provided to Eli Lilly. FDA also stated that results based on protocol-specified primary analysis of PFS (i.e., investigator assessment) as well as the independent review will be provided in the FDA review of the application. Eli Lilly expressed understanding and had no further questions.

Following discussion on the above sections of the label, FDA stated that FDA will revise the Highlights section and provide to Eli Lilly for review and agreement. FDA stated that if all FDA-proposed edits were agreeable, Eli Lilly should submit a clean final version to the BLA.

Attachments:

- Updated FDA proposed package insert provided to Lilly on October 12, 2016, prior to the teleconference
- Initial FDA proposed package insert provided to Lilly on October 12, 2016, prior to the teleconference

Her, Leah

From: Her, Leah
Sent: Wednesday, October 12, 2016 11:16 AM
To: Jody L Roth
Subject: RE: BLA 761038 Eli Lilly - olaratumab - 101216 FDA proposed edits to label
Attachments: 101216_10 AM_FDA Comments to 100716 Olaratumab Label.docx

Importance: High

Hi Jody,

Please find attached updated version of the olaratumab labeling.

Please note that the change from today's earlier version and this version, is in section 14 only. No other section of the label was revised.

Thank you,
Leah

Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

From: Her, Leah
Sent: Wednesday, October 12, 2016 8:33 AM
To: Jody L Roth
Subject: RE: BLA 761038 Eli Lilly - olaratumab - 101216 FDA proposed edits to label
Importance: High

Hi Jody,

Thank you for your reply. I want to let you know that we may have additional edits to section 14. I am hoping to send it to you before the tcon but I'll let you know should I have any additional update.

Thank you,
Leah

Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

From: Jody L Roth [mailto:roth_jody_l@lilly.com]
Sent: Wednesday, October 12, 2016 7:26 AM
To: Her, Leah
Subject: RE: BLA 761038 Eli Lilly - olaratumab - 101216 FDA proposed edits to label

Thanks Leah. I have these and will work with our team this AM.

Regards,
Jody

Jody Roth, RAC, PMP
Advisor, Global Regulatory Affairs – Oncology
Eli Lilly and Company

Office: 317-277-6016

Mobile: (b) (6)

Fax: 317-276-1652

Email: roth.jody.l@lilly.com | Web: <http://www.lilly.com>

From: Her, Leah [<mailto:Leah.Her@fda.hhs.gov>]
Sent: Wednesday, October 12, 2016 7:03 AM
To: Jody L Roth
Subject: BLA 761038 Eli Lilly - olaratumab - 101216 FDA proposed edits to label
Importance: High

Hi Jody,

Please find attached FDA's next round of proposed edits to the olaratumab PI relating to your Biologics License Application (BLA) submitted on February 24, 2016, in preparation of our teleconference scheduled for today at 12:00 PM (EST).

Please note that FDA has accepted all your proposed edits that we were in agreement. Please review our edits and comments and determine if you are in agreement with FDA's proposed edits. Note that we would like to discuss comment 5 during the tcon.

Kindly confirm receipt; and please let me know if you have any questions.

Regards,

Leah S. Her, MS, PMP
Regulatory Health Project Manager
FDA/CDER/OHOP/DOP2
Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

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

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

/s/

LEAH S HER
10/18/2016

Her, Leah

From: Her, Leah
Sent: Friday, October 14, 2016 11:43 AM
To: Jody L Roth
Subject: RE: BLA 761038 Eli Lilly - olaratumab - FDA proposed label 101216 post teleconference
Attachments: proposed-clean.docx; proposed.docx

Hi Jody,

We have no further comments to the label that you submitted on 10/13/16. Please submit both the proposed track and clean to the BLA. Let me know if you have any questions.

Thank you,
Leah

Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

From: Jody L Roth [mailto:roth_jody_l@lilly.com]
Sent: Thursday, October 13, 2016 12:54 PM
To: Her, Leah
Subject: RE: BLA 761038 Eli Lilly - olaratumab - FDA proposed label 101216 post teleconference

Dear Leah,

Enclosed is the updated label with our changes.

We mainly had small formatting changes. We did change content in Section 6.1 to be consistent with FDA changes in the highlights and we correct the spelling of LARTRUVO in section 8.

I will not file this to the BLA until I hear back from FDA if this is acceptable.

Regards,
Jody

*Jody Roth, RAC, PMP
Advisor, Global Regulatory Affairs – Oncology
Eli Lilly and Company*

*Office: 317-277-6016
Mobile: (b) (6)
Fax: 317-276-1652
Email: roth_jody_l@lilly.com | Web: <http://www.lilly.com>*

From: Jody L Roth
Sent: Thursday, October 13, 2016 11:14 AM
To: 'Her, Leah'
Subject: RE: BLA 761038 Eli Lilly - olaratumab - FDA proposed label 101216 post teleconference

Yes I will be happy to do this.

Regards,
Jody Roth, RAC, PMP
Advisor, Global Regulatory Affairs – Oncology
Eli Lilly and Company

Office: 317-277-6016
Mobile: (b) (6)
Fax: 317-276-1652
Email: roth_jody_l@lilly.com | Web: <http://www.lilly.com>

From: Her, Leah [<mailto:Leah.Her@fda.hhs.gov>]
Sent: Thursday, October 13, 2016 11:05 AM
To: Jody L Roth
Subject: RE: BLA 761038 Eli Lilly - olaratumab - FDA proposed label 101216 post teleconference

Hi Jody,

Thank you for your email. Can you please send it to me via email first before sending through the gateway for a quick review?

Thank you,
Leah

Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

From: Jody L Roth [mailto:roth_jody_l@lilly.com]
Sent: Thursday, October 13, 2016 10:58 AM
To: Her, Leah
Subject: RE: BLA 761038 Eli Lilly - olaratumab - FDA proposed label 101216 post teleconference

Dear Leah,
We have been working on the label through the night and early this morning. Our plan is to provide you the updated label via a formal submission to the BLA by end of business today.

I will send you a mail once we have submitted and it has made it through the gateway.

Regards,
Jody

Jody Roth, RAC, PMP
Advisor, Global Regulatory Affairs – Oncology
Eli Lilly and Company

Office: 317-277-6016

Mobile: (b) (6)

Fax: 317-276-1652

Email: roth.jody.l@lilly.com | Web: <http://www.lilly.com>

From: Her, Leah [<mailto:Leah.Her@fda.hhs.gov>]

Sent: Wednesday, October 12, 2016 8:18 PM

To: Jody L Roth

Subject: BLA 761038 Eli Lilly - olaratumab - FDA proposed label 101216 post teleconference

Importance: High

Hi Jody,

Please find attached updated label with FDA's proposed edits in the HL section. Please note that the FPI has been updated as discussed and agreed upon during our teleconference earlier today. Please review FDA's proposed edits in the HL section and if you have no additional questions and agree to these edits, please send me via email a clean, word version of the final label, followed by a formal submission via the gateway. *The formal submission should be done as soon as possible, following the email.*

Kindly confirm receipt; and please let me know if you have any questions.

Regards,

Leah S. Her, MS, PMP
Regulatory Health Project Manager
FDA/CDER/OHOP/DOP2
Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

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

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

/s/

LEAH S HER
10/18/2016

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 23, 2016
TIME: 2:00 - 2:30 PM (EST)
LOCATION: Teleconference
APPLICATION: BLA 761038
DRUG NAME: olaratumab

TYPE OF MEETING: Teleconference with Special Government Employee (SGE), Hussein Tawbi, M.D., cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:

Patricia Keegan – Director, DOP2
Marc Theoret – Clinical Team Lead, DOP2
Meredith Chuk – Clinical Reviewer, DOP2
Leslie Doros – Clinical Reviewer, DOP2
Leah Her – Regulatory Health Project Manager, DOP2

EXTERNAL CONSTITUENT ATTENDEES:

Hussein Tawbi, M.D.

BACKGROUND: Dr. Hussein Tawbi agreed to serve and was cleared as an SGE for this original BLA. Prior to this teleconference, background materials and draft product labeling were provided along with three specific questions from the Division for Dr. Tawbi to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

FDA Questions for Discussion During Teleconference:

1. Although the results of the primary endpoint of progression-free survival for Trial JGDG met the criteria in the pre-specified trial design, they did not reach a level of statistical significance generally associated with a registration trial. Do the overall survival results provide sufficient evidence to support the treatment of patients with advanced soft tissue sarcoma with olaratumab? How does the size of the trial, the heterogeneity of the population with regards to histology, and the types of post-trial therapy received by patients in both arms impact your response?

Discussion During Teleconference: Dr. Tawbi started out by requesting clarification on whether the Applicant is requesting regular approval. FDA informed Dr. Tawbi that the application is being considered for accelerated approval and as a condition of accelerated approval the Applicant would be required to conduct a confirmatory trial to confirm the treatment effect. Dr. Tawbi also requested clarification on whether the summary in the briefing package was provided by the Applicant. FDA responded that the information in the briefing package was generated by FDA based on information submitted by the Applicant to the BLA. Dr. Tawbi expressed understanding of FDA's clarifications and stated an overall viewpoint that the data didn't provide sufficient evidence for the use of olaratumab for patients with soft tissue sarcoma. His specific concerns were the small trial size, number of subsets of sarcoma (including types that are not generally considered sensitive to chemotherapy), lack of central pathology review, missing data regarding tumor grade, imbalance in pre- and post-trial therapy, and lack of understanding of the biologic effect of the drug due to an inadequate pharmacodynamics assay.

Dr. Tawbi stated that the design was reasonable for a phase 2 trial and was not bothered that the PFS results did not achieve traditional levels of statistical significance as they were clinically relevant. He stated that the improvement in overall survival was remarkable; however, he felt that confirmation of the results was needed.

2. As a treating physician or patient, would you be comfortable prescribing or receiving olaratumab in combination with doxorubicin for the first-line treatment of advanced soft tissue sarcoma based on the results of Trial JGDG?

Discussion During Teleconference: FDA requested Dr. Tawbi's thoughts on the use of olaratumab as a first-line treatment in soft tissue sarcoma. Dr. Tawbi stated that he would rather see the results of another trial in first-line with overall survival as a primary endpoint and where the biologic effect of the drug was more clearly characterized. Dr. Tawbi requested clarification on the time between an accelerated approval and the results of the confirmatory trial. FDA explained that the timing of results of a confirmatory trial is dependent upon the design of the trial and when it is initiated. FDA clarified that if the clinical benefit is not confirmed in the subsequent trial, the product can be withdrawn from the market. Dr. Tawbi acknowledged FDA's clarifications. Dr. Tawbi stated that the submitted data was interesting and the effect size remarkable; however, he stated that he wouldn't want olaratumab to become the standard of care without results from a confirmatory trial as there were too many variables (i.e., pretreatment, post-therapy treatment, crossover, heterogeneity, etc.) confounding the data.

Dr. Tawbi stated that the addition of olaratumab to doxorubicin had a reasonable safety profile which would not preclude him from prescribing olaratumab. However, Dr. Tawbi emphasized that although the submitted data suggested activity of olaratumab, which is not undermined by safety issues; more data was needed to understand the impact of the drug.

3. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of olaratumab treatment?

Discussion During Teleconference: Dr. Tawbi stated that overall, the label contained adequate description of the efficacy data; however, he expressed concerns regarding the adequacy of that data in describing the true magnitude of the treatment effect. Dr. Tawbi stated that the section regarding infusion-related reactions could be further clarified regarding what to do when such events occur. FDA informed Dr. Tawbi that clarification would be made in the label.

Dr. Tawbi had no further comments or questions.

ATTACHMENTS: Background information provided to Dr. Tawbi via email (HTawbi@mdanderson.org) on September 13, 2016, which included:

- Briefing Document for FDA Teleconference to Discuss BLA 761038
- Draft Labeling of July 22, 2016



Hussein Tawbi, M.D.
Sent via Email Communication

Dear Dr. Tawbi:

We refer to the teleconference held/correspondence on July 13, 2016, between yourself and Drs. Meredith Chuk and Leslie Doros and Ms. Leah Her of the Division of Oncology Products 2 (DOP2), regarding the possibility of your assistance in the review of a pending Biologics License Application (BLA) 761038, submitted by Eli Lilly and Company (Lilly). Please note that information concerning this application is **confidential**.

In this application, Lilly seeks approval of olaratumab (proposed as Lartruvo), in combination with doxorubicin, for the treatment of advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery.

We have received notification from the CDER Division of Advisory Committee and Consultant Management (DACCM) that you are cleared to serve as a Special Government Employee (SGE) for the review of this pending BLA.

Please review the attached written materials. We will discuss the enclosed information during a teleconference scheduled for **Friday, September 23, 2016 / 12:30 to 1:00 PM (EST)**. We will provide toll-free call in information in advance of this teleconference.

Enclosed is a summary of the single randomized trial submitted with this application, Trial JGDG, and the proposed olaratumab product labeling for your review. The questions we would like to discuss during this teleconference are listed below; please let us know if you would like any additional information in order to aid in the discussion.

FDA Questions for Discussion During the Teleconference:

1. Although the results of the primary endpoint of progression-free survival for Trial JGDG met the criteria in the pre-specified trial design, they did not reach a level of statistical significance generally associated with a registration trial. Do the overall survival results provide sufficient evidence to support the treatment of patients with advanced soft tissue sarcoma with olaratumab? How does the size of the trial, the heterogeneity of the population with regards to histology, and the types of post-trial therapy received by patients in both arms impact your response?
2. As a treating physician or patient, would you be comfortable prescribing or receiving olaratumab in combination with doxorubicin for the first-line treatment of advanced soft tissue sarcoma based on the results of Trial JGDG?

3. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of olaratumab treatment?

Thank you for your time and insights.

If you have questions, please contact me at 240-402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S., P.M.P.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:

1. BLA 761038 Summary Information
2. Draft olaratumab product labeling
3. Timekeeper Payroll Record

**Briefing Document for FDA Teleconference to Discuss BLA 761038 – olaratumab injection,
for intravenous use
Eli Lilly and Company**

Protocol 15B IE-JGDG (Trial JGDG)

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

Cancer Type

Patients with histologically or cytologically confirmed soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery

Study Design

- Trial JGDG is a two-stage, open-label, multicenter trial evaluating the anti-tumor activity of olaratumab, when administered in combination with doxorubicin, compared with single-agent doxorubicin for the treatment of patients with advanced soft tissue sarcoma (STS) whose disease is not amenable to treatment with surgery or radiation, and who have not received prior anthracycline therapy
- The first stage of the trial was a single-arm assessment of the tolerability of olaratumab given in combination with doxorubicin in patients with advanced STS. The second stage of this trial was an open-label, randomized, two-arm, active-controlled study.
- Randomization stratification factors were:
 - PDGFR α expression (positive vs. negative)
 - Number of prior therapies (0 vs. 1 or more)
 - Histologic tumor type (leiomyosarcoma vs. synovial sarcoma vs. other)
 - ECOG PS (0-1 vs. 2)
- The primary endpoint of the phase 2 portion was progression-free survival (PFS) as determined by the investigator by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were overall survival (OS) and confirmed overall response rate (ORR).
- Statistical considerations: For the phase 2 portion, assuming a hazard ratio of 0.67 with a median PFS of 2 months in the control arm and 3 months in the experimental arm, a total of 130 patients with 110 events for the final analysis were needed to provide 80% power at a 2-sided alpha level of 20%. An interim analysis of PFS was planned after 80 PFS events. Two-sided nominal alpha of 0.0001 and 0.1999 were allocated to the interim and final analysis for PFS. No pre-specified statistical criteria, power analysis, or statistical procedure to adjust for multiplicity was planned for the key secondary endpoints of OS and ORR.

Patient Population

- Key eligibility criteria:
 - Age $\geq$ 18 years
 - Histologically confirmed, malignant soft tissue sarcoma (excluding Kaposi's sarcoma) with measurable disease according to RECIST, version 1.1
 - Advanced STS, not amenable to treatment with surgery or radiotherapy; no limit on number of prior therapies
 - Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
 - No prior treatment with doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenediones or therapy with any agent that targets PDGF or PDGFR
 - Left ventricular ejection fraction (LVEF) $\geq$ 50% at baseline

Treatment Regimen

- Patients were randomized (1:1) to one of two arms:
 - olaratumab + doxorubicin: doxorubicin 75 mg/m² followed by olaratumab 15 mg/kg on day 1 and 8 of each 21-day cycle
 - doxorubicin: doxorubicin 75 mg/m² on day 1 of each 21-day cycle
- Treatment continued for up to eight cycles or until disease progression or unacceptable treatment-related toxicity. During Cycles 5 through 8, dexrazoxane could be administered prior to doxorubicin at the discretion of the treating physician. In the absence of disease progression or other withdrawal criteria, patients in experimental arm who completed 8 cycles of doxorubicin could continue to receive olaratumab as a single agent at the same dose and schedule until progression. Patients on the control arm were also eligible to receive single-agent olaratumab upon disease progression or inability to receive further doxorubicin due to toxicity. Disease assessments were conducted every 6 weeks.

Efficacy

- Trial JGDG was conducted at 16 centers in the U.S. Demographic and baseline disease characteristics and information regarding prior therapy are summarized in Tables 1-4.

Table 1: Demographics and Baseline Disease Characteristics

Variable	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Age		
Mean (SD)	56.8 (12.5)	58.3 (12.5)
Median (min-max)	58.5 (22-85)	58.0 (29-86)
18 - <65	48 (73)	43 (64)
$\geq$ 65	18 (27)	24 (35)
Sex		
Male	26 (39)	33 (49)
Female	40 (61)	34 (51)

Race		
White	55 (83)	60 (90)
Black	6 (9)	5 (7)
Asian	2 (3)	2 (3)
Other	3 (5)	0
ECOG performance status ^a		
0-1	62 (94)	63 (94)
2	4 (6)	4 (6)
Tumor PDGFR α status ^a		
Positive	58 (88)	59 (88)
Negative	8 (12)	8 (12)
Tumor histology ^a		
Leiomyosarcoma	25 (38)	26 (39)
Synovial sarcoma	1 (1)	2 (3)
Other	40 (61)	39 (58)
Prior systemic therapy ^{a,b}		
0	27 (41)	31 (46)
1 or more	39 (59)	36 (54)
Tumor grade		
Grade 1	7 (11)	8 (12)
Grade 2	5 (8)	7 (10)
Grade 3	29 (44)	29 (43)
Grade cannot be assessed or unknown	25 (38)	23 (34)
Duration of disease (months)		
Mean (SD)	31.9 (41.4)	34.7 (53.1)
Median (range)	15 (0.5-223.5)	14.9 (0.3-258.6)
Metastatic disease	66 (100)	67 (100)
Sites of metastatic disease		
Lung	42 (64)	42 (63)
Soft tissue	22 (33)	33 (49)
Liver	26 (39)	22 (33)
Peritoneal	15 (23)	23 (34)
Lymph nodes	16 (24)	21 (31)
Bone	10 (15)	18 (27)
Other	8 (12)	16 (24)
Pleural	10 (15)	9 (13)
Skin	3 (5)	0

^a Randomization factors based on IVRS

^b Includes adjuvant and neoadjuvant therapy

Table 2: Detailed Histology by Independent Review of Pathology Forms

Histology	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
“Other”		
Liposarcoma	8 (12.1)	14 (20.9)
Dedifferentiated	4	6
Myxoid	2	3
Well-differentiated	1	3
Pleomorphic	1	1
Liposarcoma NOS	0	1
Undifferentiated pleomorphic sarcoma	7 (10.6)	8 (11.9)
Angiosarcoma	4 (6.1)	3 (4.5)
Undifferentiated sarcoma NOS	2 (3)	4 (6)
Extraskeletal myxoid chondrosarcoma	2 (3)	2 (3)
Malignant peripheral nerve sheath tumor	3 (4.5)	0
Myxofibrosarcoma	2 (3)	1 (1.5)
Malignant solitary fibrous tumor	2 (3)	1 (1.5)
Endometrial stromal sarcoma	2 (3)	1 (1.5)
Chondrosarcoma	0	2 (3)
Epithelioid sarcoma	2 (3)	0
Fibrosarcoma	1 (1.5)	1 (1.5)
Low-grade fibromyxoid sarcoma	1 (1.5)	1 (1.5)
Alveolar soft part sarcoma	1 (1.5)	0
Chondroblastic osteosarcoma	0	1 (1.5)
Clear cell sarcoma of soft tissue	1 (1.5)	0
Extra-renal rhabdoid tumor	0	1 (1.5)
Extraskeletal osteosarcoma	0	1 (1.5)
Undifferentiated round cell sarcoma	1 (1.5)	0
Leiomyosarcoma	25 (37.9)	25 (37.3)
Synovial sarcoma	1 (1.5)	1 (1.5)

Table 3: Previous Anticancer Therapy

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Lines of therapy (excluding adjuvant and neoadjuvant)		
0	40 (60.6)	47 (70.1)
1	14 (21.2)	12 (17.9)
2	8 (12.1)	7 (10.4)
3	2 (3)	1 (1.5)
4	2 (3)	0
Type of previous anticancer therapy		
Neoadjuvant	3 (4.5)	10 (14.9)
Adjuvant	17 (25.8)	10 (14.9)
Previous surgery		
Yes	55 (83)	57 (85.1)
No	11 (16.7)	10 (14.9)
Previous radiotherapy		
Yes	31 (47)	32 (47.8)
No	35 (53)	35 (52.2)

Table 4: Prior Chemotherapy in ≥3% of Patients in Either Arm

Therapy	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Gemcitabine	29 (43.9)	30 (44.8)
Docetaxel	28 (42.4)	30 (44.8)
Paclitaxel	3 (4.5)	2 (3)
Bevacizumab	2 (3)	3 (4.5)
Investigational drug	4 (6.1)	1 (1.5)
Ifosfamide	3 (4.5)	1 (1.5)
Trabectedin	3 (4.5)	2 (3)
Letrozole	3 (4.5)	1 (1.5)
Palbociclib	2 (3)	2 (3)
Fluorouracil	0	2 (3)

- Patient disposition and post-trial therapy are summarized in Tables 5 and 6

Table 5: Summary of Patient Disposition by Treatment Discontinuation

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Progressive disease, radiographic	42 (63.6)	27 (40.3)
Adverse event	5 (7.6)	11 (16.4)
Completed treatment ^a	0	11 (16.4)
Withdrawal of consent	5 (7.6)	6 (9)
Progressive disease, symptomatic	3 (4.5)	7 (10.4)
Physician decision	6 (9.1)	0
Randomized but not treated	2 (3)	2 (3)
Death	2 (3)	1 (1.5)
Other ^b	1 (1.5)	2 (3)

^a Completed 8 cycles of doxorubicin

^b Other reasons for discontinuation: Olaratumab + doxorubicin=gradual increase in lesions that did not meet RECIST criteria; Doxorubicin=patient crossed over to study drug, non-compliance, each n=1

Table 6: Post-study Therapy in ≥ 3% of Patients in Either Arm

Therapy	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Any systemic therapy	44 (66.7)	46 (68.7)
1 regimen	18 (27.3)	20 (29.9)
2 regimens	12 (18.2)	14 (20.9)
3 regimens	9 (13.6)	6 (9)
4 regimens	1 (1.5)	2 (3)
>4 regimens	4 (6.1)	4 (6)
Olaratumab	0	30 (44.8)
Gemcitabine	15 (22.7)	11 (16.4)
Pazopanib	15 (22.7)	10 (14.9)
Docetaxel	14 (21.2)	8 (11.9)
Dacarbazine	12 (18.2)	8 (11.9)
Trabectedin	11 (16.7)	3 (4.5)
Ifosfamide	8 (12.1)	8 (11.9)
Investigational drug	8 (12.1)	2 (3)
Doxorubicin	1 (1.5)	5 (7.5)
Eribulin	3 (4.5)	2 (3)
Everolimus	2 (3)	2 (3)
Vinorelbine	2 (3)	2 (3)
Alisertib	1 (1.5)	2 (3)
Etoposide	1 (1.5)	2 (3)
Paclitaxel	2 (3)	1 (1.5)
Sorafenib	2 (3)	0
Sunitinib	2 (3)	0

- Efficacy results are summarized in Tables 7 - 11 and Figures 1 and 2

Table 7: PFS Analyses per Investigator Assessment

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Number of events, n (%)	55 (83)	48 (72)
Progressive disease, n (%)	54(82)	43 (64)
Death, n (%)	1 (2)	5 (7)
Median PFS (months), 95% CI	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
Cox stratified HR (95% CI)	0.67 (0.44, 1.02)	
P value, stratified log-rank test	0.06	

Figure 1: Kaplan-Meier Curves for PFS per Investigator Assessment

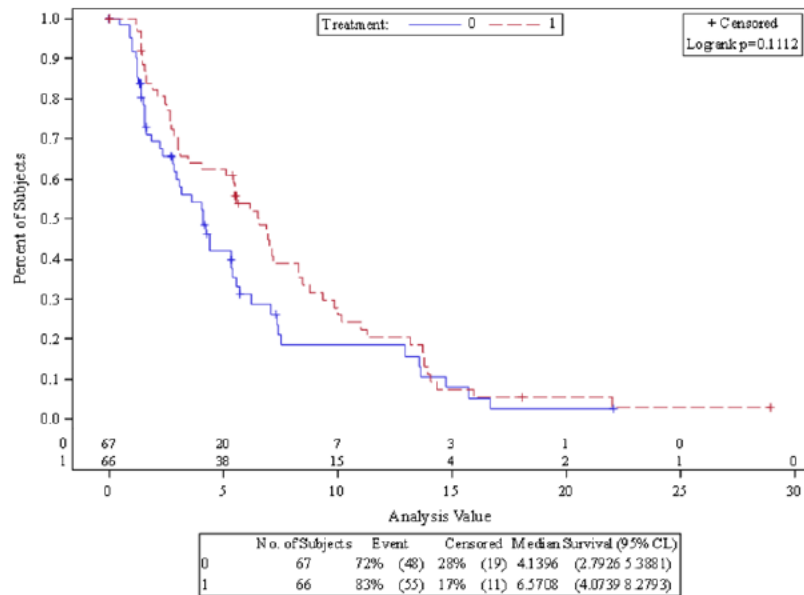
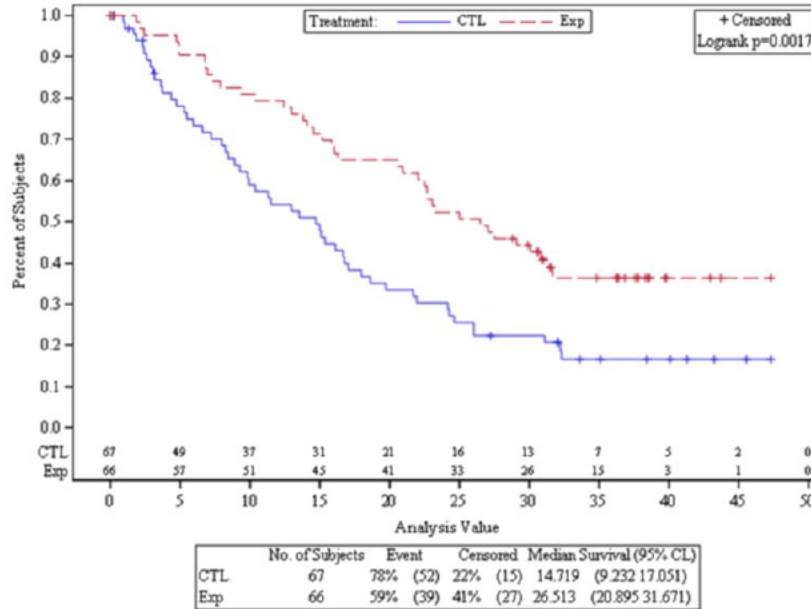


Table 8: PFS Analyses by Blinded Independent Central Review

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Number of events, n (%)	37 (56)	34 (51)
Progressive disease, n (%)	36(55)	32 (48)
Death, n (%)	1 (2)	2 (3)
Median PFS (months), 95% CI	8.2 (5.5, 9.8)	4.4 (3.1, 7.4)
Cox stratified HR (95% CI)	0.67 (0.40, 1.12)	
P value, stratified log-rank test	0.12	

Table 9: OS Analyses

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Number of deaths, n (%)	39 (59)	52 (78)
Median OS in months, (95% CI)	26.5 (20.9, 31.7)	14.7 (9.2, 17.1)
Cox stratified HR (95% CI)	0.46 (0.30, 0.71)	
P value, stratified log-rank test	0.0003	

Figure 2: Kaplan-Meier curves for overall survival**Table 10: OS sensitivity analyses**

	Olaratumab + Doxorubicin N=66 HR (95%)	Doxorubicin N=67 HR (95%)
Post PD (BICR) OS ^{a,b,c}	0.46 (0.26, 0.81)	
Post PD (INV) OS ^{a,b,c}	0.55 (0.34, 0.89)	
Censored at initiation of any subsequent anti-cancer therapy ^a	0.49 (0.23, 1.04)	
Censored at initiation of subsequent specific anti-cancer therapy ^{a,d}	0.43 (0.24, 0.76)	
Analyses excluding patients who completed:		
<= 7 cycles of doxorubicin therapy ^{a,c}	0.38 (0.17, 0.86)	
<= 6 cycles of doxorubicin therapy ^{a,c}	0.42 (0.19, 0.91)	
<= 5 cycles of doxorubicin therapy ^{a,c}	0.41 (0.21, 0.81)	
<= 4 cycles of doxorubicin therapy ^{a,c}	0.42 (0.22, 0.80)	

Abbreviations PD=progressive disease; BICR=blinded independent central review; INV=investigator
^a Stratified by prior systemic therapy per CRF and histology per independent review of pathology forms
^b From the date of documented PD to the date of death from any cause
^c Based on a subgroup of patients
^d Limited to pazopanib, eribulin, gemcitabine + docetaxel, doxorubicin, and trabectedin

Table 11: ORR results

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Investigator		
Overall Response	12 (18)	8 (12)
CR	2 (3)	1 (2)
PR	10 (15)	7 (10)
95% CI	(9.8, 29.6)	(5.3, 22.2)
Blinded central review		
Overall Response	12 (18)	5 (8)
CR	3 (5)	1 (2)
PR	9 (14)	4 (6)
95% CI	(9.8, 29.6)	(2.5, 16.6)

Safety

- Median duration of treatment:
 - Olaratumab plus doxorubicin arm: olaratumab = 26.1 weeks; doxorubicin = 21.3 weeks
 - Doxorubicin arm: doxorubicin=12.3 weeks
- The most significant toxicities related to olaratumab were:
 - Infusion-related reactions
 - Neutropenia
 - Musculoskeletal pain
- Adverse events (AEs) leading to treatment discontinuation occurred in 12.5% of patients in the olaratumab plus doxorubicin arm and 16.9% in the single-agent doxorubicin arm.
 - The most common treatment emergent adverse events (TEAEs) leading to dose modifications of olaratumab were neutropenia (31 [48.4%]) and thrombocytopenia (8 [12.5%]). There were more patients with AEs leading to modification of doxorubicin in the olaratumab plus doxorubicin arm (23 [35.9%]) than in the single-agent doxorubicin arm (17 [26.2%]).
 - The most common AEs leading to modification of doxorubicin were neutropenia (13 [20.3%] versus 6 [9.2%] in the olaratumab plus doxorubicin arm versus the single-agent doxorubicin arm) and febrile neutropenia (3 [4.7%] versus 4 [6.2%]). The most common AE that led to dose reductions or dose delays in either arm was neutropenia.
- The proportion of deaths that occurred within 30 days of the last dose of treatment was higher in the single-agent doxorubicin arm (9.2%) versus (4.7%) in the olaratumab plus

doxorubicin arm. Death due to an AE was the primary cause of death in the single-arm doxorubicin arm in four (6.2%) patients. All deaths in the olaratumab plus doxorubicin arm were due to progressive disease; no deaths occurred due to an AE.

- The rate of non-fatal serious adverse events (SAEs) was comparable between arms. SAEs occurred in 27 (42.2%) patients in the olaratumab plus doxorubicin arm compared to 25 (38.5%) patients in the single-agent doxorubicin arm. The rate of Grade 3 SAEs was higher in the olaratumab plus doxorubicin arm (31.3% versus 21.5%). The most commonly occurring SAEs in the olaratumab plus doxorubicin arm were febrile neutropenia (12.5%), musculoskeletal pain (4.7%), and neutropenia (4.7%).
- In the olaratumab plus doxorubicin arm, the most common TEAEs were nausea (73.4%), fatigue (68.8%), musculoskeletal pain (64.1%), neutropenia (57.8%), and mucositis (53.1%). The most frequently reported TEAEs observed in at least a 20% point difference in the olaratumab + doxorubicin arm than in the single-agent doxorubicin arm, respectively, were musculoskeletal pain (64.1% vs. 24.6%), nausea (73.4% vs. 52.3%), neutropenia (57.8% vs. 35.4%), and vomiting (45.3% vs. 18.5%). TEAEs in $\geq 20\%$ of the patients are summarized in Table 12.

Table 13: TEAEs in ≥ 20% of Patients

Preferred Term Consolidated TEAE Category	Olaratumab + Doxorubicin N=64 n(%)		Single-agent Doxorubicin N=65 n(%)		Single-agent Olaratumab after Single-agent Doxorubicin Treatment N=30 n(%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Patients with any AE	63 (98.4)	51 (79.7)	64 (98.5)	45 (69.2)	26 (80.0)	8 (17.8)
Nausea	47 (73.4)	1 (1.6)	34 (52.3)	2 (3.1)	6 (20.0)	1 (3.3)
Fatigue ¹	44 (68.8)	6 (9.4)	45 (69.2)	2 (3.1)	6 (20.0)	2 (6.7)
Musculoskeletal Pain ²	41 (64.1)	5 (7.8)	16 (24.6)	1 (1.5)	7 (23.3)	2 (6.7)
Neutropenia ^{3,4}	37 (57.8)	34 (53.2)	23 (35.4)	22 (32.3)	0	0
Mucositis ⁵	34 (53.1)	2 (3.1)	23 (35.4)	3 (4.6)	2 (6.7)	0
Alopecia	33 (51.6)	0	26 (40.0)	0	2 (6.7)	0
Vomiting	29 (45.3)	0	12 (18.5)	0	5 (16.7)	0
Infections and Infestations ⁶	27 (42.2)	5 (7.8)	27 (41.5)	7 (10.8)	7 (23.3)	0
Anemia ^{4,7}	26 (40.6)	8 (12.5)	24 (36.9)	6 (9.2)	5 (16.7)	1 (3.3)
Leukopenia ⁸	26 (40.6)	0	12 (18.5)	0	1 (3.3)	0
Constipation	22 (34.4)	0	21 (32.3)	1 (1.5)	3 (10.0)	0
Diarrhea	22 (34.4)	2 (3.1)	15 (23.1)	0	5 (16.7)	0
Decreased Appetite	20 (31.3)	1 (1.6)	13 (20.0)	0	3 (10.0)	2 (6.7)
Abdominal Pain ⁹	15 (23.4)	2 (3.1)	9 (13.8)	0	3 (10.0)	0
Pyrexia	15 (23.4)	0	12 (18.5)	0	3 (10.0)	0
Thrombocytopenia ^{4,10}	16 (25.0)	7 (10.9)	14 (21.5)	5 (7.7)	0	0
Neuropathy ¹¹	14 (21.9)	0	7 (10.8)	0	3 (10.0)	0
Headache	13 (20.3)	0	6 (9.2)	0	1 (3.3)	0
Cough	14 (21.9)	0	12 (18.5)	0	3 (10.0)	0
AESIs						
Infusion-related Reactions ¹²	8 (12.5)	2 (3.1)	0	0	3 (10.0)	1 (3.3)
Cardiac Arrhythmias ¹³	10 (15.6)	0	10 (15.4)	1 (1.5)	4 (13.3)	0
Cardiac Dysfunction ¹⁴	15 (23.4)	1 (1.6)	12 (16.9)	0	4 (13.3)	0

Abbreviations: TEAE = treatment-emergent adverse events; AESI = adverse event of special interest; N = number of treated patients; n = number of patients with given event.

¹Preferred terms patients experienced were fatigue and asthenia.

²Preferred terms patients experienced were arthralgia, back pain, bone pain, flank pain, groin pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.

³Preferred terms patients experienced were neutropenia and neutrophil count decreased.

⁴As reported by the Investigator. These do not represent actual laboratory values.

⁵Preferred terms patients experienced were mucosal inflammation, oropharyngeal pain, and stomatitis.

⁶Includes all preferred terms within the MedDRA™ system organ class of Infections and Infestations.

⁷Preferred terms patients experienced were anemia and hemoglobin decreased.

⁸Preferred terms patients experienced were leukopenia and white blood cell count decreased.

⁹Preferred terms patients experienced were abdominal pain upper, abdominal pain, and abdominal pain lower.

¹⁰Preferred terms patients experienced were thrombocytopenia and platelet count decreased.

¹¹Preferred terms patients experienced were neuropathy peripheral, paresthesia, peripheral sensory neuropathy, and hypoesthesia.

¹²Preferred terms patients experienced were face edema, hypersensitivity, infusion related reaction

¹³Preferred terms patients experienced were tachycardia, bradycardia, bundle branch block left, electrocardiogram QT prolonged, heart rate increased, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, supraventricular extrasystoles, atrial fibrillation, syncope.

¹⁴Preferred terms patients experienced edema peripheral, ejection fraction decreased, cardiac failure congestive, hepatojugular reflux, jugular vein distention, left ventricular.

- Grade ≥3 TEAEs were reported in 79.7% of patients in the olaratumab plus doxorubicin arm and 69.2% of patients in the single-agent doxorubicin arm. The most common Grade ≥3 TEAEs occurring in patients in the olaratumab plus doxorubicin arm included neutropenia, anemia, febrile neutropenia, and thrombocytopenia. The most common Grade 4 event on both study arms was neutropenia 22 (34.4%) vs. 16 (24.6%).

- Infusion-related reactions (IRRs) occurred in 14.9% (14 of 94) of patients in Trial JGDG. IRRs occurred in Cycles 1 and 2, were mainly Grade 1 or 2 (10 of 14 [71.4%]). All Grade ≥ 3 IRRs occurred with the first infusion of olaratumab. Patients with a Grade ≥ 3 were permanently discontinued from therapy. Premedication was not required but was administered in the majority of cases. Of the 14 patients who experienced an IRR, eight (57.1%) had received premedication with an anti-histamine, corticosteroid, or both. A total of 10 (62.5%) patients with a Grade 1 or 2 IRR underwent subsequent administration of olaratumab. Three patients experienced an IRR; all were Grade 1 or 2. Across the eight supportive studies, the incidence and timing of events was comparable to Trial JGDG.
 - Grade 5 infusion-related reaction (IRR): One patient who received olaratumab monotherapy after discontinuation of doxorubicin experienced a fatal IRR. This event occurred in 75 year-old man who had several baseline cardiac comorbidities (ischemic cardiomyopathy, myocardial infarction, ventricular tachycardia, stent placement, heart valve replacement, as well as an implantable defibrillator) who discontinued doxorubicin after two doses due to a decrease in ejection fraction (43%). Ten minutes into the first infusion of olaratumab on Cycle 1 Day 1, the patient developed loss of consciousness and was found to be unresponsive and pulseless; ECG showed ventricular fibrillation and CPR was unsuccessful. The reported event of cardiac arrest was deemed by the Investigator and the Applicant to be possibly related to olaratumab. The Applicant determined this to be an IRR given the temporal administration of olaratumab.
- The incidence of neutropenia as assessed by laboratory testing was comparable between arms for all grades (64.1% in the olaratumab plus doxorubicin arm versus 60.3% in the single-agent doxorubicin arm). The incidence of Grade 4 neutropenia was higher in the olaratumab plus doxorubicin arm (31.3%) versus the single-agent doxorubicin arm (19.0%). This higher incidence of Grade 4 neutropenia did not translate into increased rates of febrile neutropenia, infections, discontinuations, or deaths.
- Musculoskeletal pain occurred more frequently in patients in the olaratumab plus doxorubicin arm (64.1% versus 24.6% of patients in the doxorubicin arm). Grade 3 to 4 musculoskeletal pain occurred in five patients (7.8%) in the olaratumab plus doxorubicin arm versus one (1.5%) patient in the doxorubicin arm. For the five patients that experienced a Grade 3 event, four patients had preexisting pain that worsened and one patient had an infection at the site of pain. There was one Grade 3 musculoskeletal event that led to discontinuation in the olaratumab plus doxorubicin arm. The majority of events were low grade, and mitigated with supportive care and analgesics. Across the eight supportive studies, the incidence of musculoskeletal pain varied from 6.3% to 71.9%. Overall, in the olaratumab-containing arms and olaratumab monotherapy trial, the incidence of musculoskeletal pain was higher (49.5% versus 43.4% in the control arms).

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/s/

LEAH S HER
10/18/2016

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 21, 2016
TIME: 1:00 - 1:30 PM (EST)
LOCATION: Teleconference
APPLICATION: BLA 761038
DRUG NAME: olaratumab

TYPE OF MEETING: Teleconference with Special Government Employee (SGE), James Liebmann, M.D., cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:

Marc Theoret – Clinical Team Lead, DOP2
Meredith Chuk – Clinical Reviewer, DOP2
Leslie Doros – Clinical Reviewer, DOP2
Leah Her – Regulatory Health Project Manager, DOP2

EXTERNAL CONSTITUENT ATTENDEES:

James Liebmann, M.D.

BACKGROUND: Dr. James Liebmann agreed to serve and was cleared as an SGE for this original BLA. Prior to this teleconference, background materials and draft product labeling were provided along with three specific questions from the Division for Dr. Liebmann to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

FDA Questions for Discussion During Teleconference:

1. Although the results of the primary endpoint of progression-free survival for Trial JGDG met the criteria in the pre-specified trial design, they did not reach a level of statistical significance generally associated with a registration trial. Do the overall survival results provide sufficient evidence to support the treatment of patients with advanced soft tissue sarcoma with olaratumab? How does the size of the trial, the heterogeneity of the population with regards to histology, and the types of post-trial therapy received by patients in both arms impact your response?

Discussion During Teleconference: Dr. Liebmann expressed an overall viewpoint that based on the small sample size, heterogeneous patient population, and disparities in pre- and

post-treatment therapies, the data didn't provide sufficient evidence to support the use of olaratumab in patients with soft tissue sarcoma, and felt that olaratumab's approval should be delayed until the results of the confirmatory trial are available. FDA acknowledged Dr. Liebmann's concerns and inquired whether the fact that the confirmatory trial results would not be available for several more years impacts Dr. Liebmann's opinion. Dr. Liebmann stated that that information does not change his opinion.

In response to FDA's question above, Dr. Liebmann stated that although the primary endpoint was progression-free survival, he didn't have concerns with the failure to achieve traditional levels of statistical significance for PFS as overall survival was most important. Dr. Liebmann stated that the results were impressive; however, he expressed concerns about whether they were real given the small sample size of the trial and that moving a few patients in each arm could affect the outcome. FDA inquired whether Dr. Liebmann had any concerns regarding the amount of doxorubicin received in both treatment arms, Dr. Liebmann stated that he did have concerns. FDA stated that FDA has run various sensitivity analyses and, although the magnitude of hazard ratio may be changed, the effect still remained. The difference in cumulative doxorubicin doses received between treatment arms did not appear to be a determinant of the survival effect based on these sensitivity analyses.

Regarding Table 5 of the briefing package, Dr. Liebmann questioned the higher number of patients with progressive disease (radiographic) in the olaratumab plus doxorubicin arm relative to doxorubicin arm. FDA stated that other reasons for discontinuation, such as completed treatment, which was not an option for patients in the olaratumab + doxorubicin arm, and adverse events made up the majority of the discrepancy.

2. As a treating physician or patient, would you be comfortable prescribing or receiving olaratumab in combination with doxorubicin for the first-line treatment of advanced soft tissue sarcoma based on the results of Trial JGDG?

Discussion During Teleconference: Dr. Liebmann stated that the data itself were not compelling enough for him to prescribe olaratumab; however, if FDA grants approval, then he stated that he and other prescribers would likely feel obligated to use olaratumab. Dr. Liebmann stated that from a safety perspective, the results were as expected for a monoclonal antibody and he did not have any concerns with the safety profile.

2. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of olaratumab treatment?

Discussion During Teleconference: Dr. Liebmann stated that overall, the label summarized what occurred in the trial and contained appropriate language and information. Under the Indications and Usage section of the Highlights, Dr. Liebmann commented on the reference to the accelerated approval language where it states "Continued approval for this indication may be contingent..." Instead of "may" Dr. Liebmann asked whether it should be changed to "will be." FDA acknowledged Dr. Liebmann's comments and stated that the general language used in the label is from the regulations and is standard for products under accelerated approval; however, a confirmatory trial is ongoing.

Dr. Liebmann had no further comments or questions.

ATTACHMENTS: Background information provided to Dr. Liebmann via email (James.Liebmann@umassmemorial.org) on September 13, 2016, which included:

- Briefing Document for FDA Teleconference to Discuss BLA 761038
- Draft Labeling of July 22, 2016



James Liebmann, M.D.
Sent via Email Communication

Dear Dr. Liebmann:

We refer to the teleconference held/correspondence on May 31, 2016, between yourself and Drs. Meredith Chuk and Leslie Doros and Ms. Leah Her of the Division of Oncology Products 2 (DOP2), regarding the possibility of your assistance in the review of a pending Biologics License Application (BLA) 761038, submitted by Eli Lilly and Company (Lilly). Please note that information concerning this application is **confidential**.

In this application, Lilly seeks approval of olaratumab (proposed as Lartruvo), in combination with doxorubicin, for the treatment of advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery.

We have received notification from the CDER Division of Advisory Committee and Consultant Management (DACCM) that you are cleared to serve as a Special Government Employee (SGE) for the review of this pending BLA.

Please review the attached written materials. We will discuss the enclosed information during a teleconference scheduled for **Wednesday, September 21, 2016 / 1:00 to 1:30 PM (EST)**. We will provide toll-free call in information in advance of this teleconference.

Enclosed is a summary of the single randomized trial submitted with this application, Trial JGDG, and the proposed olaratumab product labeling for your review. The questions we would like to discuss during this teleconference are listed below; please let us know if you would like any additional information in order to aid in the discussion.

FDA Questions for Discussion During the Teleconference:

1. Although the results of the primary endpoint of progression-free survival for Trial JGDG met the criteria in the pre-specified trial design, they did not reach a level of statistical significance generally associated with a registration trial. Do the overall survival results provide sufficient evidence to support the treatment of patients with advanced soft tissue sarcoma with olaratumab? How does the size of the trial, the heterogeneity of the population with regards to histology, and the types of post-trial therapy received by patients in both arms impact your response?
2. As a treating physician or patient, would you be comfortable prescribing or receiving olaratumab in combination with doxorubicin for the first-line treatment of advanced soft tissue sarcoma based on the results of Trial JGDG?

3. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of olaratumab treatment?

Thank you for your time and insights.

If you have questions, please contact me at 240-402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S., P.M.P.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:

1. BLA 761038 Summary Information
2. Draft olaratumab product labeling
3. Timekeeper Payroll Record

**Briefing Document for FDA Teleconference to Discuss BLA 761038 – olaratumab injection,
for intravenous use
Eli Lilly and Company**

Protocol 15B IE-JGDG (Trial JGDG)

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

Cancer Type

Patients with histologically or cytologically confirmed soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery

Study Design

- Trial JGDG is a two-stage, open-label, multicenter trial evaluating the anti-tumor activity of olaratumab, when administered in combination with doxorubicin, compared with single-agent doxorubicin for the treatment of patients with advanced soft tissue sarcoma (STS) whose disease is not amenable to treatment with surgery or radiation, and who have not received prior anthracycline therapy
- The first stage of the trial was a single-arm assessment of the tolerability of olaratumab given in combination with doxorubicin in patients with advanced STS. The second stage of this trial was an open-label, randomized, two-arm, active-controlled study.
- Randomization stratification factors were:
 - PDGFR α expression (positive vs. negative)
 - Number of prior therapies (0 vs. 1 or more)
 - Histologic tumor type (leiomyosarcoma vs. synovial sarcoma vs. other)
 - ECOG PS (0-1 vs. 2)
- The primary endpoint of the phase 2 portion was progression-free survival (PFS) as determined by the investigator by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were overall survival (OS) and confirmed overall response rate (ORR).
- Statistical considerations: For the phase 2 portion, assuming a hazard ratio of 0.67 with a median PFS of 2 months in the control arm and 3 months in the experimental arm, a total of 130 patients with 110 events for the final analysis were needed to provide 80% power at a 2-sided alpha level of 20%. An interim analysis of PFS was planned after 80 PFS events. Two-sided nominal alpha of 0.0001 and 0.1999 were allocated to the interim and final analysis for PFS. No pre-specified statistical criteria, power analysis, or statistical procedure to adjust for multiplicity was planned for the key secondary endpoints of OS and ORR.

Patient Population

- Key eligibility criteria:
 - Age $\geq$ 18 years
 - Histologically confirmed, malignant soft tissue sarcoma (excluding Kaposi's sarcoma) with measurable disease according to RECIST, version 1.1
 - Advanced STS, not amenable to treatment with surgery or radiotherapy; no limit on number of prior therapies
 - Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
 - No prior treatment with doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenediones or therapy with any agent that targets PDGF or PDGFR
 - Left ventricular ejection fraction (LVEF) $\geq$ 50% at baseline

Treatment Regimen

- Patients were randomized (1:1) to one of two arms:
 - olaratumab + doxorubicin: doxorubicin 75 mg/m² followed by olaratumab 15 mg/kg on day 1 and 8 of each 21-day cycle
 - doxorubicin: doxorubicin 75 mg/m² on day 1 of each 21-day cycle
- Treatment continued for up to eight cycles or until disease progression or unacceptable treatment-related toxicity. During Cycles 5 through 8, dexrazoxane could be administered prior to doxorubicin at the discretion of the treating physician. In the absence of disease progression or other withdrawal criteria, patients in experimental arm who completed 8 cycles of doxorubicin could continue to receive olaratumab as a single agent at the same dose and schedule until progression. Patients on the control arm were also eligible to receive single-agent olaratumab upon disease progression or inability to receive further doxorubicin due to toxicity. Disease assessments were conducted every 6 weeks.

Efficacy

- Trial JGDG was conducted at 16 centers in the U.S. Demographic and baseline disease characteristics and information regarding prior therapy are summarized in Tables 1-4.

Table 1: Demographics and Baseline Disease Characteristics

Variable	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Age		
Mean (SD)	56.8 (12.5)	58.3 (12.5)
Median (min-max)	58.5 (22-85)	58.0 (29-86)
18 - <65	48 (73)	43 (64)
$\geq$ 65	18 (27)	24 (35)
Sex		
Male	26 (39)	33 (49)
Female	40 (61)	34 (51)

Race		
White	55 (83)	60 (90)
Black	6 (9)	5 (7)
Asian	2 (3)	2 (3)
Other	3 (5)	0
ECOG performance status ^a		
0-1	62 (94)	63 (94)
2	4 (6)	4 (6)
Tumor PDGFR α status ^a		
Positive	58 (88)	59 (88)
Negative	8 (12)	8 (12)
Tumor histology ^a		
Leiomyosarcoma	25 (38)	26 (39)
Synovial sarcoma	1 (1)	2 (3)
Other	40 (61)	39 (58)
Prior systemic therapy ^{a,b}		
0	27 (41)	31 (46)
1 or more	39 (59)	36 (54)
Tumor grade		
Grade 1	7 (11)	8 (12)
Grade 2	5 (8)	7 (10)
Grade 3	29 (44)	29 (43)
Grade cannot be assessed or unknown	25 (38)	23 (34)
Duration of disease (months)		
Mean (SD)	31.9 (41.4)	34.7 (53.1)
Median (range)	15 (0.5-223.5)	14.9 (0.3-258.6)
Metastatic disease	66 (100)	67 (100)
Sites of metastatic disease		
Lung	42 (64)	42 (63)
Soft tissue	22 (33)	33 (49)
Liver	26 (39)	22 (33)
Peritoneal	15 (23)	23 (34)
Lymph nodes	16 (24)	21 (31)
Bone	10 (15)	18 (27)
Other	8 (12)	16 (24)
Pleural	10 (15)	9 (13)
Skin	3 (5)	0

^a Randomization factors based on IVRS

^b Includes adjuvant and neoadjuvant therapy

Table 2: Detailed Histology by Independent Review of Pathology Forms

Histology	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
“Other”		
Liposarcoma	8 (12.1)	14 (20.9)
Dedifferentiated	4	6
Myxoid	2	3
Well-differentiated	1	3
Pleomorphic	1	1
Liposarcoma NOS	0	1
Undifferentiated pleomorphic sarcoma	7 (10.6)	8 (11.9)
Angiosarcoma	4 (6.1)	3 (4.5)
Undifferentiated sarcoma NOS	2 (3)	4 (6)
Extraskeletal myxoid chondrosarcoma	2 (3)	2 (3)
Malignant peripheral nerve sheath tumor	3 (4.5)	0
Myxofibrosarcoma	2 (3)	1 (1.5)
Malignant solitary fibrous tumor	2 (3)	1 (1.5)
Endometrial stromal sarcoma	2 (3)	1 (1.5)
Chondrosarcoma	0	2 (3)
Epithelioid sarcoma	2 (3)	0
Fibrosarcoma	1 (1.5)	1 (1.5)
Low-grade fibromyxoid sarcoma	1 (1.5)	1 (1.5)
Alveolar soft part sarcoma	1 (1.5)	0
Chondroblastic osteosarcoma	0	1 (1.5)
Clear cell sarcoma of soft tissue	1 (1.5)	0
Extra-renal rhabdoid tumor	0	1 (1.5)
Extraskeletal osteosarcoma	0	1 (1.5)
Undifferentiated round cell sarcoma	1 (1.5)	0
Leiomyosarcoma	25 (37.9)	25 (37.3)
Synovial sarcoma	1 (1.5)	1 (1.5)

Table 3: Previous Anticancer Therapy

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Lines of therapy (excluding adjuvant and neoadjuvant)		
0	40 (60.6)	47 (70.1)
1	14 (21.2)	12 (17.9)
2	8 (12.1)	7 (10.4)
3	2 (3)	1 (1.5)
4	2 (3)	0
Type of previous anticancer therapy		
Neoadjuvant	3 (4.5)	10 (14.9)
Adjuvant	17 (25.8)	10 (14.9)
Previous surgery		
Yes	55 (83)	57 (85.1)
No	11 (16.7)	10 (14.9)
Previous radiotherapy		
Yes	31 (47)	32 (47.8)
No	35 (53)	35 (52.2)

Table 4: Prior Chemotherapy in ≥3% of Patients in Either Arm

Therapy	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Gemcitabine	29 (43.9)	30 (44.8)
Docetaxel	28 (42.4)	30 (44.8)
Paclitaxel	3 (4.5)	2 (3)
Bevacizumab	2 (3)	3 (4.5)
Investigational drug	4 (6.1)	1 (1.5)
Ifosfamide	3 (4.5)	1 (1.5)
Trabectedin	3 (4.5)	2 (3)
Letrozole	3 (4.5)	1 (1.5)
Palbociclib	2 (3)	2 (3)
Fluorouracil	0	2 (3)

- Patient disposition and post-trial therapy are summarized in Tables 5 and 6

Table 5: Summary of Patient Disposition by Treatment Discontinuation

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Progressive disease, radiographic	42 (63.6)	27 (40.3)
Adverse event	5 (7.6)	11 (16.4)
Completed treatment ^a	0	11 (16.4)
Withdrawal of consent	5 (7.6)	6 (9)
Progressive disease, symptomatic	3 (4.5)	7 (10.4)
Physician decision	6 (9.1)	0
Randomized but not treated	2 (3)	2 (3)
Death	2 (3)	1 (1.5)
Other ^b	1 (1.5)	2 (3)

^a Completed 8 cycles of doxorubicin

^b Other reasons for discontinuation: Olaratumab + doxorubicin=gradual increase in lesions that did not meet RECIST criteria; Doxorubicin=patient crossed over to study drug, non-compliance, each n=1

Table 6: Post-study Therapy in ≥ 3% of Patients in Either Arm

Therapy	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Any systemic therapy	44 (66.7)	46 (68.7)
1 regimen	18 (27.3)	20 (29.9)
2 regimens	12 (18.2)	14 (20.9)
3 regimens	9 (13.6)	6 (9)
4 regimens	1 (1.5)	2 (3)
>4 regimens	4 (6.1)	4 (6)
Olaratumab	0	30 (44.8)
Gemcitabine	15 (22.7)	11 (16.4)
Pazopanib	15 (22.7)	10 (14.9)
Docetaxel	14 (21.2)	8 (11.9)
Dacarbazine	12 (18.2)	8 (11.9)
Trabectedin	11 (16.7)	3 (4.5)
Ifosfamide	8 (12.1)	8 (11.9)
Investigational drug	8 (12.1)	2 (3)
Doxorubicin	1 (1.5)	5 (7.5)
Eribulin	3 (4.5)	2 (3)
Everolimus	2 (3)	2 (3)
Vinorelbine	2 (3)	2 (3)
Alisertib	1 (1.5)	2 (3)
Etoposide	1 (1.5)	2 (3)
Paclitaxel	2 (3)	1 (1.5)
Sorafenib	2 (3)	0
Sunitinib	2 (3)	0

- Efficacy results are summarized in Tables 7 - 11 and Figures 1 and 2

Table 7: PFS Analyses per Investigator Assessment

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Number of events, n (%)	55 (83)	48 (72)
Progressive disease, n (%)	54(82)	43 (64)
Death, n (%)	1 (2)	5 (7)
Median PFS (months), 95% CI	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
Cox stratified HR (95% CI)	0.67 (0.44, 1.02)	
P value, stratified log-rank test	0.06	

Figure 1: Kaplan-Meier Curves for PFS per Investigator Assessment

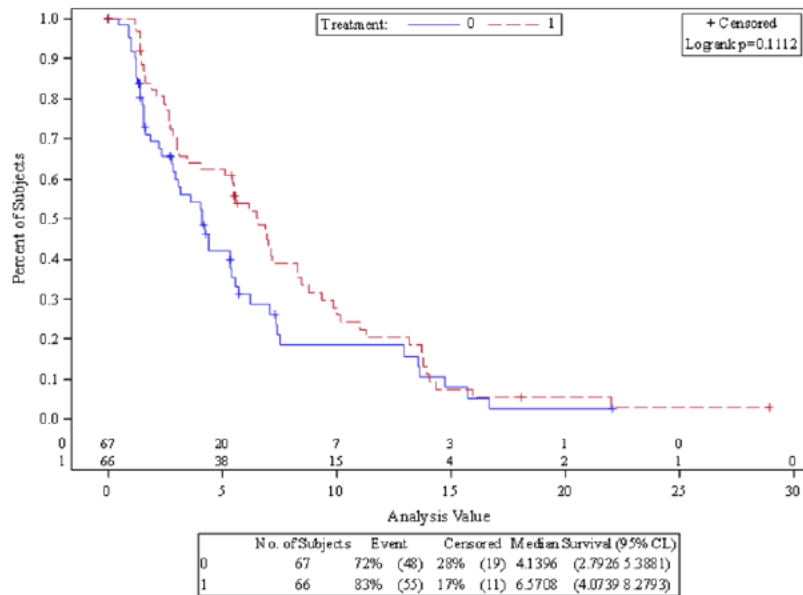


Table 8: PFS Analyses by Blinded Independent Central Review

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Number of events, n (%)	37 (56)	34 (51)
Progressive disease, n (%)	36(55)	32 (48)
Death, n (%)	1 (2)	2 (3)
Median PFS (months), 95% CI	8.2 (5.5, 9.8)	4.4 (3.1, 7.4)
Cox stratified HR (95% CI)	0.67 (0.40, 1.12)	
P value, stratified log-rank test	0.12	

Table 9: OS Analyses

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Number of deaths, n (%)	39 (59)	52 (78)
Median OS in months, (95% CI)	26.5 (20.9, 31.7)	14.7 (9.2, 17.1)
Cox stratified HR (95% CI)	0.46 (0.30, 0.71)	
P value, stratified log-rank test	0.0003	

Figure 2: Kaplan-Meier curves for overall survival

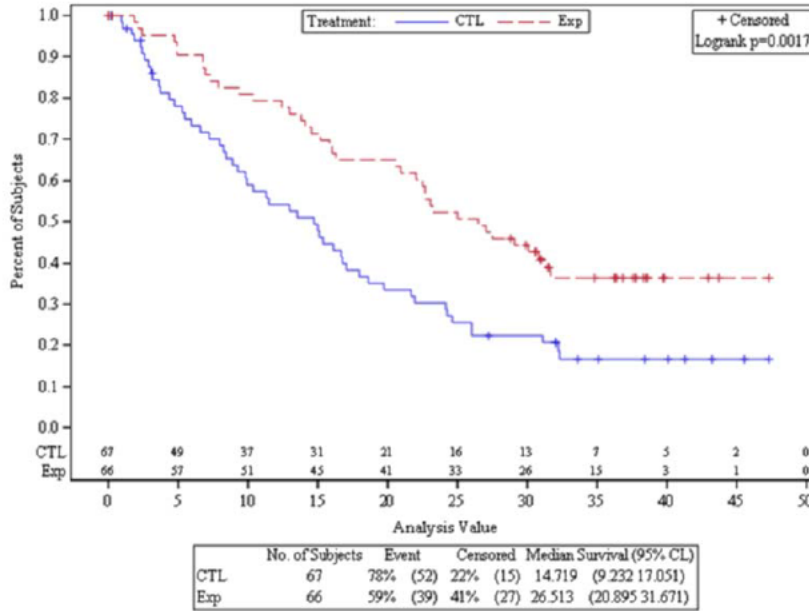


Table 10: OS sensitivity analyses

	Olaratumab + Doxorubicin N=66 HR (95%)	Doxorubicin N=67 HR (95%)
Post PD (BICR) OS ^{a,b,c}	0.46 (0.26, 0.81)	
Post PD (INV) OS ^{a,b,c}	0.55 (0.34, 0.89)	
Censored at initiation of any subsequent anti-cancer therapy ^a	0.49 (0.23, 1.04)	
Censored at initiation of subsequent specific anti-cancer therapy ^{a,d}	0.43 (0.24, 0.76)	
Analyses excluding patients who completed:		
<= 7 cycles of doxorubicin therapy ^{a,c}	0.38 (0.17, 0.86)	
<= 6 cycles of doxorubicin therapy ^{a,c}	0.42 (0.19, 0.91)	
<= 5 cycles of doxorubicin therapy ^{a,c}	0.41 (0.21, 0.81)	
<= 4 cycles of doxorubicin therapy ^{a,c}	0.42 (0.22, 0.80)	

Abbreviations PD=progressive disease; BICR=blinded independent central review; INV=investigator
^a Stratified by prior systemic therapy per CRF and histology per independent review of pathology forms
^b From the date of documented PD to the date of death from any cause
^c Based on a subgroup of patients
^d Limited to pazopanib, eribulin, gemcitabine + docetaxel, doxorubicin, and trabectedin

Table 11: ORR results

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Investigator		
Overall Response	12 (18)	8 (12)
CR	2 (3)	1 (2)
PR	10 (15)	7 (10)
95% CI	(9.8, 29.6)	(5.3, 22.2)
Blinded central review		
Overall Response	12 (18)	5 (8)
CR	3 (5)	1 (2)
PR	9 (14)	4 (6)
95% CI	(9.8, 29.6)	(2.5, 16.6)

Safety

- Median duration of treatment:
 - Olaratumab plus doxorubicin arm: olaratumab = 26.1 weeks; doxorubicin = 21.3 weeks
 - Doxorubicin arm: doxorubicin=12.3 weeks
- The most significant toxicities related to olaratumab were:
 - Infusion-related reactions
 - Neutropenia
 - Musculoskeletal pain
- Adverse events (AEs) leading to treatment discontinuation occurred in 12.5% of patients in the olaratumab plus doxorubicin arm and 16.9% in the single-agent doxorubicin arm.
 - The most common treatment emergent adverse events (TEAEs) leading to dose modifications of olaratumab were neutropenia (31 [48.4%]) and thrombocytopenia (8 [12.5%]). There were more patients with AEs leading to modification of doxorubicin in the olaratumab plus doxorubicin arm (23 [35.9%]) than in the single-agent doxorubicin arm (17 [26.2%]).
 - The most common AEs leading to modification of doxorubicin were neutropenia (13 [20.3%] versus 6 [9.2%] in the olaratumab plus doxorubicin arm versus the single-agent doxorubicin arm) and febrile neutropenia (3 [4.7%] versus 4 [6.2%]). The most common AE that led to dose reductions or dose delays in either arm was neutropenia.
- The proportion of deaths that occurred within 30 days of the last dose of treatment was higher in the single-agent doxorubicin arm (9.2%) versus (4.7%) in the olaratumab plus

doxorubicin arm. Death due to an AE was the primary cause of death in the single-arm doxorubicin arm in four (6.2%) patients. All deaths in the olaratumab plus doxorubicin arm were due to progressive disease; no deaths occurred due to an AE.

- The rate of non-fatal serious adverse events (SAEs) was comparable between arms. SAEs occurred in 27 (42.2%) patients in the olaratumab plus doxorubicin arm compared to 25 (38.5%) patients in the single-agent doxorubicin arm. The rate of Grade 3 SAEs was higher in the olaratumab plus doxorubicin arm (31.3% versus 21.5%). The most commonly occurring SAEs in the olaratumab plus doxorubicin arm were febrile neutropenia (12.5%), musculoskeletal pain (4.7%), and neutropenia (4.7%).
- In the olaratumab plus doxorubicin arm, the most common TEAEs were nausea (73.4%), fatigue (68.8%), musculoskeletal pain (64.1%), neutropenia (57.8%), and mucositis (53.1%). The most frequently reported TEAEs observed in at least a 20% point difference in the olaratumab + doxorubicin arm than in the single-agent doxorubicin arm, respectively, were musculoskeletal pain (64.1% vs. 24.6%), nausea (73.4% vs. 52.3%), neutropenia (57.8% vs. 35.4%), and vomiting (45.3% vs. 18.5%). TEAEs in $\geq 20\%$ of the patients are summarized in Table 12.

Table 13: TEAEs in ≥ 20% of Patients

Preferred Term Consolidated TEAE Category	Olaratumab + Doxorubicin N=64 n(%)		Single-agent Doxorubicin N=65 n(%)		Single-agent Olaratumab after Single-agent Doxorubicin Treatment N=30 n(%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Patients with any AE	63 (98.4)	51 (79.7)	64 (98.5)	45 (69.2)	26 (80.0)	8 (17.8)
Nausea	47 (73.4)	1 (1.6)	34 (52.3)	2 (3.1)	6 (20.0)	1 (3.3)
Fatigue ¹	44 (68.8)	6 (9.4)	45 (69.2)	2 (3.1)	6 (20.0)	2 (6.7)
Musculoskeletal Pain ²	41 (64.1)	5 (7.8)	16 (24.6)	1 (1.5)	7 (23.3)	2 (6.7)
Neutropenia ^{3,4}	37 (57.8)	34 (53.2)	23 (35.4)	22 (32.3)	0	0
Mucositis ⁵	34 (53.1)	2 (3.1)	23 (35.4)	3 (4.6)	2 (6.7)	0
Alopecia	33 (51.6)	0	26 (40.0)	0	2 (6.7)	0
Vomiting	29 (45.3)	0	12 (18.5)	0	5 (16.7)	0
Infections and Infestations ⁶	27 (42.2)	5 (7.8)	27 (41.5)	7 (10.8)	7 (23.3)	0
Anemia ^{4,7}	26 (40.6)	8 (12.5)	24 (36.9)	6 (9.2)	5 (16.7)	1 (3.3)
Leukopenia ⁸	26 (40.6)	0	12 (18.5)	0	1 (3.3)	0
Constipation	22 (34.4)	0	21 (32.3)	1 (1.5)	3 (10.0)	0
Diarrhea	22 (34.4)	2 (3.1)	15 (23.1)	0	5 (16.7)	0
Decreased Appetite	20 (31.3)	1 (1.6)	13 (20.0)	0	3 (10.0)	2 (6.7)
Abdominal Pain ⁹	15 (23.4)	2 (3.1)	9 (13.8)	0	3 (10.0)	0
Pyrexia	15 (23.4)	0	12 (18.5)	0	3 (10.0)	0
Thrombocytopenia ^{4,10}	16 (25.0)	7 (10.9)	14 (21.5)	5 (7.7)	0	0
Neuropathy ¹¹	14 (21.9)	0	7 (10.8)	0	3 (10.0)	0
Headache	13 (20.3)	0	6 (9.2)	0	1 (3.3)	0
Cough	14 (21.9)	0	12 (18.5)	0	3 (10.0)	0
AESIs						
Infusion-related Reactions ¹²	8 (12.5)	2 (3.1)	0	0	3 (10.0)	1 (3.3)
Cardiac Arrhythmias ¹³	10 (15.6)	0	10 (15.4)	1 (1.5)	4 (13.3)	0
Cardiac Dysfunction ¹⁴	15 (23.4)	1 (1.6)	12 (16.9)	0	4 (13.3)	0

Abbreviations: TEAE = treatment-emergent adverse events; AESI = adverse event of special interest; N = number of treated patients; n = number of patients with given event.

¹Preferred terms patients experienced were fatigue and asthenia.

²Preferred terms patients experienced were arthralgia, back pain, bone pain, flank pain, groin pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.

³Preferred terms patients experienced were neutropenia and neutrophil count decreased.

⁴As reported by the Investigator. These do not represent actual laboratory values.

⁵Preferred terms patients experienced were mucosal inflammation, oropharyngeal pain, and stomatitis.

⁶Includes all preferred terms within the MedDRA™ system organ class of Infections and Infestations.

⁷Preferred terms patients experienced were anemia and hemoglobin decreased.

⁸Preferred terms patients experienced were leukopenia and white blood cell count decreased.

⁹Preferred terms patients experienced were abdominal pain upper, abdominal pain, and abdominal pain lower.

¹⁰Preferred terms patients experienced were thrombocytopenia and platelet count decreased.

¹¹Preferred terms patients experienced were neuropathy peripheral, paresthesia, peripheral sensory neuropathy, and hypoesthesia.

¹²Preferred terms patients experienced were face edema, hypersensitivity, infusion related reaction

¹³Preferred terms patients experienced were tachycardia, bradycardia, bundle branch block left, electrocardiogram QT prolonged, heart rate increased, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, supraventricular extrasystoles, atrial fibrillation, syncope.

¹⁴Preferred terms patients experienced edema peripheral, ejection fraction decreased, cardiac failure congestive, hepatojugular reflux, jugular vein distention, left ventricular.

- Grade ≥3 TEAEs were reported in 79.7% of patients in the olaratumab plus doxorubicin arm and 69.2% of patients in the single-agent doxorubicin arm. The most common Grade ≥3 TEAEs occurring in patients in the olaratumab plus doxorubicin arm included neutropenia, anemia, febrile neutropenia, and thrombocytopenia. The most common Grade 4 event on both study arms was neutropenia 22 (34.4%) vs. 16 (24.6%).

- Infusion-related reactions (IRRs) occurred in 14.9% (14 of 94) of patients in Trial JGDG. IRRs occurred in Cycles 1 and 2, were mainly Grade 1 or 2 (10 of 14 [71.4%]). All Grade ≥ 3 IRRs occurred with the first infusion of olaratumab. Patients with a Grade ≥ 3 were permanently discontinued from therapy. Premedication was not required but was administered in the majority of cases. Of the 14 patients who experienced an IRR, eight (57.1%) had received premedication with an anti-histamine, corticosteroid, or both. A total of 10 (62.5%) patients with a Grade 1 or 2 IRR underwent subsequent administration of olaratumab. Three patients experienced an IRR; all were Grade 1 or 2. Across the eight supportive studies, the incidence and timing of events was comparable to Trial JGDG.
 - Grade 5 infusion-related reaction (IRR): One patient who received olaratumab monotherapy after discontinuation of doxorubicin experienced a fatal IRR. This event occurred in 75 year-old man who had several baseline cardiac comorbidities (ischemic cardiomyopathy, myocardial infarction, ventricular tachycardia, stent placement, heart valve replacement, as well as an implantable defibrillator) who discontinued doxorubicin after two doses due to a decrease in ejection fraction (43%). Ten minutes into the first infusion of olaratumab on Cycle 1 Day 1, the patient developed loss of consciousness and was found to be unresponsive and pulseless; ECG showed ventricular fibrillation and CPR was unsuccessful. The reported event of cardiac arrest was deemed by the Investigator and the Applicant to be possibly related to olaratumab. The Applicant determined this to be an IRR given the temporal administration of olaratumab.
- The incidence of neutropenia as assessed by laboratory testing was comparable between arms for all grades (64.1% in the olaratumab plus doxorubicin arm versus 60.3% in the single-agent doxorubicin arm). The incidence of Grade 4 neutropenia was higher in the olaratumab plus doxorubicin arm (31.3%) versus the single-agent doxorubicin arm (19.0%). This higher incidence of Grade 4 neutropenia did not translate into increased rates of febrile neutropenia, infections, discontinuations, or deaths.
- Musculoskeletal pain occurred more frequently in patients in the olaratumab plus doxorubicin arm (64.1% versus 24.6% of patients in the doxorubicin arm). Grade 3 to 4 musculoskeletal pain occurred in five patients (7.8%) in the olaratumab plus doxorubicin arm versus one (1.5%) patient in the doxorubicin arm. For the five patients that experienced a Grade 3 event, four patients had preexisting pain that worsened and one patient had an infection at the site of pain. There was one Grade 3 musculoskeletal event that led to discontinuation in the olaratumab plus doxorubicin arm. The majority of events were low grade, and mitigated with supportive care and analgesics. Across the eight supportive studies, the incidence of musculoskeletal pain varied from 6.3% to 71.9%. Overall, in the olaratumab-containing arms and olaratumab monotherapy trial, the incidence of musculoskeletal pain was higher (49.5% versus 43.4% in the control arms).

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/s/

LEAH S HER
10/18/2016

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 16, 2016
TIME: 9:00 - 9:30 AM (EST)
LOCATION: Teleconference
APPLICATION: BLA 761038
DRUG NAME: olaratumab

TYPE OF MEETING: Teleconference with Special Government Employee (SGE), Ms. Rebecca Ward (patient consultant), cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:

Patricia Keegan –Division Director, DOP2
Marc Theoret – Clinical Team Lead, DOP2
Meredith Chuk – Clinical Reviewer, DOP2
Leslie Doros – Clinical Reviewer, DOP2
Leah Her – Regulatory Health Project Manager, DOP2

EXTERNAL CONSTITUENT ATTENDEES:

Ms. Rebecca Ward

BACKGROUND: Ms. Rebecca Ward agreed to serve and was cleared as an SGE for this original BLA. Prior to this teleconference, background materials and draft product labeling were provided along with two specific questions from the Division for Ms. Ward to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

FDA Questions for Discussion During Teleconference:

1. As a treating physician or patient, would you be comfortable prescribing or receiving olaratumab in combination with doxorubicin for the first-line treatment of advanced soft tissue sarcoma based on the results of Trial JGDG?

Discussion During Teleconference: Ms. Ward stated that as a cancer patient and someone who has had a family member with soft tissue sarcoma, she would be comfortable in receiving or recommending olaratumab based on the information provided in the briefing package. Ms. Ward further stated that although the number of months of survival benefit over existing therapy may not seem large; as a cancer patient, the additional survival

duration would be important in her decision making to take olaratumab. Ms. Ward also observed that the toxicity profile isn't vastly different from doxorubicin alone or from other drugs that she's previously taken. Taken together, Ms. Ward stated that although data in this application is based on a limited number of patients that have many different types of sarcoma, she would be comfortable in having olaratumab labeled for all sarcomas.

2. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of olaratumab treatment?

Discussion During Teleconference: Ms. Ward stated that the label is concise, clear and easy to follow. Ms. Ward identified several typographical errors in the label. Ms. Ward also questioned the product storage information located in Section 2.4 relative to Section 16. FDA clarified FDA's intention to reduce redundant information throughout the label. FDA explained that Section 2.4 is intended for individuals preparing the product whereas Section 16 is intended for groups transporting or storing the product. Ms. Ward commented on differences between Section 12.3 and Section 14 with regards to description of patient demographics. FDA clarified that Section 12.3 contains information about patients across trials in the olaratumab development program whereas Section 14 contains information about the patients participating in the primary trial being described.

FDA inquired whether Ms. Ward had any additional comments or questions. Ms. Ward inquired about the timing of this application's decision. FDA stated that an action is targeted for late October 2016.

ATTACHMENTS: Background information provided to Ms. Ward via email (rgwardrn@gmail.com) on September 2, 2016, which included:

- Briefing Document for FDA Teleconference to Discuss BLA 761038
- Draft Labeling of July 22, 2016



Ms. Rebecca Ward
Sent via Email Communication

Dear Ms. Ward:

We refer to the teleconference held/correspondence on June 10, 2016, between yourself and Dr. Leslie Doros and Ms. Leah Her of the Division of Oncology Products 2 (DOP2), regarding the possibility of your assistance in the review of a pending Biologics License Application (BLA) 761038, submitted by Eli Lilly and Company (Lilly). Please note that information concerning this application is **confidential**.

In this application, Lilly seeks approval of olaratumab (proposed as Lartruvo), in combination with doxorubicin, for the treatment of advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery.

We have received notification from the CDER Division of Advisory Committee and Consultant Management (DACCM) that you are cleared to serve as a Special Government Employee (SGE) for the review of this pending BLA.

Please review the attached written materials. We will discuss the enclosed information during a teleconference scheduled for **Friday, September 16, 2016 / 9:00 to 9:30 AM (EST)**. We will provide toll-free call in information in advance of this teleconference.

Enclosed is a summary of the single randomized trial submitted with this application, Study 15B-IE-JGDG, and the proposed olaratumab product labeling for your review. The questions we would like to discuss during this teleconference are listed below; please let us know if you would like any additional information in order to aid in the discussion.

FDA Questions for Discussion During the Teleconference:

1. As a treating physician or patient, would you be comfortable prescribing or receiving olaratumab in combination with doxorubicin for the first-line treatment of advanced soft tissue sarcoma based on the results of Trial JGDG?
2. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of olaratumab treatment?

Thank you for your time and insights.

If you have questions, please contact me at 240-402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S., P.M.P.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:

1. BLA 761038 Summary Information
2. Draft olaratumab product labeling

**Briefing Document for FDA Teleconference to Discuss BLA 761038 – olaratumab injection,
for intravenous use
Eli Lilly and Company**

Protocol 15B IE-JGDG

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

Cancer Type

Patients with histologically or cytologically confirmed soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery

Study Design

- Trial JGDG is a two-stage, open-label, multicenter trial evaluating the anti-tumor activity of olaratumab, when administered in combination with doxorubicin, compared with single-agent doxorubicin for the treatment of patients with advanced soft tissue sarcoma (STS) whose disease is not amenable to treatment with surgery or radiation, and who had not received prior anthracycline therapy
- The first stage of the trial was a single-arm assessment of the tolerability of olaratumab, given in combination with doxorubicin in patients with advanced STS. The second stage of this trial was an open-label, randomized, two-arm, active-controlled study.
- Patients were stratified according to:
 - PDGFR α expression (positive vs. negative)
 - Number of prior therapies (0 vs. 1 or more)
 - Histologic tumor type (Leiomyosarcoma vs. synovial sarcoma vs. other)
 - ECOG PS (0-1 vs. 2)
- The primary endpoint of the phase 2 portion was progression free survival (PFS) as determined by the investigator by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were overall survival (OS) and confirmed overall response rate (ORR).
- Statistical considerations: For the phase 2 portion, assuming a hazard ratio of 0.67 with a median PFS of 2 months in the control arm and 3 months in the experimental arm, a total of 130 patients with 110 events for the final analysis were needed to provide 80% power at a 2-sided alpha level of 20%. An interim analysis of PFS was planned after 80 PFS events. Two-sided nominal alpha of 0.0001 and 0.1999 were allocated to the interim and final analysis for PFS. No pre-specified statistical criteria, power analysis, or statistical procedure to adjust for multiplicity was planned for the key secondary endpoints of OS and ORR.

Patient Population

- Key eligibility criteria:
 - Age $\geq$ 18 years
 - Histologically confirmed, malignant soft tissue sarcoma (excluding Kaposi's sarcoma) with measurable disease according to RECIST, version 1.1
 - Advanced STS, not amenable to treatment with surgery or radiotherapy; no limit on number of prior therapies
 - Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2
 - No prior treatment with doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenediones or therapy with any agent that targets PDGF or PDGFR
 - Left ventricular ejection fraction (LVEF) $\geq$ 50% at baseline

Treatment Regimen

- Patients were randomized (1:1) to one of two arms:
 - olaratumab + doxorubicin: doxorubicin 75 mg/m² followed by olaratumab 15 mg/kg on day 1 and 8 of each 21-day cycle
 - doxorubicin: doxorubicin 75 mg/m² on day 1 of each 21-day cycle
- Treatment continued for up to eight cycles or until disease progression or unacceptable treatment-related toxicity. During Cycles 5 through 8, dexrazoxane could be administered prior to doxorubicin at the discretion of the treating physician. In the absence of disease progression or other withdrawal criteria, patients in experimental arm who completed 8 cycles of doxorubicin could continue to receive olaratumab as a single agent at the same dose and schedule until progression. Patients on the control arm were also eligible to receive single-agent olaratumab upon disease progression or inability to receive further doxorubicin due to toxicity. Disease assessments were conducted every 6 weeks.

Efficacy

- Trial JGDG was conducted at 16 centers in the U.S. Demographic and baseline disease characteristics and information regarding prior therapy are summarized in Tables 1-4.

Table 1: Demographics and Baseline Disease Characteristics

Variable	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Age		
Mean (SD)	56.8 (12.5)	58.3 (12.5)
Median (min-max)	58.5 (22-85)	58.0 (29-86)
18 - <65	48 (73)	43 (64)
$\geq$ 65	18 (27)	24 (35)
Sex		
Male	26 (39)	33 (49)
Female	40 (61)	34 (51)

Race		
White	55 (83)	60 (90)
Black	6 (9)	5 (7)
Asian	2 (3)	2 (3)
Other	3 (5)	0
ECOG performance status ^a		
0-1	62 (94)	63 (94)
2	4 (6)	4 (6)
Tumor PDGFR α status ^a		
Positive	58 (88)	59 (88)
Negative	8 (12)	8 (12)
Tumor histology ^a		
Leiomyosarcoma	25 (38)	26 (39)
Synovial sarcoma	1 (1)	2 (3)
Other	40 (61)	39 (58)
Prior systemic therapy ^{a,b}		
0	27 (41)	31 (46)
1 or more	39 (59)	36 (54)
Tumor grade		
Grade 1	7 (11)	8 (12)
Grade 2	5 (8)	7 (10)
Grade 3	29 (44)	29 (43)
Grade cannot be assessed or unknown	25 (38)	23 (34)
Duration of disease (months)		
Mean (SD)	31.9 (41.4)	34.7 (53.1)
Median (range)	15 (0.5-223.5)	14.9 (0.3-258.6)
Metastatic disease	66 (100)	67 (100)
Sites of metastatic disease		
Lung	42 (64)	42 (63)
Soft tissue	22 (33)	33 (49)
Liver	26 (39)	22 (33)
Peritoneal	15 (23)	23 (34)
Lymph nodes	16 (24)	21 (31)
Bone	10 (15)	18 (27)
Other	8 (12)	16 (24)
Pleural	10 (15)	9 (13)
Skin	3 (5)	0

^a Randomization factors based on IVRS

^b Includes adjuvant and neoadjuvant therapy

Table 2: Detailed Histology by Independent Review of Pathology Forms

Histology	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
“Other”		
Liposarcoma	8 (12.1)	14 (20.9)
Dedifferentiated	4	6
Myxoid	2	3
Well-differentiated	1	3
Pleomorphic	1	1
Liposarcoma NOS	0	1
Undifferentiated pleomorphic sarcoma	7 (10.6)	8 (11.9)
Angiosarcoma	4 (6.1)	3 (4.5)
Undifferentiated sarcoma NOS	2 (3)	4 (6)
Extraskeletal myxoid chondrosarcoma	2 (3)	2 (3)
Malignant peripheral nerve sheath tumor	3 (4.5)	0
Myxofibrosarcoma	2 (3)	1 (1.5)
Malignant solitary fibrous tumor	2 (3)	1 (1.5)
Endometrial stromal sarcoma	2 (3)	1 (1.5)
Chondrosarcoma	0	2 (3)
Epithelioid sarcoma	2 (3)	0
Fibrosarcoma	1 (1.5)	1 (1.5)
Low-grade fibromyxoid sarcoma	1 (1.5)	1 (1.5)
Alveolar soft part sarcoma	1 (1.5)	0
Chondroblastic osteosarcoma	0	1 (1.5)
Clear cell sarcoma of soft tissue	1 (1.5)	0
Extra-renal rhabdoid tumor	0	1 (1.5)
Extraskeletal osteosarcoma	0	1 (1.5)
Undifferentiated round cell sarcoma	1 (1.5)	0
Leiomyosarcoma	25 (37.9)	25 (37.3)
Synovial sarcoma	1 (1.5)	1 (1.5)

Table 3: Previous Anticancer Therapy

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Lines of therapy (excluding adjuvant and neoadjuvant)		
0	40 (60.6)	47 (70.1)
1	14 (21.2)	12 (17.9)
2	8 (12.1)	7 (10.4)
3	2 (3)	1 (1.5)
4	2 (3)	0
Type of previous anticancer therapy		
Neoadjuvant	3 (4.5)	10 (14.9)
Adjuvant	17 (25.8)	10 (14.9)
Previous surgery		
Yes	55 (83)	57 (85.1)
No	11 (16.7)	10 (14.9)
Previous radiotherapy		
Yes	31 (47)	32 (47.8)
No	35 (53)	35 (52.2)

Table 4: Prior Chemotherapy in ≥3% of Patients in Either Arm

Therapy	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Gemcitabine	29 (43.9)	30 (44.8)
Docetaxel	28 (42.4)	30 (44.8)
Paclitaxel	3 (4.5)	2 (3)
Bevacizumab	2 (3)	3 (4.5)
Investigational drug	4 (6.1)	1 (1.5)
Ifosfamide	3 (4.5)	1 (1.5)
Trabectedin	3 (4.5)	2 (3)
Letrozole	3 (4.5)	1 (1.5)
Palbociclib	2 (3)	2 (3)
Fluorouracil	0	2 (3)

- Patient disposition and post-trial therapy are summarized in Tables 5 and 6

Table 5: Summary of Patient Disposition by Treatment Discontinuation

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Progressive disease, radiographic	42 (63.6)	27 (40.3)
Adverse event	5 (7.6)	11 (16.4)
Completed treatment ^a	0	11 (16.4)
Withdrawal of consent	5 (7.6)	6 (9)
Progressive disease, symptomatic	3 (4.5)	7 (10.4)
Physician decision	6 (9.1)	0
Randomized but not treated	2 (3)	2 (3)
Death	2 (3)	1 (1.5)
Other ^b	1 (1.5)	2 (3)

^a Completed 8 cycles of doxorubicin

^b Other reasons for discontinuation: Olaratumab + doxorubicin=gradual increase in lesions that did not meet RECIST criteria; Doxorubicin=patient crossed over to study drug, non-compliance, each n=1

Table 6: Post-study Therapy in ≥ 3% of Patients in Either Arm

Therapy	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Any systemic therapy	44 (66.7)	46 (68.7)
1 regimen	18 (27.3)	20 (29.9)
2 regimens	12 (18.2)	14 (20.9)
3 regimens	9 (13.6)	6 (9)
4 regimens	1 (1.5)	2 (3)
>4 regimens	4 (6.1)	4 (6)
Olaratumab	0	30 (44.8)
Gemcitabine	15 (22.7)	11 (16.4)
Pazopanib	15 (22.7)	10 (14.9)
Docetaxel	14 (21.2)	8 (11.9)
Dacarbazine	12 (18.2)	8 (11.9)
Trabectedin	11 (16.7)	3 (4.5)
Ifosfamide	8 (12.1)	8 (11.9)
Investigational drug	8 (12.1)	2 (3)
Doxorubicin	1 (1.5)	5 (7.5)
Eribulin	3 (4.5)	2 (3)
Everolimus	2 (3)	2 (3)
Vinorelbine	2 (3)	2 (3)
Alisertib	1 (1.5)	2 (3)
Etoposide	1 (1.5)	2 (3)
Paclitaxel	2 (3)	1 (1.5)
Sorafenib	2 (3)	0
Sunitinib	2 (3)	0

- Efficacy results are summarized in Tables 7 - 11 and Figures 1 and 2

Table 7: PFS Analyses per Investigator Assessment

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Number of events, n (%)	55 (83)	48 (72)
Progressive disease, n (%)	54(82)	43 (64)
Death, n (%)	1 (2)	5 (7)
Median PFS (months), 95% CI	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
Cox stratified HR (95% CI)	0.67 (0.44, 1.02)	
P value, stratified log-rank test	0.06	

Figure 1: Kaplan-Meier Curves for PFS per Investigator Assessment

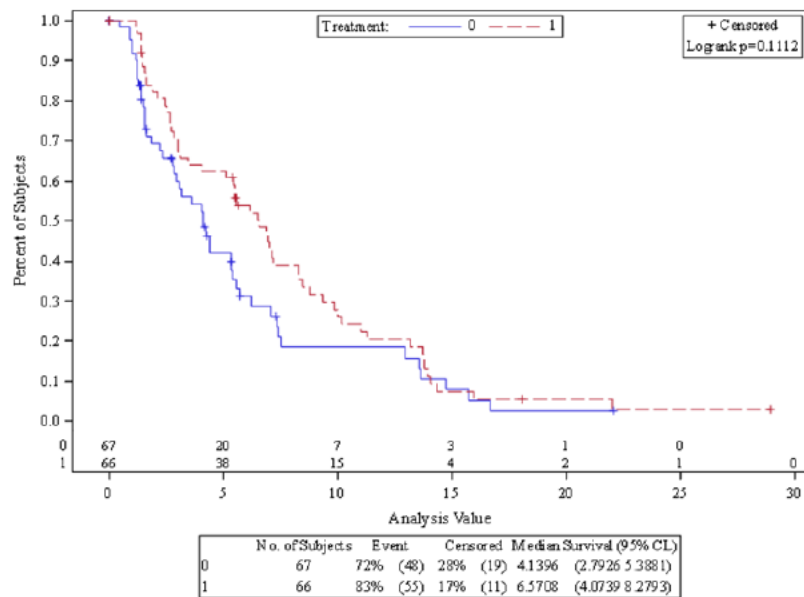
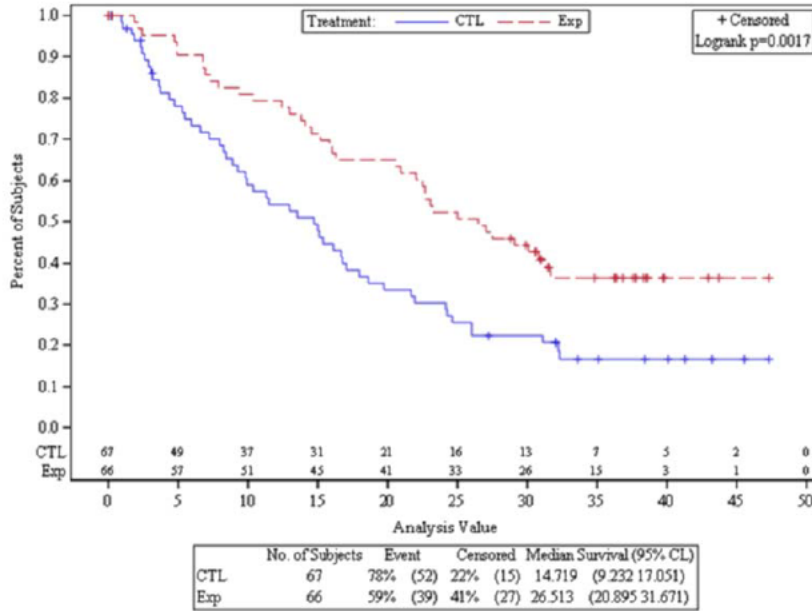


Table 8: PFS Analyses by Blinded Independent Central Review

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Number of events, n (%)	37 (56)	34 (51)
Progressive disease, n (%)	36(55)	32 (48)
Death, n (%)	1 (2)	2 (3)
Median PFS (months), 95% CI	8.2 (5.5, 9.8)	4.4 (3.1, 7.4)
Cox stratified HR (95% CI)	0.67 (0.40, 1.12)	
P value, stratified log-rank test	0.12	

Table 9: OS Analyses

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Number of deaths, n (%)	39 (59)	52 (78)
Median OS in months, (95% CI)	26.5 (20.9, 31.7)	14.7 (9.2, 17.1)
Cox stratified HR (95% CI)	0.46 (0.30, 0.71)	
P value, stratified log-rank test	0.0003	

Figure 2: Kaplan-Meier curves for overall survival**Table 10: OS sensitivity analyses**

	Olaratumab + Doxorubicin N=66 HR (95%)	Doxorubicin N=67 HR (95%)
Post PD (BICR) OS ^{a,d}	0.46 (0.26, 0.81)	
Post PD (INV) OS ^{a,d}	0.55 (0.34, 0.89)	
Censored at any subsequent anti-cancer therapy ^a	0.49 (0.23, 1.04)	
Censored at subsequent specific anti-cancer therapy ^{a,b}	0.43 (0.24, 0.76)	
Exclude ≤ 8 cycles of doxorubicin therapy ^{a,b,c,d}	0.52 (0.32, 0.81)	
Exclude ≤ 6 cycles of doxorubicin therapy ^{a,d}	0.53 (0.34, 0.83)	
Exclude ≤ 5 cycles of doxorubicin therapy ^{a,d}	0.51 (0.33, 0.80)	
Exclude ≤ 4 cycles of doxorubicin therapy ^{a,d}	0.52 (0.34, 0.81)	

Abbreviations PD=progressive disease; BICR=blinded independent central review, INV=investigator

^a Stratified by prior systemic therapy per CRF and histology per independent review of pathology forms

^b Limited to pazopanib, eribulin, gemcitabine + docetaxel, doxorubicin, and trabectedin

^c Both ≤ 7 and ≤ 8 cycles of doxorubicin therapy had the same population

^d Based on a subgroup of patients

Table 11: ORR results

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Investigator		
Overall Response	12 (18)	8 (12)
CR	2 (3)	1 (2)
PR	10 (15)	7 (10)
95% CI	(9.8, 29.6)	(5.3, 22.2)
Blinded central review		
Overall Response	12 (18)	5 (8)
CR	3 (5)	1 (2)
PR	9 (14)	4 (6)
95% CI	(9.8, 29.6)	(2.5, 16.6)

Safety

- Median duration of treatment:
 - Olaratumab plus doxorubicin arm: olaratumab = 26.1 weeks; doxorubicin = 21.3 weeks
 - Doxorubicin arm: doxorubicin=12.3 weeks
- The most significant toxicities related to olaratumab were:
 - Infusion-related reactions
 - Neutropenia
 - Musculoskeletal pain
- Adverse events (AEs) leading to treatment discontinuation occurred in 12.5% of patients in the olaratumab plus doxorubicin arm and 16.9% in the single-agent doxorubicin arm.
 - The most common treatment emergent adverse events (TEAEs) leading to dose modifications of olaratumab were neutropenia (31 [48.4%]) and thrombocytopenia (8 [12.5%]). There were more patients with AEs leading to modification of doxorubicin in the olaratumab plus doxorubicin arm (23 [35.9%]) than in the single-agent doxorubicin arm (17 [26.2%]).
 - The most common AEs leading to modification of doxorubicin were neutropenia (13 [20.3%] versus 6 [9.2%] in the olaratumab plus doxorubicin arm versus the single-agent doxorubicin arm) and febrile neutropenia (3 [4.7%] versus 4 [6.2%]). The most common AE that led to dose reductions or dose delays in either arm was neutropenia.
- The proportion of deaths that occurred within 30 days of the last dose of treatment was higher in the single-agent doxorubicin arm (9.2%) versus (4.7%) in the olaratumab plus doxorubicin arm. Death due to an AE was the primary cause of death in the single-arm

doxorubicin arm in four (6.2%) patients. All deaths in the olaratumab plus doxorubicin arm were due to progressive disease; no deaths occurred due to an AE.

- The rate of non-fatal serious adverse events (SAEs) was comparable between arms. SAEs occurred in 27 (42.2%) patients in the olaratumab plus doxorubicin arm compared to 25 (38.5%) patients in the single-agent doxorubicin arm. The rate of Grade 3 SAEs was higher in the olaratumab plus doxorubicin arm (31.3% versus 21.5%). The most commonly occurring SAEs in the olaratumab plus doxorubicin arm were febrile neutropenia (12.5%), musculoskeletal pain (4.7%), and neutropenia (4.7%).
- In the olaratumab plus doxorubicin arm, the most common TEAEs were nausea (73.4%), fatigue (68.8%), musculoskeletal pain (64.1%), neutropenia (57.8%), and mucositis (53.1%). The most frequently reported TEAEs observed in at least a 20% point difference in the olaratumab + doxorubicin arm than in the single-agent doxorubicin arm, respectively, were musculoskeletal pain (64.1% vs. 24.6%), nausea (73.4% vs. 52.3%), neutropenia (57.8% vs. 35.4%), and vomiting (45.3% vs. 18.5%). TEAEs in $\geq 20\%$ of the patients are summarized in Table 12.

Table 13: TEAEs in ≥ 20% of Patients

Preferred Term Consolidated TEAE Category	Olaratumab + Doxorubicin N=64 n(%)		Single-agent Doxorubicin N=65 n(%)		Single-agent Olaratumab after Single-agent Doxorubicin Treatment N=30 n(%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Patients with any AE	63 (98.4)	51 (79.7)	64 (98.5)	45 (69.2)	26 (80.0)	8 (17.8)
Nausea	47 (73.4)	1 (1.6)	34 (52.3)	2 (3.1)	6 (20.0)	1 (3.3)
Fatigue ¹	44 (68.8)	6 (9.4)	45 (69.2)	2 (3.1)	6 (20.0)	2 (6.7)
Musculoskeletal Pain ²	41 (64.1)	5 (7.8)	16 (24.6)	1 (1.5)	7 (23.3)	2 (6.7)
Neutropenia ^{3,4}	37 (57.8)	34 (53.2)	23 (35.4)	22 (32.3)	0	0
Mucositis ⁵	34 (53.1)	2 (3.1)	23 (35.4)	3 (4.6)	2 (6.7)	0
Alopecia	33 (51.6)	0	26 (40.0)	0	2 (6.7)	0
Vomiting	29 (45.3)	0	12 (18.5)	0	5 (16.7)	0
Infections and Infestations ⁶	27 (42.2)	5 (7.8)	27 (41.5)	7 (10.8)	7 (23.3)	0
Anemia ^{4,7}	26 (40.6)	8 (12.5)	24 (36.9)	6 (9.2)	5 (16.7)	1 (3.3)
Leukopenia ⁸	26 (40.6)	0	12 (18.5)	0	1 (3.3)	0
Constipation	22 (34.4)	0	21 (32.3)	1 (1.5)	3 (10.0)	0
Diarrhea	22 (34.4)	2 (3.1)	15 (23.1)	0	5 (16.7)	0
Decreased Appetite	20 (31.3)	1 (1.6)	13 (20.0)	0	3 (10.0)	2 (6.7)
Abdominal Pain ⁹	15 (23.4)	2 (3.1)	9 (13.8)	0	3 (10.0)	0
Pyrexia	15 (23.4)	0	12 (18.5)	0	3 (10.0)	0
Thrombocytopenia ^{4,10}	16 (25.0)	7 (10.9)	14 (21.5)	5 (7.7)	0	0
Neuropathy ¹¹	14 (21.9)	0	7 (10.8)	0	3 (10.0)	0
Headache	13 (20.3)	0	6 (9.2)	0	1 (3.3)	0
Cough	14 (21.9)	0	12 (18.5)	0	3 (10.0)	0
AESIs						
Infusion-related Reactions ¹²	8 (12.5)	2 (3.1)	0	0	3 (10.0)	1 (3.3)
Cardiac Arrhythmias ¹³	10 (15.6)	0	10 (15.4)	1 (1.5)	4 (13.3)	0
Cardiac Dysfunction ¹⁴	15 (23.4)	1 (1.6)	12 (16.9)	0	4 (13.3)	0

Abbreviations: TEAE = treatment-emergent adverse events; AESI = adverse event of special interest; N = number of treated patients; n = number of patients with given event.

¹Preferred terms patients experienced were fatigue and asthenia.

²Preferred terms patients experienced were arthralgia, back pain, bone pain, flank pain, groin pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.

³Preferred terms patients experienced were neutropenia and neutrophil count decreased.

⁴As reported by the Investigator. These do not represent actual laboratory values.

⁵Preferred terms patients experienced were mucosal inflammation, oropharyngeal pain, and stomatitis.

⁶Includes all preferred terms within the MedDRA™ system organ class of Infections and Infestations.

⁷Preferred terms patients experienced were anemia and hemoglobin decreased.

⁸Preferred terms patients experienced were leukopenia and white blood cell count decreased.

⁹Preferred terms patients experienced were abdominal pain upper, abdominal pain, and abdominal pain lower.

¹⁰Preferred terms patients experienced were thrombocytopenia and platelet count decreased.

¹¹Preferred terms patients experienced were neuropathy peripheral, paresthesia, peripheral sensory neuropathy, and hypoesthesia.

¹²Preferred terms patients experienced were face edema, hypersensitivity, infusion related reaction

¹³Preferred terms patients experienced were tachycardia, bradycardia, bundle branch block left, electrocardiogram QT prolonged, heart rate increased, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, supraventricular extrasystoles, atrial fibrillation, syncope.

¹⁴Preferred terms patients experienced edema peripheral, ejection fraction decreased, cardiac failure congestive, hepatojugular reflux, jugular vein distention, left ventricular.

- Grade ≥3 TEAEs were reported in 79.7% of patients in the olaratumab plus doxorubicin arm and 69.2% of patients in the single-agent doxorubicin arm. The most common Grade ≥3 TEAEs occurring in patients in the olaratumab plus doxorubicin arm included neutropenia, anemia, febrile neutropenia, and thrombocytopenia. The most common Grade 4 event on both study arms was neutropenia 22 (34.4%) vs. 16 (24.6%).

- Infusion-related reactions (IRRs) occurred in 14.9% (14 of 94) of patients in Trial JGDG. IRRs occurred in Cycles 1 and 2, were mainly Grade 1 or 2 (10 of 14 [71.4%]). All Grade ≥ 3 IRRs occurred with the first infusion of olaratumab. Patients with a Grade ≥ 3 were permanently discontinued from therapy. Premedication was not required but was administered in the majority of cases. Of the 14 patients who experienced an IRR, eight (57.1%) had received premedication with an anti-histamine, corticosteroid, or both. A total of 10 (62.5%) patients with a Grade 1 or 2 IRR underwent subsequent administration of olaratumab. Three patients experienced an IRR; all were Grade 1 or 2. Across the eight supportive studies, the incidence and timing of events was comparable to Trial JGDG.
 - Grade 5 infusion-related reaction (IRR): One patient who received olaratumab monotherapy after discontinuation of doxorubicin experienced a fatal IRR. This event occurred in 75 year-old man who had several baseline cardiac comorbidities (ischemic cardiomyopathy, myocardial infarction, ventricular tachycardia, stent placement, heart valve replacement, as well as an implantable defibrillator) who discontinued doxorubicin after two doses due to a decrease in ejection fraction (43%). Ten minutes into the first infusion of olaratumab on Cycle 1 Day 1, the patient developed loss of consciousness and was found to be unresponsive and pulseless; ECG showed ventricular fibrillation and CPR was unsuccessful. The reported event of cardiac arrest was deemed by the Investigator and the Applicant to be possibly related to olaratumab. The Applicant determined this to be an IRR given the temporal administration of olaratumab.
- The incidence of neutropenia as assessed by laboratory testing was comparable between arms for all grades (64.1% in the olaratumab plus doxorubicin arm versus 60.3% in the single-agent doxorubicin arm). The incidence of Grade 4 neutropenia was higher in the olaratumab plus doxorubicin arm (31.3%) versus the single-agent doxorubicin arm (19.0%). This higher incidence of Grade 4 neutropenia did not translate into increased rates of febrile neutropenia, infections, discontinuations, or deaths.
- Musculoskeletal pain occurred more frequently in patients in the olaratumab plus doxorubicin arm (64.1% versus 24.6% of patients in the doxorubicin arm). Grade 3 to 4 musculoskeletal pain occurred in five patients (7.8%) in the olaratumab plus doxorubicin arm versus one (1.5%) patient in the doxorubicin arm. For the five patients that experienced a Grade 3 event, four patients had preexisting pain that worsened and one patient had an infection at the site of pain. There was one Grade 3 musculoskeletal event that led to discontinuation in the olaratumab plus doxorubicin arm. The majority of events were low grade, and mitigated with supportive care and analgesics. Across the eight supportive studies, the incidence of musculoskeletal pain varied from 6.3% to 71.9%. Overall, in the olaratumab-containing arms and olaratumab monotherapy trial, the incidence of musculoskeletal pain was higher (49.5% versus 43.4% in the control arms).

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/s/

LEAH S HER
10/18/2016

Her, Leah

From: Her, Leah
Sent: Wednesday, October 12, 2016 8:18 PM
To: Jody L Roth
Subject: BLA 761038 Eli Lilly - olaratumab - FDA proposed label 101216 post teleconference
Attachments: 101216 FDA Final Edits to 100716 Olaratumab Label.docx

Importance: High

Hi Jody,

Please find attached updated label with FDA's proposed edits in the HL section. Please note that the FPI has been updated as discussed and agreed upon during our teleconference earlier today. Please review FDA's proposed edits in the HL section and if you have no additional questions and agree to these edits, please send me via email a clean, word version of the final label, followed by a formal submission via the gateway. *The formal submission should be done as soon as possible, following the email.*

Kindly confirm receipt; and please let me know if you have any questions.

Regards,

Leah S. Her, MS, PMP
Regulatory Health Project Manager
FDA/CDER/OHOP/DOP2
Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

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LEAH S HER
10/12/2016

Her, Leah

From: Her, Leah
Sent: Thursday, October 06, 2016 8:10 AM
To: Jody L Roth
Subject: BLA 761038 Eli Lilly - olaratumab - follow up on a CMC PMC

Hi Jody,

The CMC Team has determined that the following PMC discussed during our late cycle meeting is no longer necessary as it is a part of your (b) (4); therefore, the PMC is being cancelled:



The other CMC PMC and clinical PMR as discussed during the late cycle meeting, remains.

Please let me know if you have any questions.

Kindly confirm receipt.

Regards,

Leah S. Her, MS, PMP
Regulatory Health Project Manager
FDA/CDER/OHOP/DOP2
Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

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LEAH S HER
10/12/2016

**April Monthly Meeting Agenda/Summary
April 11, 2016**

BLA 761038

Product: Olaratumab for Injection
Submission Date: February 24, 2016
Received Date: February 24, 2016
Sponsor: Eli Lilly and Company
Proposed Propriety Name: LARTRUVO (due by OSE: 5-24-2016)

Proposed Indication: 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

Review Status: Priority Review – 8 months

Current Review Team for BLA 761038:

Patricia Keegan	Division Director
Marc Theoret	CDTL
Meredith Chuk	Clinical
Whitney Helms	Nonclinical (TL)
Emily Wearne	Nonclinical
Hong Zhao	Clinical Pharmacology (TL)
Ruby Leong	Clinical Pharmacology
Kun He	Biostatistics (TL)
Huanyu (Jade) Chen	Biostatistics
Rashmi Rawat CMC (TL)	
Chikako Torigoe	CMC reviewer
Ruth Maduro	RPM
Sue Kang	OSE (TL)
Latonia Ford	OSE SRPM
Leslie Doros	Clinical
Lauren Iacono-Connor	OSI Reviewer
Alice (Chi-Ming) Tu	DEMPA TL
Barbara Fuller	DMPP Reviewer (TL)
Jibril Abdus-Samad	OBP labeling
Ruth Moore	Microbiology
Natalia Pripuzova	Drug Product Reviewer
Patricia Hughes	Microbiology
Monica Markovski	Microbiology
Coleen Thomas	Microbiology
Melinda Bauerlien	OBP Regulatory Project Manager
Nazia Fatima	OPDP labeling Reviewer
Jessica Cleck	OPDP labeling

Naomi Redd
Mei-Yean Chen

DRISK (TL)
DRISK reviewer

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process.

Agenda Items:

1. **Amy McKee**
 - Introduction of SharePoint site to the review team
2. **Marc Theoret**
 - Use of consistent formatting for review/tables
3. **Filing Date (April 24, 2016)**
 - Filing reviews due by COB on Tuesday, April 19, 2016
Completed reviews:
 - ClinPharm (Huanyu Chen) – Fileable
 - CMC (Chikako Torigoe) – Fileable
 - Non-clinical (Emily Wearne) – Fileable
 - Clinical (Meredith Chuk, Leslie Doros) – Fileable
4. **74-day letter (May 8, 2016)**
5. **Review Status:**
 - a. Review requested - This is a Priority review
 - b. Orphan Drug Designation - granted October 9, 2014

6. **Dates milestone letters must issue based on a priority review**

Milestone	6 month review	
Acknowledgment Letter		Sent: March 7, 2016
Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing letter issues? •If the filing issues are not identified, we will need to send a	April 24, 2016	

“Notification of Review Status” letter.		
Deficiencies Identified Letter (74 Day Letter) to include first round of draft labeling	May 8, 2016	
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner’s Target date) and to OPDP/DMPP		
Week after the proposed labeling PMR/PMC has been sent, discuss the Labeling with Applicant		
Review Target Due Dates:		
<i>Primary Review Due</i>	July 28, 2016	
<i>Secondary Review Due</i>	August 1, 2016	
<i>CDTL Review Due</i>	October 3, 2016	
<i>Division Director Review Due</i>	October 24, 2016	
<i>Compliance Check List (BLA)</i>	September 26, 2016	
Compile and circulate Action Letter and Action Package	October 3, 2016	
FINAL Action Letter Due	October 24, 2016	

4. Upcoming/TBD Internal Team Meetings:

a. Bi-monthly T-cons with Lilly (clinical and Stats)

- April 19, 2016 (1:00pm)
- May 3, 2016 (2:00pm)
- May 18, 2016 (1:00pm)

b. Monthly Team Meetings:

April 11, 2016 (2:00pm)

May 23, 2016 (9:00am)
June 16, 2016 (1:00pm)
July 18, 2016 (2:00pm)
August 31, 2016 (11:00pm)
September 22, 2016 (1:30pm)

- c. **Mid-Cycle Meeting Date:** May 20, 2016 (11:00am)
- d. **Labeling Meetings:**

Meeting Date	Discipline Attendance Required	Label Section(s) to be discussed	Length of Meeting	Meeting Date & time
<i>1st meeting</i>	Non-clinical, Maternal Health Team (MHT), Clinical	12, 13, 8.1-8.4, 5 (if warning for embryo-fetal toxicity)	1.5 hours	June 10, 2016
<i>2nd meeting</i>	CMC, DMEPA, Clinical	3, 11, 16 and carton and container labeling	1 hour	June 17, 2016
<i>3rd meeting</i>	Clinical Pharmacology, DMEPA, Clinical	2, 7, 8.5, 8.6, 8.7, 12.2, 12.3 and 6.2 (Immunogenicity)	1.5 hours	June 22, 2016
<i>4th meeting</i>	Clinical, Statistics	1, 14	1 hour	July 1, 2016
<i>5th meeting</i>	Clinical	6	1 hour	July 1, 2016
<i>6th meeting</i>	Clinical	4, 5, 2, 10, 17	1.5 hours	July 6, 2016
<i>7th meeting</i>	Initially include all review disciplines (to hold time)	Any items not covered during originally scheduled time	1 hour	July 8, 2016
<i>When PI is substantially complete, send label to applicant, OPDP and Patient Labeling Team</i>				
<i>8th Meeting (Schedule 2-3 weeks after labeling sent to applicant)</i>	Review revised labeling from applicant, include all review disciplines and OPDP and PLT		1.5 hours	To be scheduled

- e. **Post Mid-Cycle meeting:** June 1, 2016 (10:00am)
 - f. **Late-Cycle meeting:** September 1, 2016 (1:00pm)
 - g. **Wrap-up meeting:** September 23, 2016 (11:00am)
5. **ODAC:** September 13/14, 2016
6. **Inspection status**

Planned inspections:	Scheduled dates for inspection	Status	Preliminary Outcome	Site Number
Sponsor: Eli Lilly	Pending (start May 9th)	ORA/EMA (Joint) planning stage	N/A	N/A
CRO: (b) (4) (IRC)	Pending (start in (b) (4))	ORA planning stage	N/A	N/A
CI: Kim, Edward	Pending	ORA planning stage	N/A	Site 15: SEA-DO
CI: Tap, William	Planned start date in April/May. FDA HQ (OSI) will observe this EMA inspection.	EMA Planning stage	N/A. FDA plans to use findings of EMA inspection in support of BLA 761038.	Site 1: NYK-DO
CI: Van Tine, Brian	March 21-28, 2016	Completed	NAI (no issued)	Site 12: KAN-DO

7. **Issues –**

- h. Clinical IR forwarded to sponsor on April 8, 2016. Response Due: **5:00pm, April 13, 2016**
- i. Label /PI: Currently under review by CDTL

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/s/

LEAH S HER

10/04/2016

Leah Her on behalf of Ruth Maduro

**Planning Meeting Summary
 March 4, 2016**

BLA 761038

Product: **Olaratumab**
Submission Dates: December 10, December 17, January 19, January 27, February 11, February 22, February 24 – (Rolling Submission)
Received Date: February 24, 2016 – clock starts
Sponsor: Eli Lilly and Company
Proposed: 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

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss

Agenda Items:

1. Review Status:

- Priority Review requested. 3-4-2016 discussion: 8 months
- Orphan Drug Designation: Granted, October 9, 2014
- The clinical development of olaratumab has been conducted under IND 121500
- Proprietary Name (b) (4) conditional acceptance on July 19, 2015 – withdrawn on February 25, 2015 – submitted new propriety name request on February 24, 2015 for LARTRUVO – Goal date May 24, 2016

2. Dates Milestone Letters Must Issue

Milestone	Priority review – (6 month review) August 25, 2016. 3-4-2016 discussion: October 2016
Acknowledgement Letter – currently under CPMS review Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting?	Target Date: Wednesday, March 9, 2016 Target Date: Friday, March 25, 2016 3-4-2016 discussion: April 24, 2016
Deficiencies Identified Letter	Target Date:

(74 Day Letter)	May 8, 2016 (Sunday)
FINAL Action Letter Due	Target Date: Thursday, August 25, 2016 3-4-2016 discussion: October 2016

3. Product label

- Received 1-19-2016
- Forwarded to review team 1-22-2016
- SharePoint link: [http://sharepoint.fda.gov/orgs/CDER-OHOP-DOP2/Shared%20Documents/RPM Information/Ruth Maduro/BLA/BLA%20761038%20\(Eli%20Lilly%20and%20Company\)/BLA%20761038%20proposed%20label%20\(1-19-2016\).docx](http://sharepoint.fda.gov/orgs/CDER-OHOP-DOP2/Shared%20Documents/RPM%20Information/Ruth%20Maduro/BLA/BLA%20761038%20(Eli%20Lilly%20and%20Company)/BLA%20761038%20proposed%20label%20(1-19-2016).docx)

4. Discussion on Application

- Grant priority review?
Yes

5. Potential Consults Needed:

OPDP	* To be completed
Medication Error	* To be completed
OSE (REMS)	* To be completed
Maternal Health	* To be completed
QT-IRT	* To be determined
OSI	* Completed – March 3, 2016
Pediatric Page/PeRC	* NA – Orphan Drug designation 10-9-2014
Patient Labeling Team (DMPP)	* To be completed
SEALD	* To be addressed by Jennie Chang

Are there any additional consults we need?

None discussed

6. Upcoming Internal Team Meetings:

- **Filing Meeting:** Will be scheduled
 Please bring Filing review (TL signature) and Interim Deliverables
 Please be prepared to identify significant filing issues for day 74 letter
- **Mid-Cycle Meeting: Will be scheduled**
- **Late-Cycle Meeting: Will be scheduled**
- **Labeling Meetings:**
 - To be scheduled NLT filing meeting

Proposed schedule for labeling meetings. 3-4-2016 discussion: order of review to be revised by CDTL (Marc Theoret)

Discipline	Label Section	Meeting Date
Clinical	4, 5, 17	TBA
Clinical and Statistics	1, 14	TBA
Clinical Pharmacology, Clinical	2, 7, 8.5, 8.6, 8.7, 12.2, 12.3	TBA
CMC, DMEPA, Clinical	3, 11, 16	TBA
Clinical, Maternal Health Team, Nonclinical	8.1, 8.3, 8.4, 12.1, 13	TBA

Team Meetings/Monthly Meetings

- To be scheduled NLT filing meeting

7. Applicant Orientation Presentation

- Scheduled – March 14, 2016 (confirmed with sponsor)

8. ODAC

- Will this application be presented at ODAC? 3-4-2016 discussion: the review team will need to hold 2 or 3 meetings prior to ODAC.

13/14 September 2016

9. Miscellaneous Items or Issues:

- Will information be disseminated via burst and a press release?

Both burst and press release

10. Review Team

Patricia Keegan	Division Director
Marc Theoret	CDTL
Meredith Chuk	Clinical
Whitney Helms	Nonclinical (TL)
Emily Wearne	Nonclinical
Hong Zhao	Clinical Pharmacology (TL)
Ruby Leong	Clinical Pharmacology
Kun He	Biostatistics (TL)
Huanyu (Jade) Chen	Biostatistics
Rashmi Rawat	CMC (TL)
Chikako Torigoe	CMC reviewer
Ruth Maduro	RPM
Sue Kang	OSE (TL)
Latonia Ford	OSE SRPM
Leslie Doros	Clinical
Lauren Iacono-Connor	OSI Reviewer

Alice (Chi-Ming) Tu	DEMPA TL
Barbara Fuller	DMPP Reviewer (TL)
Jibril Abdus-Samad	CMC OBP labeling

11. Other 3-4-2016 discussions

- ADV ASCO June 3-7
- Jennie Chang will send the labeling comments to Annmarie by the 1st week in April 2016
- The label will be forwarded to the sponsor ahead of the 74th Day letter
- Amy Mcfee provided a SharePoint presentation to the review team regarding the Pilot program. SharePoint site and template document provided. CDTL has editing rights.

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/s/

LEAH S HER

10/04/2016

Leah Her on behalf of Ruth Maduro



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

Memorandum

Date: October 3, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Labeling Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

Please find attached FDA’s additional edits and comments to your revised package insert (PI) labeling submitted on August 5, 2016. Please provide a response via email correspondence **by 4 PM (EST) on Monday, October 10, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

In the areas of the label that you agree with FDA’s proposed edits, please accept the tracked change to aid in reviewability. For those edits that you do not agree with, provide justification as a comment (cite “From Eli Lilly” in the comment). For any edits you wish to propose, add via track changes and provide justification as a comment (cite “From Eli Lilly” in the comment). Lastly, when making edits to the label, please update formatting as necessary.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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

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/s/

LEAH S HER
10/03/2016

Wrap Up Meeting Summary
September 23, 2016

Application: BLA 761038
Product: Proposed as LARTRUVO (olaratumab) Injection, 500 mg/50 mL (10 mg/mL)
Submission Date: February 24, 2016
Received Date: February 24, 2016
Sponsor: Eli Lilly and Company
Proposed Indication: 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.

Meeting Objective:

- Develop a comprehensive understanding of safety, efficacy and quality of proposed product through presentations of key findings of all reviews, consults and inspections
- Identify any issues that could preclude an approval action
- Come to agreement on a preliminary decision on the regulatory action
- Begin internal discussions regarding potential post-marketing commitments and labeling

Attendees: Richard Pazdur, Patricia Keegan, Marc Theoret, Meredith Chuk, Leslie Doros, Leah Her, Whitney Helms, Emily Wearne, Rashmi Rawat, Hong Zhao, Huanyu Chen, Natalia Pripuzova, Jeff Summers, Latonia Ford, Chi-Ming Tu, Chikako Torigoe, Kun He, Mei-Yean Chen, Nazia Fatima, Monica Commerford Markowski), Afrouz Nayernama, Leyla Sahin, Carolyn McCloskey

1. Application Milestone:

Discussion: The schedule of this application was discussed, with a focus on upcoming milestones. The review of the application is on track. The action date is October 24, 2016.

2. Discipline Specific Reviews of Application

Discussion: No discipline specific issues were discussed. This application is under the shared review pilot. All core disciplines (except CMC, who is generating a separate review) have completed their portions in the shared review and have uploaded a memorandum to this effect in DARRTS.

3. Status of Information Requests (by discipline)

Discussion: A follow-up clinical information request was issued regarding Lilly's September 20, 2016, emailed response to FDA's September 19, 2016, request for information, pertaining to Lilly's counter-proposed labeling. Response is due by mid-day September 26, 2016. There are no other outstanding information requests and all other responses have been submitted through the gateway.

4. Consults Status

Discussion: During this period, OPDP completed a review for the proposed package insert and carton and container labeling. All consults have been completed.

The Team briefly discussed the status of SGEs. Discussions with 2 of 3 SGEs have been completed; the teleconference with the last SGE is scheduled for the afternoon of September 23, 2016.

5. Labeling Discussion

Discussion: The labeling review is still ongoing. An internal labeling meeting is scheduled for September 26, 2016. RPM will schedule a potential labeling discussion meeting with the Applicant for 1st week in October 2016.

6. PMCs/PMRs:

- Clinical –
 - A PMR to “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”

Discussion: The PMR development template has been cleared by the Deputy Director for Safety.

- Chemistry, Manufacturing and Controls (CMC) –

-

(b) (4)

- PMC 2 to “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.”

Discussion: CMC micro confirmed that PMC 1 is no longer needed as the Applicant will be providing the information along with additional data from the (b) (4). An addendum will be added to both the microbiology and executive CMC reviews. The Applicant will be notified. The PMR/PMC development template for PMC 2 has been completed.

7. Press Release and Burst:

Discussion: Notification was provided to the Press Office and IO RPMs. The draft of both the Press Release and ASCO burst will be provided for review.

8. Discussion of Proposed Action To be Taken

Discussion: The Team confirmed that the action will be accelerated approval.

9. Other Pending Items

Discussion: The Team briefly discussed pending items, responsible person(s) and status.

10. MISC Items or Issues

Discussion: The Team briefly discussed the shared review sign-off procedure. The multi-disciplinary review procedure document was reviewed. RPM will generate a plan with timeline to circulate to the Team members participating in the pilot.

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/s/

LEAH S HER
09/29/2016



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

Memorandum

Date: September 23, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

We also refer to your September 20, 2016, electronic (email) communication, wherein you provided responses to our September 19, 2016, request for information, regarding the proposed package insert.

The Clinical Reviewer has the following additional request for information. Please provide a response via email correspondence **by 12 PM (EST) on Monday, September 26, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Comments:

1. In regards to your response to our comment 2, you stated that  (b) (4) . It was noted that Appendix 16 of the CSR contains the Compliance and/or Drug Concentration Data which has a link to the listing for Premedication Administration. Provide the location of Appendix 21 or a copy of this appendix so that this data that was submitted may be verified. In addition, provide an explanation for the differences between the data in Appendix 16 versus Appendix 21.

2. Provide a narrative for the following patients who experienced a dose reduction due to a non-heme adverse event which provides the mg/kg dosage they received and the outcome of administration of doxorubicin if the dose reduction was done on Day 1:
 - a. 015-1007 who had a dose reduction due to Grade 3 neuropathy
 - b. 015-1009 who had a dose reduction due to subject tolerance
 - c. 015-1012 had an AE of lower abdominal pain in the setting of Grade 4 neutropenia in the previous cycle

3. For all patients who experienced a dose reduction in the investigational arm, provide a per cycle breakdown for each subject with the following information:
 - a. USUBJID
 - b. Dose of olaratumab (mg/kg) for each subsequent cycle
 - c. Dose of doxorubicin (mg/kg) for each subsequent cycle
 - d. Adverse event recurrence after rechallenge

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
09/23/2016

Pre-Late Cycle and Team Meeting Summary
August 29, 2016 / 12:30 – 1:00 PM (EST)

Application: BLA 761038
Product: Proposed as LARTRUVO (olaratumab) Injection, 500 mg/50 mL (10 mg/mL)
Submission Date: February 24, 2016
Received Date: February 24, 2016
Applicant: Eli Lilly and Company
Proposed Indication: 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.

Objective: To prepare for the Late Cycle Meeting (LCM), including discussion of:

- review issues
- contents of LCM background package due to Applicant
- logistics and goals of LCM teleconference

Attendees: Patricia Keegan, Meredith Chuk, Leslie Doros, Monica Hughes, Leah Her, Emily Wearne, Chikako Torigoe, Rashmi Rawat, Hong Zhao, Ruby Leong, Jennie Chang, Nazia Fatima, Sarah Thomas, Lauren Iacono-Connor, Afrouz Nayernama

1. Application Milestone

Discussion: The schedule of this application was discussed, with a focus on upcoming milestones. The review of the Application is on track.

2. Discipline Review Letters

Discussion: No Discipline Review Letters have been issued to date or will be issued.

3. Substantive Review Issues (by discipline)

Discussion: The Clinical Team discussed concerns relating to the uncertainty of the magnitude of the clinical effect given the small size and heterogenous population of Trial JGDG which is supporting this application. No issues were identified by any other disciplines.

4. Status of Information Requests (by discipline)

Discussion: There are no outstanding responses to information requests. The Team confirmed that there will be none issued for discussion at the late cycle meeting.

5. Advisory Committee Meeting

Discussion: An Advisory Committee Meeting is not planned. The Team discussed the status of the Special Government Employee (SGE) clearance. Two have been cleared, one is under 502 clearance, and one was waived due to conflict of interest at the initial screen. The two cleared SGEs will be consulted mid-September 2016. SGE background packages will be provided to the SGEs around end of August 2016. The Applicant will be provided the scope of the preliminary questions for the SGEs in the late cycle meeting package.

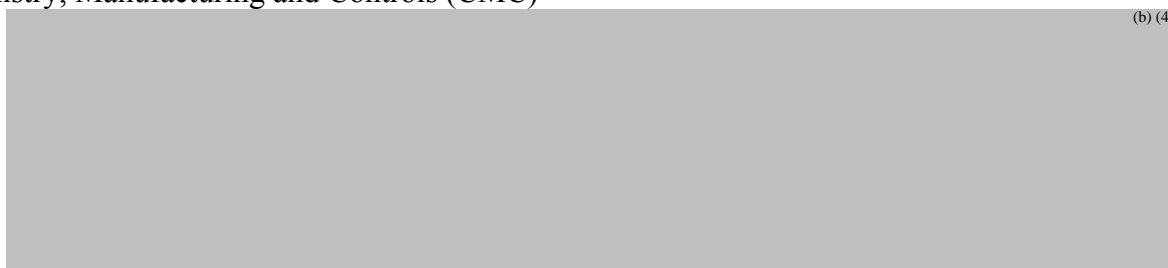
6. REMS or other Risk Management Actions

Discussion: The Team discussed that there were no REMS- or risk management plan-related issues. Final DRISK review was uploaded in DARRTS on July 28, 2016.

7. Postmarketing Requirements/Commitments

- Clinical –
 - A PMR to “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”
- Pharm/Tox – No PMRs/PMCs identified to date
- Chemistry, Manufacturing and Controls (CMC) –

○



- PMC 2 to “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.”
- Clinical Pharmacology/Pharmacometrics – No PMRs/PMCs identified to date

Discussion: For the Clinical PMR, the Team discussed that interim analysis submission would be useful to understand any potential futility concerns. The Team discussed providing the Applicant advice on how to provide interim analysis data to the FDA while still remaining blinded to the trial, if requested by the Applicant. The CMC Review Team confirmed that the Applicant’s response to the above two PMCs were acceptable. The Team confirmed that there were no additional PMRs/PMCs anticipated. The Team was reminded that PMR/PMC Development Templates should be finalized 4 weeks before end of the review cycle.

8. Major Labeling Issues

Discussion: The Team discussed at a high level, the revised labeling submitted by the Applicant on August 5, 2016. In particular, the Team noted that the Applicant has modified (b) (4) the Package Insert. The Team briefly discussed the Applicant’s rationale. The Team agreed that this will be discussed with the Applicant in general terms during the late cycle meeting. The next internal meeting to discuss the revised label is planned for September 16, 2016, and information requests will be sent to the Applicant for any additional required information.

9. OSI Summary of Inspections

Discussion: No significant deficiencies were identified. The Clinical Inspections Summary was uploaded in DARRTS on July 29, 2016.

10. Manufacturing Facility Inspection

Discussion: No significant deficiencies were identified. The Manufacturing Facility Inspection information can be found in Appendix C of the CMC final review uploaded in Panorama on July 28, 2016.

11. Review Plans to be communicated to Applicant during LCM

Discussion: The review is ongoing. The Team determined that an update will be provided on SGE, labeling, and PMR/PMC.

12. Miscellaneous Items

Discussion: None.

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/s/

LEAH S HER
09/23/2016

Mid-Cycle Meeting Summary
May 20, 2016 / 11:00 – 11:30 AM (EST)

Application: BLA 761038
Product: Proposed as LARTRUVO (olaratumab) Injection, 500 mg/50 mL (10 mg/mL)
Submission Date: February 24, 2016
Received Date: February 24, 2016
Applicant: Eli Lilly and Company
Proposed Indication: 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.

Objective: The purpose of this meeting was to:

- Discuss key findings & identify issues that could preclude an approval action
- Discuss labeling, potential for PMCs/PMRs and REMS
- Revise review plan if needed
- Develop plan for the mid-cycle communication

Attendees: Richard Pazdur, Patricia Keegan, Jeffrey Summers, Amy McKee, Marc Theoret, Meredith Chuk, Leslie Doros, Whitney Helms, Emily Wearne, Rajeshwari Sridhara, Kun He, Jade Chen, Brian Booth, Hong Zhao, Ruby Leong, Jerry Yu, Fang Li, Rashmi Rawat, Chikaka Torigoe, Colleen Thomas, Monica Markovski, Ruth Moore, Monica Hughes, Leah Her, Sarah Thomas, Mei-Yean Chen, Afrouz Nayernama, Margaret Thompson, Dow Chung Chi, Damiette Smit, Christy Osgood, Deveonne Hamilton-Stokes, Nazia Fatima, Sharon Mills, Leyla Sahin, Tamara Johnson, Latonia Ford, Carolyn McCloskey, Jiang Liu

Discussion During Meeting:

1. Slides were presented by the following disciplines (in order):

- Regulatory Introduction – Leah Her
- CMC – Chikaka Torigoe
- Nonclinical – Emily Fox
- Clinical Pharmacology/Pharmacometrics – Ruby Leong, Fang Li
- Clinical/Statistical – Meredith Chuk, Leslie Doros, Jade Chen

2. Key issues:

- CMC:

Discussion: The CMC Team stated that no issues have been identified to date. Manufacturing site inspection for drug substance has been completed. Manufacturing site inspection for drug product (Eli Lilly, IN) will be waived.

- Nonclinical:

Discussion: The Nonclinical Team stated that no issues have been identified to date. A warning for embryofetal toxicity will be added in the label.

- Clinical Pharmacology/Pharmacometrics:

Discussion: The Clinical Pharmacology/Pharmacometrics Team stated that no issues have been identified to date. However, clarification will be requested regarding dataset discrepancy and exposure-response analyses calculations.

- Clinical/Statistical:

Discussion: The Clinical/Statistical Team indicated that:

- Data from Study JGDG appeared to provide uncertainty in the magnitude of clinical benefit and accelerated approval pathway is likely
- Primary safety risks identified to-date included infusion-related reactions, musculoskeletal pain, (b)(4), and neutropenia which will be communicated in the label
- Concerns were raised with respect to Study JGDG design and robustness of progression-free survival (PFS) due to small effect size

In addition, a brief update on the status of clinical site inspections was discussed. Two of the four planned clinical sites and the Applicant were completed. The third site was inspected by EMA and FDA can use the EMA-findings in support of this application. The inspection of the last site, (b)(4) is currently being planned.

3. Advisory Committee:

Discussion: The Team determined at this point in time that an ODAC will not be held for this application. Special Government Employees (SGEs) will be consulted individually.

4. REMS:

Discussion: The Team determined at this point in time that a REMS will not be needed.

5. PMC/PMR:

- CMC:

Discussion: The CMC Team indicated that a PMC (b)(4) will be requested (previously agreed with Applicant during the pre-BLA/CMC only meeting).

- Nonclinical:

Discussion: The Nonclinical Team indicated that no PMC/PMR has been identified at this point in time.

- Clinical Pharmacology/Pharmacometrics:

Discussion: The Clinical Pharmacology/Pharmacometrics Team indicated that no PMC/PMR has been identified at this point in time.

- Clinical/Statistical:

Discussion: The Clinical/Statistical Team indicated that a clinical trial designed to confirm the clinical benefit of olaratumab in combination with doxorubicin in patients with advanced, unresectable soft tissue sarcoma will likely be a post-marketing requirement as per Subpart E of the Accelerated Approval regulations (previously discussed with Applicant).

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/s/

LEAH S HER
09/22/2016



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

Memorandum

Date: September 20, 2016
From: Leah Her, Regulatory Health Project Manager - CDER/OHOP/DOP2
Subject: **BLA 761038 – Eli Lilly and Company**
Clinical and Statistical Data Review

Date and Time of Teleconference: May 18, 2016, approximately 1:00 - 2:00 PM (EST)

FDA Participants:

Meredith Chuk	Clinical Reviewer, DOP2
Leslie Doros	Clinical Reviewer, DOP2
Leah Her	Regulatory Health Project Manager, DOP2
Huanyu (Jade) Chen	Statistical Reviewer, DBV

Sponsor Participants:

Kathryn Winkley Robison	Project management Associate
Chirag Jani	Sr. Specialist Statistical Programming, Statistics and Data Management
Patrick M Peterson	Olaratumab Statistics Lead - Oncology
Ashwin Shahir	Medical Advisor, Global Patient Safety
Stephanie Roberson	Clinical Project manager associate
Isabella T Smalera	Regulatory Submissions
Kelley J Fisher	Manager, Clinical Data Management
Robert L Ilaria, Jr.	Sr. Medical Director, Olaratumab
Byran K Litton	Olaratumab Product Team Leader
Jody Roth	Olaratumab Regulatory Lead, Global Regulatory Affairs
Symantha Ann Melemed	Olaratumab Product Team Leader

This was a FDA-initiated meeting to discuss clinical and statistical data, in support of the pending Biologics License Application (BLA) 761038 received on February 24, 2016, for the proposed use of 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. In advance of this meeting on May 17, 2016, FDA provided an agenda and clinical and statistical comments for discussion during the meeting. These correspondences are attached to this tcon memo. Preliminary responses to these comments were provided via email by Eli Lilly on May 18, 2016.

Summary of the TCON:

Following introductions by all participants, FDA noted that the goal of the meeting was to discuss the clinical and statistical comments provided on May 17, 2016. FDA also thanked Eli Lilly for providing preliminary responses in advance of the tcon as preliminary responses were not originally requested by FDA.

Statistical

FDA started by requesting clarification on Eli Lilly's preliminary response to statistical comment #1. Specifically, FDA stated that the initial concern pertained to the potential perceived duplication in the death dates for some patients, as deaths were noted under both "end of treatment" and "end of study," which was a few days later, for example, for the same patient. FDA provided examples to highlight the concern. Eli Lilly acknowledged and clarified that the discrepancy may have resulted from the definitions utilized, where Eli Lilly stated that the "end of treatment date" referred to the last dose date and the "end of study date" referred to the death date. FDA confirmed with Eli Lilly that in order to determine the actual reason for discontinuation of treatment, FDA would have to refer to the death form.

FDA also provided clarification regarding statistical comment #4, stating that this request was made as Eli Lilly's April 1, 2016, response to the March 25, 2016, clinical information request, pertaining to the randomization code (comment #8) did not provide the exact information that FDA needed. FDA stated that the original log file used to generate the randomization code for assignment of patients into treatment arms was needed.

Eli Lilly acknowledged and committed to providing the original SAS code login output.

Clinical

FDA referred to Eli Lilly's preliminary response to clinical comment #1. Specifically, FDA stated that preliminary review of the data in the BLA appeared to show that a larger number of patients discontinued treatment due to adverse events (AE) compared to the number provided by Eli Lilly, and FDA requested clarification on this difference. FDA provided examples to highlight the concern. Eli Lilly stated that this discrepancy may have resulted from different use of definitions by FDA and Eli Lilly, where Eli Lilly clarified that their response was based on adverse drug reactions (ADRs) and not AEs used by FDA. FDA expressed concerns in the use of ADRs, and stated that for the purpose of determining patients who discontinued study therapy due to toxicity, data analysis needs to be in terms of AEs and not only ADRs.

Eli Lilly acknowledged and committed to providing an updated response to clinical comment #1.

FDA also referred to Eli Lilly's May 13, 2016, response to the second May 5, 2016, clinical information request. FDA requested further discussion on comment #6. FDA stated that the question related to the patient with chondroblastic osteosarcoma, not chondrosarcoma. Eli Lilly acknowledged and committed to providing further clarification of Eli Lilly's May 13, 2016, response.

In addition, FDA referred Eli Lilly to clinical comment #3. FDA inquired on the large discordance in the progression free survival (PFS) as assessed by the investigator and central review. FDA also observed that there was a large number of censoring by the central review. FDA provided some examples to highlight the concern. Eli Lilly stated that the further explanation of central review's assessment was available in Eli Lilly's response to clinical comment #4. FDA acknowledged and requested that Eli Lilly provide a single table providing analysis of the discordance, containing patient identifier, date of PFS assessment by investigator, date of censoring by central review, detailed explanation of the reason for censoring, and date of disposition event. FDA also requested that the updated table be provided in either excel or some sort of a transport file.

Eli Lilly acknowledged and committed to providing the requested information. Eli Lilly stated that the table format to be provided to FDA will need to be discussed internally.

Attachments:

- Tcon agenda provided on May 17, 2016
- Statistical comments and information request provided on May 17, 2016
- Clinical comments and information request provided on May 17, 2016

Her, Leah

From: Her, Leah
Sent: Tuesday, May 17, 2016 5:01 PM
To: Jody L Roth
Subject: BLA 761038 Eli Lilly - olaratumab - 5/18/16 tcon agenda
Attachments: BLA 761038 Eli Lilly - olaratumab - FDA Request for Information (statistical); BLA 761038 Eli Lilly - olaratumab - FDA Request for Information (clinical)

Importance: High

Hi Jody,

Reference is made to your Biologics License Application (BLA) submitted on February 24, 2016. In preparation of our tcon tomorrow, please find below agenda.

Tomorrow's tcon agenda:

- Discuss clinical comments communicated 5/17/16 (attached)
- Discuss some of your responses provided to the second 5/5/16, clinical information request
- Discuss statistical comments communicated 5/17/16 (attached)

Kindly confirm receipt and please let me know if you have any questions.

Regards,

Leah S. Her, M.S.
Regulatory Health Project Manager
FDA/CDER/OHOP/DOP2
Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

Her, Leah

From: Her, Leah
Sent: Tuesday, May 17, 2016 10:37 AM
To: Jody L Roth
Subject: BLA 761038 Eli Lilly - olaratumab - FDA Request for Information (statistical)

Importance: High

Hi Jody,

Reference is made to your Biologics License Application (BLA) submitted on February 24, 2016. In preparation of our tcon tomorrow, please find below statistical comments. I am following up to see if we will have any clinical review items; however, I wanted to send this to you as soon as possible in the interim. Kindly confirm receipt and let me know if you have any questions.

Statistical Comments:

1. Clarify the following four patients' date of death and primary cause of death.

(b) (4)



2. What is eDT stand for in the SUPPDM domain?

(b) (4)



- 3. Provide a summary of interim analyses for PFS and OS. The CSR and DSMB meeting minutes submitted on March 23, 2016 did not include this information.

Table 1. Clinical cut-off date	DSMB Meeting*	Number of events		HR (95% CI)		P value	
		PFS	OS	PFS	OS	PFS	OS

- 4. Provide SAS program, log, and output used to generate randomization number.

Regards,

Leah S. Her, M.S.
 Regulatory Health Project Manager
 FDA/CDER/OHOP/DOP2
 Tel: 240-402-6611
 Fax: 301-796-9849
 Email: leah.her@fda.hhs.gov

Her, Leah

From: Her, Leah
Sent: Tuesday, May 17, 2016 4:58 PM
To: Jody L Roth
Subject: BLA 761038 Eli Lilly - olaratumab - FDA Request for Information (clinical)

Importance: High

Hi Judy,

Reference is made to your Biologics License Application (BLA) submitted on February 24, 2016. In preparation of our tcon tomorrow, please find below clinical comments. In addition, we wish for you to submit your formal response to the below comments **on or before 12 PM (EST), Thursday, May 19, 2016.**

Clinical Comments:

1. Please provide a listing of the patients who discontinued any study drug by arm and which drug to support the proposed text in the label: [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
2. Provide the reason for the discrepancy between the M staging in FA.xpt where only (b) (4) of the control arm patients and (b) (4) of the experimental arm patients are listed as having M1 disease (rest are either blank or listed as "unknown") but as per XM.xpt, (b) (4) of the (b) (4) randomized patients have sites of metastatic disease listed.
3. Please confirm if the location of primary tumor at diagnosis was captured.

Please note that I will also be sending to you a separate communication shortly with couple clinical comments which will also be due by 12 PM (EST), Thursday, May 19, 2016. I will also follow up with a final tcon agenda.

Kindly confirm receipt and let me know if you have any questions.

Regards,

Leah S. Her, M.S.
Regulatory Health Project Manager
FDA/CDER/OHOP/DOP2
Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

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/s/

LEAH S HER
09/20/2016

Monthly Team Meeting Summary
July 18 2016 / 2:00 – 2:30 PM (EST)

Application: BLA 761038
Product: Proposed as LARTRUVO (olaratumab) Injection, 500 mg/50 mL (10 mg/mL)
Submission Date: February 24, 2016
Received Date: February 24, 2016
Applicant: Eli Lilly and Company
Proposed Indication: 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

Objective: Standing Monthly Team meeting to discuss review status and share information
Attendees: Marc Theoret, Meredith Chuk, Leslie Doros, Whitney Helms, Leah Her, Emily Wearne, Chikako Torigoe, Ruby Leong, Lauren Iacono-Connor, Fang Li, Mei-Yean Chen, Nazia Fatima, Sarah Thomas, Latonia Ford, Sharon Mills

1. Review of Application Milestone:

Discussion: The schedule of this application was discussed, with a focus on upcoming milestones. The Team discussed the date of the label comments/PMR/PMC to the Applicant. The review of the Application is on track.

2. Pilot – Multidisciplinary Review Sign-Off Procedure:

Discussion: The Team discussed the BLA 761038 multidisciplinary review procedure document communicated to the core disciplines on July 14, 2016, which intended to clarify the shared review process. It was discussed that timing of signatures would have to be coordinated when finalizing the review document. The Team did not have any additional questions.

3. Team Updates:

Discussion on 7/18/16: The Clinical Team provided a brief update on the status of the Special Government Employee (SGE) screening. Three of 4 SGEs passed the initial screening and are currently being assessed by the Conflict of Interest (COI) staff, and the last one was waived due to conflict of interest at the initial screen. No other disciplines had any specific updates. The Team confirmed that review is on track.

4. Information Request Status:

Discussion: The Team discussed outstanding Clinical (2) and CMC (1) Information Requests and the expected timing of the Applicant's response. No other disciplines noted outstanding Information Requests.

5. Consult Status:

Discussion: DEMPA completed a review for the revised carton and container labels. In addition, OSI status was discussed. It was also determined that based on safety review to date, a medguide or patient package insert would not be needed; therefore, the DMPP consult will be withdrawn.

6. Potential PMR/PMCs:

Discussion: The CMC Team indicated that a PMC will be needed for a study to re-assess the drug substance and drug product specifications. The CMC Team will provide the specific PMC language once it clears internally.

7. Labeling:

Discussion: The FDA proposed label is with senior leadership for final review prior to being sent to the Applicant.

8. Next Team Meeting: Wednesday, August 31, 2016 / 11:00 – 11:30 AM (EST)

Discussion: The Team was reminded that this meeting will also serve as the internal pre-late cycle meeting (pre-LCM).

9. Discussion of any miscellaneous items or other issues:

Discussion: The Team was reminded that the LCM background materials were due to the Applicant no later than Friday, September 2, 2016.

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/s/

LEAH S HER
09/20/2016

Monthly Team Meeting Summary
June 16, 2016 / 1:00 – 1:30 PM (EST)

Application: BLA 761038
Product: Proposed as LARTRUVO (olaratumab) Injection, 500 mg/50 mL (10 mg/mL)
Submission Date: February 24, 2016
Received Date: February 24, 2016
Applicant: Eli Lilly and Company
Proposed Indication: 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

Objective: Standing Monthly Team meeting to discuss review status and share information
Attendees: Marc Theoret, Meredith Chuk, Whitney Helms, Leah Her, Emily Wearne, Chikako Torigoe, Ruby Leong, Lauren Iacono-Connor, Fang Li, Mei-Yean Chen, Nazia Fatima, Sarah Thomas, Latonia Ford

1. Application Milestone:

Discussion: The schedule of this application was discussed, with a focus on upcoming milestones. The review of the Application is on track.

2. Pilot – Multidisciplinary Review Template:

Discussion: This application will be under the shared review pilot, and the multidisciplinary review template was discussed. The Team was reminded that the shared review was for core disciplines only, with the exclusion of CMC, as CMC will be preparing a separate review. The Team was also reminded to only edit their discipline-specific sections. It was discussed that further clarification on the logistics will be needed.

3. Team Updates:

Discussion: The Clinical Team provided a brief update on the status of the Special Government Employee (SGE) screening. Initial screening has been completed for 3 of 4 SGEs. The last potential SGE screening teleconference is scheduled for June 20, 2016. No other disciplines had any specific updates. The Team confirmed that review is on track.

4. Consult Status:

Discussion: The following consults were completed: 1) QT/IRT, 2) DEMPA. Other consults are on track. No medguide or patient package insert was submitted by the Applicant; however, it was discussed that further review was needed to make a determination on the need for a DMPP consult.

5. Potential PMR/PMCs:

Discussion: The Team briefly discussed the two identified PMR/PMC that have been previously communicated to the Applicant during the Post Mid-Cycle Communication:

- Clinical PMR - A clinical trial designed to confirm the clinical benefit of olaratumab in combination with doxorubicin in patients with advanced, unresectable soft tissue sarcoma
- CMC PMC - [REDACTED] (b) (4)

The Team confirmed that no other PMR/PMC has been identified to date. The Team was reminded that PMR/PMC Development Template will need to be completed.

6. Labeling:

Discussion: The Team was provided the link to the labels for review and edits in preparation of the upcoming labeling meetings. The Team discussed the labeling meeting schedule.

7. Next Team Meeting: Monday, July 18, 2016 / 2:00 – 2:30 PM (EST)

Discussion: None.

8. Discussion of any miscellaneous items or other issues:

Discussion: The Team briefly discussed the status of information requests, and pending responses from the Applicant.

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/s/

LEAH S HER
09/20/2016



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

Memorandum

Date: September 19, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

The Clinical Reviewer has the following request for information. Please provide a response via email correspondence **by 4 PM (EST) on Tuesday, September 20, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Comments:

1. Under Section 5.1 Infusion-related reaction, it states “All 59 patients with Grade 1 or 2 IRR resumed LARTRUVO, 12 (20%) of these patients had a Grade 1 or 2 IRR with rechallenge.” Provide data on the use of premedication and rate of infusion for the 12 (20%) patients who had a subsequent IRR after rechallenge.

2. In Section 6.1 Clinical Trials Experience, it states “

(b) (4)

(b) (4)

3. In Section 6.1 Clinical Trials Experience, it states “In Trial 1, (b) (4) adverse reactions resulting in permanent discontinuation of LARTRUVO (b) (4) (b) (4) In the Clinical Study Report Table JGDG.12.25 (p189), there were 5 (7.8%) patients in the olatumab plus doxorubicin arm who discontinued olatumab due to an adverse event. Provide a rationale for this discrepancy.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
09/19/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761038

INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) submission dated and received February 24, 2016, submitted under section 351(a) of the Public Health Service Act for Olaratumab, Injection for Intravenous Infusion.

We are reviewing your submission and have the following request for information. We request a prompt written response by August 18, 2016 in order to continue our evaluation of your application.

(b) (4)

BLA 761038

Page 2

If you have questions, call me, at (301) 796-0906.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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

Memorandum

Date: July 22, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Labeling Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

Please find attached FDA’s preliminary edits and comments to your revised package insert (PI) labeling submitted on May 6, 2016. Please provide a response via email correspondence **by 4 PM (EST) on Friday, August 5, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

In the areas of the label that you agree with FDA’s proposed edits, please accept the tracked change to aid in reviewability. For those edits that you do not agree with, provide justification as a comment (cite “From Eli Lilly” in the comment). For any edits you wish to propose, add via track changes and provide justification as a comment (cite “From Eli Lilly” in the comment). Lastly, when making edits to the label, please update formatting as necessary.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
07/22/2016



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

Memorandum

Date: July 22, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Proposed Post Marketing Commitments and Requirement

Eli Lilly and Company
 Attention: Jody Roth, M.S., P.M.P., R.A.C.
 Director, Global Regulatory Affairs – U.S.
 Lilly Corporate Center
 Drop Code 2543
 Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

We propose the following Post Marketing Commitments (PMCs) and Post Marketing Requirements (PMRs). Please note that additional PMR and PMC proposals may be forthcoming while your application is under review. Provide your agreement and your proposed scheduled milestone dates to the below proposal. We remind you to use due diligence in proposing timelines for completion of these trials. Please provide a response **by 4 PM (EST) on Friday, August 5, 2016, or sooner if possible.**

POST MARKETING REQUIREMENT

Clinical

1. 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 Date:	
Study/Clinical Trial Completion Date:	
Final Report Submission Date:	
Interim Report Submission Date:	

POST MARKETING COMMITMENT

Chemistry, Manufacturing and Controls

2.



PMR/PMC Schedule
Milestones:

Final Protocol Submission Date: _____
Study/Clinical Trial Completion Date: _____
Final Report Submission Date: _____

Chemistry, Manufacturing and Controls

3. 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.

PMR/PMC Schedule
Milestones:

Final Protocol Submission Date: _____
Study/Clinical Trial Completion Date: _____
Final Report Submission Date: _____

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
07/22/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761038

INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth, MS, PMP,
RAC Director, Global Regulatory
Affairs-US Lilly Corporate Center
Indianapolis, IN 46285

Dear Director Roth:

Please refer to your Biologics License Application 761040 received December 17, 2015, submitted under section 351(a) of the Public Health Service Act for Lartruvo (Olaratumab), Injection for Intravenous Infusion.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB: July 27, 2016 in order to continue our evaluation of your application.

1. Update BLA section 3.2.S.4, 3.2.S.7.2, 3.2.P.5 and 3.2.P.8.2 with the revised acceptance criteria for DS and DP release and stability specifications as per your counter-proposal (dated July 19, 2016) in response to FDA -IR dated July 14.
2. The Post-approval Stability Protocol and Stability Commitments sections (3.2.S.7.2 and 3.2.P.8.2) do not include information regarding the intention to submit data from the stability studies. Provide commitments to submit the data from all ongoing stability studies, including the leachable studies, and the data from annual stability lots in the BLA annual reports.

If you have any questions, please contact Melinda Bauerlien at 301-796-0906.

Sincerely,

Andrew
Shiber -S

Digitally signed by Andrew Shiber-S
DN: cn=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Andrew Shiber-S,
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Date: 2016.07.20 13:24:12 -0400

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



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

Memorandum

Date: July 18, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

The Clinical Reviewer has the following request for information. Please provide a response via email correspondence **by 4 PM (EST) on Wednesday, July 20, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Comments:

1. Please provide the definition used for important protocol deviations.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
07/18/2016



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

Memorandum

Date: July 15, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

The Clinical Reviewer has the following request for information. Please provide a response via email correspondence **by 4 PM (EST) on Wednesday, July 20, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Comments:

1. Please confirm the reason patient CP15-0806/015-1014 was randomized and did not receive study drug. Dataset states this patient was a screen failure for failure to meet eligibility criteria but was randomized.
2. Confirm the total number and individual patient numbers of patients who were screen failures and reason for screen failure in the phase 2 portion. CSR states (b) (4) screen failures, and there are (b) (4) listed as not meeting eligibility criteria, but (b) (4) patients are listed in datasets as screen failures. Also confirm if there were some patients with more than one reason for screen failure (e.g. failure to meet eligibility criteria and withdrawal of consent)

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
07/15/2016



BLA 761038

INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) submission dated and received February 24, 2016, submitted under section 351(a) of the Public Health Service Act for Olaratumab, Injection for Intravenous Infusion.

We are reviewing your submission and have the following request for information. We request a prompt written response by July 19, 2016 in order to continue our evaluation of your application.

Information Request

- Your proposed DS and DP release and stability criteria (b) (4)
(b) (4)
We
recommend tightening these acceptance criteria as per the table below:

	Test	Lilly's proposed acceptance criteria (%)	FDA recommended acceptance criteria (%)
Drug Substance Specifications	(b) (4)		
Drug Product specifications			

2. Provide assigned population doubling or generation number for the olaratumab master cell bank lot 05B00111 and working cell bank, lot 05B00159.

If you have questions, call me, at (301) 796-0906.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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

Memorandum

Date: July 11, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

The Clinical Reviewer has the following request for information. Please provide a response via email correspondence **by 12 PM (EST) on Friday, July 15, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Comments:

1. In Table JGDG.12.13 Exposure to Doxorubicin by Study Arm, verify if the relative dose intensity % are correct. There appears to be an error in dose calculations and therefore RDI for patients 002-1001 ((b) (4) % RDI) and 003-1009 ((b) (4) % RDI).
2. Provide narratives for the following patients:
 - a. 015-1005 with Grade 3 musculoskeletal chest pain
 - b. 010-1003 with Grade 3 pain in extremity
3. Across the nine studies used in the primary and secondary/supportive studies for safety, provide the following information in Table format for all patients who experienced a Grade 3 Musculoskeletal Pain using preferred terms arthralgia, back pain, bone pain, flank pain, groin pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.
 - a. USUBJID
 - b. Preferred term of AE musculoskeletal pain

- c. Narcotic use prior to adverse event of AE musculoskeletal pain
- d. Narcotic use for AE musculoskeletal pain
- e. Duration of AE musculoskeletal pain
- f. Hospitalization due to musculoskeletal pain
- g. Dose modifications due to AE musculoskeletal pain
- h. Discontinuations due to AE musculoskeletal pain
- a. Patient disposition at the time of AE musculoskeletal pain

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
07/11/2016



BLA 761038

INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) presubmission dated and received December 17, 2015, submitted under section 351(a) of the Public Health Service Act for Olaratumab, Injection for Intravenous Infusion.

We are reviewing your submission and have the following request for information. We request a prompt written response by July 11, 2016 in order to continue our evaluation of your application.

Module 3.2.S:

Section 3.2.S.2.5, Process Validation and/or Evaluation

1. Please provide the validation reports for [REDACTED] (b) (4) of olaratumab drug substance.
2. Please specify whether [REDACTED] (b) (4) of olaratumab drug substance and indicate [REDACTED] (b) (4).
3. Please describe the routine endotoxin testing [REDACTED] (b) (4)

Additionally, please address the following comments regarding your responses (dated 12 May 2016) to *Module 3.2.S* Questions 1b, 5, and 6 of the FDA Request for Information (dated 28 April 2016).

1. Please clarify whether [REDACTED] (b) (4)
[REDACTED] (b) (4)

2. Please submit to the BLA a QA-approved protocol for the commercial scale verification [REDACTED] (b) (4)

3. Please provide the report [REDACTED] (b) (4)

If you have questions, call me, at (301) 796-0906.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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

Memorandum

Date: July 1, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Labeling (Carton and Container) Review Comments and Information
Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

We have the following comments regarding your proposed container labels and carton labeling submitted on January 27, 2016. Please provide a response via email correspondence **by 4 PM (EST) on Tuesday, July 12, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Comments:

General

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals.
2. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

Carton Labeling and Container Label

3. Revise the statement [REDACTED] (b) (4) to read “Usual Dose: See prescribing information.”
4. 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. Additionally, [REDACTED] (b) (4)

[REDACTED] The instructions to dilute the product on the PDP are adequate for communicating what is required for safe use of the product [REDACTED] (b) (4)

5. 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.”

Container Label

6. Add the statement “Keep refrigerated” to the PDP underneath the statement “Discard unused portion,” similar to what is presented on the carton labeling PDP.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
07/01/2016



BLA 761038

MID-CYCLE COMMUNICATION

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for “olaratumab injection for intravenous use.”

We also refer to the teleconference between representatives of your firm and the FDA on June 1, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

MID-CYCLE COMMUNICATION

Meeting Date and Time: June 1, 2016

Application Number: BLA 761038
Product Name: olaratumab (proposed as LARTRUVO)
Indication: 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.

Applicant Name: Eli Lilly and Company

Meeting Chair: Marc Theoret
Meeting Recorder: Leah Her

FDA ATTENDEES

Amy McKee	Deputy Director (Acting), OHOP
Patricia Keegan	Director, OHOP/DOP2
Marc Theoret	Clinical Team Lead, OHOP/DOP2 & Cross Disciplinary Team Leader (CDTL)
Meredith Chuk	Clinical Reviewer, OHOP/DOP2
Leslie Doros	Clinical Reviewer, OHOP/DOP2
Monica Hughes	Chief, Project Management Staff, OHOP/DOP2
Leah Her	Regulatory Health Project Manager, OHOP/DOP2
Karen Hennessy	Safety Regulatory Healthy Project Manager, OHOP/DOP2
Whitney Helms	Nonclinical Supervisor, OHOP/DHOT
Emily Wearne	Nonclinical Reviewer, OHOP/DHOT
Rajeshwari Sridhara	Director, OB/DBV
Kun He	Statistical Team Lead, OB/DBV
Huanyu (Jade) Chen	Statistical Reviewer, OB/DBV
Rashmi Rawat	Product Quality Branch Chief, OPQ/OBP/DBRRII
Chikaka Torigoe	Product Quality Reviewer, OPQ/OBP/DBRRII
Ruby Leong	Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Fang Li	Pharmacometrics Reviewer, OTS/OCP/DPM
Lauren Iacono Connor	Interdisciplinary Scientist, OC/OSI/DCCE/GCPAB
Mei-Yean Chen	Medical Officer, OSE/OMEPRM/DRISK
Peter Waldron	Medical Officer, OSE/OPE/DPVII
Sarah Thomas	Medical Officer, OSE/OMEPRM/DMEPA
Latonia Ford	Safety Regulatory Project Manager, OSE/PMS
Sharon Mills	Patient Labeling Reviewer, OMP/OMPI/DMPP

EASTERN RESEARCH GROUP

Christopher Sese Independent Assessor

APPLICANT ATTENDEES

Richard Brian Gaynor	Senior Vice President Oncology – Clinical & Production Development – Medical Affairs
Symantha Ann Melemed	Olaratumab Product Team Leader
Patrick M. Peterson	Olaratumab Statistics Lead – Oncology
Jonathan Shane Denne	Vice President-MDU-Oncology
Jody Roth	Olaratumab Regulatory Lead, Global Regulatory Affairs
Allen S Melemed	Distinguished Medical Fellow & Senior Director North America Regulatory – Oncology Distinguished Medical Fellow
Robert Metcalf	Vice President Regulatory Affairs – North America
Stephen Knowles	Senior Director Global Patient Safety, Medical & Benefit-Risk Management
Ashwin Shahir	Medical Advisor, Global Patient Safety
Raffael Kurek	Global Patient Safety Medical – Senior Director
Marsha E. Millikan	Advisor – Global Patient Safety Expedited Reporting and Clinical Case Management
Ken Lipetz	Advisor – Global Patient Safety Medical and Medical and Benefit-Risk Management
Robert W. Baker	Vice President – Global Patient Safety
Robert L. ILaria, Jr.	Senior Medical Director, Olaratumab
ILaria Conti	Senior Medical Advisor, Olaratumab
Damien Cronier	Principal Research Scientist Global PK/PD & Pharmacometrics
Lawrence Carl Starke	Director Regulatory CMC
Vijayapal R. Reddy	Senior Research Advisor Non-Clinical Safety Assessment
Stephanie Robertson	Clinical Project Manager Associate

INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

SIGNIFICANT ISSUES

Clinical/Statistics

1. There are concerns regarding the robustness of the progression-free survival (PFS) results in addition to the small effect size in PFS relative to the observed effect size in overall

survival (OS). FDA is still reviewing PFS results using re-randomization test on the intent-to-treat population via different stratification factor combinations, asymmetric tumor assessment, and censoring rules.

Discussion: FDA stated that analyses of the PFS data are ongoing. FDA acknowledged that Eli Lilly has performed and provided results of various sensitivity analyses for PFS and stated that no additional information is needed at this time.

Nonclinical

2. A warning for embryofetal toxicity is likely to be added to the olaratumab label.

Discussion: Eli Lilly acknowledged FDA's comment. No discussion occurred.

Clinical Pharmacology

3. No significant issues have been identified to date.

Discussion: Eli Lilly acknowledged FDA's comment. No discussion occurred.

Chemistry, Manufacturing and Controls

4. No significant issues have been identified to date.

Discussion: Eli Lilly acknowledged FDA's comment. No discussion occurred.

PENDING INFORMATION REQUESTS

Clinical

5. As requested in the April 27, 2016, FDA request for information, and discussed at the April 29, 2016, teleconference, provide Lilly's plan for conducting an additional interim overall survival (OS) analysis in the intent-to-treat population in Study JGDJ at approximately 30% of planned total OS events for the final OS analysis.

Discussion: FDA acknowledged Eli Lilly's May 6, 2016, submission to the BLA wherein Eli Lilly provided a written summary of the verbal discussion that took place during the April 29, 2016, teleconference between FDA and Eli Lilly. FDA stated that Eli Lilly did not specify whether or not an additional interim OS analysis, as requested during the April 29, 2016, teleconference, will be conducted. FDA stressed the importance of the early interim analysis to provide additional information regarding the treatment effect of olaratumab on the overall survival of patients with advanced soft tissue sarcoma. (b) (4)

(b) (4). FDA clarified that the request for an earlier interim analysis of Trial JGDJ is to provide additional information regarding the treatment effect of olaratumab in order to benefit patients and the decision whether or not to continue the ongoing trial would be up to Eli Lilly. FDA also clarified that it would be possible to conduct and submit these results in a manner that would ensure Eli Lilly remains blinded to the results. Eli Lilly

expressed understanding and committed to submitting to BLA 761038 a written response to FDA's April 27, 2016, request, as discussed during the April 29, 2016, teleconference.

Clinical Pharmacology

6. On May 27, 2016, FDA provided clinical pharmacology review comments and information request which is due by June 3, 2016.

Discussion: Eli Lilly acknowledged FDA's comment. No discussion occurred.

Chemistry, Manufacturing and Controls

7. On May 18, 2016, FDA provided CMC review comments and information request which is due by June 7, 2016.

Discussion: Eli Lilly acknowledged FDA's comment. No discussion occurred.

MAJOR SAFETY CONCERNS/RISK MANAGEMENT

8. No unanticipated safety concerns have been identified at this point in the review and it is not expected that a REMS will be needed.

Discussion: Eli Lilly acknowledged FDA's comment. No discussion occurred.

ADVISORY COMMITTEE MEETING

9. There are no plans for an advisory committee meeting at this time; however, Special Government Employees (SGEs) with expertise in soft tissue sarcoma will be consulted during review of this application.

Discussion: Eli Lilly requested clarification on whether a decision on an advisory committee meeting could be made at a later time. FDA clarified that plans to obtain advice from individual SGEs during its review of the application but does not anticipate a need for an advisory committee.

LATE-CYCLE MEETING / OTHER PROJECTED MILESTONES

10. Late-Cycle Meeting with Applicant
 - a. Wednesday, September 7, 2016 / 12:00 – 1:00 PM (EST) via teleconference
 - b. Background package to the Applicant planned for Monday, September 5, 2016

Discussion: Eli Lilly acknowledged FDA's comment. No discussion occurred.

11. Proposed Labeling and Potential PMRs/PMCs to Applicant
 - a. Monday, September 26, 2016

Discussion: Eli Lilly acknowledged FDA's comment. No discussion occurred.

ADDITIONAL DISCUSSION

After discussion of the above agenda items, FDA inquired

(b) (4)

(b) (4)

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/s/

LEAH S HER
07/01/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761038

INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth
Director, Global Regulatory Affairs
Drop Code 2538
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated and received December 10, 2015, submitted under section 351(a) of the Public Health Service Act for Compound LY3012207 (Olaratumab).

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by June 28, 2016 in order to continue our evaluation of your BLA.

1. It is not clear whether [REDACTED] (b) (4)
[REDACTED] (b) (4)
2. It is not clear whether [REDACTED] (b) (4)
[REDACTED] (b) (4)

If you have any questions, please contact Melinda Bauerlien, Regulatory Business Process Manager, at (301) 796-0906 or Melinda.Bauerlien@fda.hhs.gov.

Sincerely,

Anita N.
Brown -S

Digitally signed by Anita N. Brown -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Anita N. Brown -S,
0.9.2342.19200300.100.1.1=2000546
085
Date: 2016.06.23 14:15:47 -04'00'

Anita Brown
Regulatory Business Process Manager
Offices of Process and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



BLA 761038

INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) presubmission dated and received December 17, 2015, submitted under section 351(a) of the Public Health Service Act for Olaratumab, Injection for Intravenous Infusion.

We are reviewing your submission and have the following request for information. We request a prompt written response by June 27, 2016 in order to continue our evaluation of your application.

1. In order to support your proposed dating period for the commercial drug product manufactured at Lilly, you may wish to provide a "simple stability update" which is defined as follows: Stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. This update will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA.
2. To evaluate the comparability of the DP manufactured at (b)(4) and Lilly DP facility, the stability data for the comparison of the degradation profiles between the (b)(4) and Lilly DP should be provided in graphical presentation depicting rate of change in the stability indicating attributes of the product over time under recommended, accelerated and stress storage conditions. Also include the 6 month stability testing data point in these analyses for (b)(4) and Lilly DP lots, if available.

3. [Redacted] (b)(4)

4. [Redacted] (b)(4)

(b) (4)

5.

(b) (4)

If you have questions, call me, at (301) 796-0906.

Sincerely,

Melinda J.
Bauerlien -S

Digitally signed by Melinda J. Bauerlien -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300178565,
cn=Melinda J. Bauerlien -S
Date: 2016.06.16 11:53:32 -04'00'

Melinda Bauerlien, M.S.

Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



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

Memorandum

Date: June 13, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

The Clinical Reviewer has the following request for information. Please provide a response via email correspondence **by 4 PM (EST) on Monday, June 20, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Comments:

1. Provide the following information for patients in the olaratumab plus doxorubicin arm and those that received olaratumab monotherapy after discontinuation of doxorubicin:
 - a. For each cycle of treatment, provide the total number of patients who experienced an adverse event consolidated term musculoskeletal pain and the grade (e.g., 29 patients in cycle 1 had an adverse event of musculoskeletal pain, 10 patients with Grade 1, 19 patients with Grade 2).
 - b. Provide a breakdown of the total number of patients who experienced recurrent musculoskeletal pain and the worst shift from baseline.
2. Provide a breakdown of the total number of patients administered premedication prior to any dose of olaratumab in the olaratumab plus doxorubicin arm and those that received olaratumab monotherapy after discontinuation of doxorubicin for the first two cycles of treatment, and the premedications that were administered. (e.g., On Cycle 1 Day 1, 40 of 64 patients in the olaratumab arm plus doxorubicin were given a premedication(s), 20 with an antihistamine, and 10 with an antihistamine and corticosteroid).

3. For patients who experienced any grade infusion-related reaction in the olaratumab plus doxorubicin arm and those that received olaratumab monotherapy after discontinuation of doxorubicin, provide the premedications that were administered to each patient prior to the infusion-related reaction or state that they did not receive any premedication.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
06/13/2016



BLA 761038

INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) presubmission dated and received December 17, 2015, submitted under section 351(a) of the Public Health Service Act for Olaratumab, Injection for Intravenous Infusion.

We are reviewing your submission and have the following request for information. We request a prompt written response by June 15, 2016 in order to continue our evaluation of your application.

Section 3.2.P.3.3, Description of the Manufacturing Process and Process Controls

Please move the description of the routing environmental monitoring program from **Section 3.2.A.1** to **Section 3.2.P.3.3**, Description of the Manufacturing Process and Process Controls.

Section 3.2.P.3.4, Control of Critical Steps and Intermediates

Please update **Section 3.2.P.3.4** of the BLA with the additional quality microbiology information provided in the amendment dated May 9, 2016 (sequence 0023) regarding (b) (4) the bioburden test method description.

Section 3.2.P.3.5, Process Validation and/or Evaluation

(b) (4)

Section 3.2.P.5.2, Analytical Procedures

(b) (4)

If you have questions, call me, at (301) 796-0906.

Sincerely,

Melinda J.
Bauerlien -S

Digitally signed by Melinda J. Bauerlien -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19290300.100.1.1=1300178565,
cn=Melinda J. Bauerlien -S
Date: 2016.06.08 08:22:15 -0400

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



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

Memorandum

Date: June 2, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

The Clinical Reviewer has the following request for information. Please provide a response via email correspondence **by 4 PM (EST) on Friday, June 3, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Clinical Comments:

1. In Table JGDG 12.22 Summary of Deaths under “Primary Cause” of death as “other”, provide the cause for the one patient in the investigational arm and the one patient in the control arm.
2. For patient 011-1006, provide additional supporting evidence for the attribution of death due to progressive disease and not pneumonia. In your April 12, 2016, response to question 7 of our April 6, 2016, information request, in which we requested justification for the attribution of progressive disease, you stated that the chest x-ray on (b) (6) showed a large left upper lobe mass as evidence of progressive disease in this patient. This reviewer was unable to confirm that this was not stable disease since a CT scan of the chest performed one day after the chest x-ray stated that the “dominant left upper lobe...without significant interval change”. A CT scan of the chest performed on (b) (6) showed a 7.4 cm left upper lobe mass.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
06/02/2016



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

Memorandum

Date: May 27, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Pharmacology Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

The Clinical Pharmacology Reviewer has the following request for information. Please provide a response via email correspondence **by 4 PM (EST) on Friday, June 3, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Clinical Pharmacology Comments:

1. Please provide an explanation of the discrepancy in events rate in the dataset (adttem.xpt) in Study JGDG for primary efficacy analysis and the datasets for population pharmacokinetics (PK)/ pharmacodynamics (PD) analysis.
2. Please specify in detail how the Cmin in Cycle 1 and Cavg values used for the exposure-response analyses were calculated. In addition, clarify if dose-reduction were accounted for in the calculations.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
05/27/2016



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

Memorandum

Date: May 27, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Post Mid-Cycle Communication Agenda

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act) for “olaratumab injection for intravenous use.”

Please find attached agenda for the Post Mid-Cycle Communication Meeting scheduled as a teleconference for **Wednesday, June 1, 2016 between 10:00 – 11:00 AM (EST)**. We are confirming the following teleconference number:

Teleconference No.:
Conference ID:

(b) (4)

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

- Post Mid-Cycle Communication Meeting Agenda

POST MID-CYCLE COMMUNICATION MEETING AGENDA

Meeting Date and Time: June 1, 2016 / 10:00 – 11:00 AM (EST)
Location: NA; teleconference

Application Number: BLA 761038
Applicant Name: Eli Lilly and Company
Product Name: olaratumab (proposed as LARTRUVO)
Proposed Indication: 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.

INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

SIGNIFICANT ISSUES

Clinical/Statistics

1. There are concerns regarding the robustness of the progression-free survival (PFS) results in addition to the small effect size in PFS relative to the observed effect size in overall survival (OS). FDA is still reviewing PFS results using re-randomization test on the intent-to-treat population via different stratification factor combinations, asymmetric tumor assessment, and censoring rules.

Nonclinical

2. A warning for embryofetal toxicity is likely to be added to the olaratumab label.

Clinical Pharmacology

3. No significant issues have been identified to date.

Chemistry, Manufacturing and Controls

4. No significant issues have been identified to date.

PENDING INFORMATION REQUESTS

Clinical

5. As requested in the April 27, 2016, FDA request for information, and discussed at the April 29, 2016, teleconference, provide Lilly's plan for conducting an additional interim overall survival (OS) analysis in the intent-to-treat population in Study JGDJ at approximately 30% of planned total OS events for the final OS analysis.

Clinical Pharmacology

6. On May 27, 2016, FDA provided clinical pharmacology review comments and information request which is due by June 3, 2016.

Chemistry, Manufacturing and Controls

7. On May 18, 2016, FDA provided CMC review comments and information request which is due by June 7, 2016.

MAJOR SAFETY CONCERNS/RISK MANAGEMENT

8. No unanticipated safety concerns have been identified at this point in the review and it is not expected that a REMS will be needed.

ADVISORY COMMITTEE MEETING

9. There are no plans for an advisory committee meeting at this time; however, Special Government Employees (SGEs) with expertise in soft tissue sarcoma will be consulted during review of this application.

LATE-CYCLE MEETING / OTHER PROJECTED MILESTONES

10. Late-Cycle Meeting with Applicant
 - a. Wednesday, September 7, 2016 / 12:00 – 1:00 PM (EST) via teleconference
 - b. Background package to the Applicant planned for Monday, September 5, 2016
11. Proposed Labeling and Potential PMRs/PMCs to Applicant
 - a. Monday, September 26, 2016

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/s/

LEAH S HER
05/27/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 29, 2016

Application Number: BLA 761038

Product Name: Olaratumab injection for intravenous infusion (proposed as Lartruvo)

Sponsor/Applicant Name: Eli Lilly and Company

Subject: Teleconference to discuss FDA's proposal for an additional interim analysis of Study JGDJ

FDA Participants

Patricia Keegan, M.D., Division Director, Division of Oncology Products 2

Marc Theoret, M.D., Clinical Team Leader

Meredith Chuk, M.D., Clinical Reviewer

Leslie Doros, M.D., Clinical Reviewer

Rajeshwari Sridhara, Ph.D., Division Director, Division of Biostatistics

Kun He, Ph.D., Statistics Team Leader

Hyanyu Chen, Ph.D., Statistics Reviewer

Ruth Maduro, Regulatory Project Manager

Sponsor/Applicant Participants

Byran Litton, MBA, Olaratumab Product Team Leader

Robert Ilaria, Jr., MD, Sr. Medical Director, Olaratumab

Ashwin Shahir, MD, Medical Advisor, Global Patient Safety

Ilaria Conti, MD, Senior Medical Advisor, Global Medical – Olaratumab

Allen Melemed, MD, Senior Director, Global Regulatory Affairs

Jon Denne, PhD, Senior Director, Statistics – Oncology

Patrick Peterson PhD, Olaratumab Statistics Lead - Oncology

Jian Chen, Olaratumab Statistics

Jody Roth, MS, RAC, Olaratumab Regulatory Lead, Global Regulatory Affairs

Kelley Fisher, Manager, Clinical Data Management

Stephanie Roberson- clinical project management;

Tracy Rausch – clinical project management

BACKGROUND:

This was a FDA-initiated meeting to discuss data submitted in support of pending Biologics License Application (BLA) 761038 received on February 24, 2016, for the proposed use of 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. In advance of this meeting, on April 26, 2016, FDA sent comments for discussion during the meeting. This communication is attached to this tcon memo.

DISCUSSION:

FDA requested a status update regarding the enrollment and overall survival (OS) events to date on Study JGDJ. (b) (4)

(b) (4)

FDA and Lilly discussed FDA's request for an additional interim analysis of Study JDGJ. (b) (4)

(b) (4)

(b) (4) FDA stated that because Study JGDG had a small sample size and a heterogeneous patient population there is uncertainty with regard to the magnitude of the treatment effect on survival; therefore an interim analysis for Study JDGJ may provide independent substantiation and a more accurate estimation of the magnitude of the treatment effect of olaratumab. FDA requested that Lilly submit the revised protocol and revised statistical analysis plan (SAP) to IND 121500 for FDA review.

Lilly stated that they would prepare a written proposal for the requested interim analysis and submit it to FDA by close-of business on Monday, May 2, 2016. FDA requested that Lilly also consider in their response the potential role of the DSMC in conducting this interim analysis. FDA and Lilly agreed that further discussion will occur in a teleconference already scheduled for Tuesday, May 3, 2016, following review of the written proposal.

Her, Leah

From: Maduro, Ruth
Sent: Tuesday, April 26, 2016 11:59 AM
To: roth_jody_l@lilly.com
Cc: Maduro, Ruth
Subject: Teleconference and Discussion points 4-29-2016 (BLA 761038)

Importance: High

Dear Ms. Roth –

As discussed in our telephone conversation of 4-22-2016, I have scheduled a Teleconference for **Friday, April 29, 2016, at 10:00am EST**. The teleconference is scheduled for 30-minutes (10:00am to 10:30am). Kindly ensure that Lilly’s statistical, clinical, dataset management, and other members that you may deem necessary, are available for the teleconference.

The below are provided as discussion points for the April 29, 2016, teleconference:

FDA requests that Eli Lilly conduct an interim OS analysis in the intent-to-treat population in Study JGDJ at approximately 30% of planned total OS events for the final OS analysis, in order to provide a more accurate estimation of the magnitude of the treatment effect on OS . The protocol and statistical analysis plan should be formally amended to include the plan for this additional interim analysis of OS, which should assess both futility and efficacy. Please note that Eli Lilly may choose alpha spending function other than O’Brien-Fleming, such as Pocock method or other method for this specific interim analysis.

FDA further requests that the proposed plan for this additional interim analysis be submitted to BLA 761038 for FDA for review and discussion at a teleconference prior to formally amending the clinical protocol and SAP.

Kindly provide a call-in number and passcode for the meeting (i.e. by **3:00pm on Thursday, March 28, 2016**), and ensure that members from Lilly’s clinical, statistical, and dataset management teams will be available for the meeting.

Kindly confirm receipt of this email communication.

Regards,
Ruth

Ruth Maduro

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: (240)402-4232

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/s/

LEAH S HER

05/25/2016

Due to RPM transition, this communication was generated by R. Maduro and uploaded by L. Her

Her, Leah

From: Her, Leah
Sent: Friday, May 06, 2016 7:58 AM
To: Jody L Roth
Cc: Maduro, Ruth
Subject: RE: Clinical comment and information request 5-5-2016 #2 (BLA 761038)

Hi Jody,

Please see clarification below in blue and let me know if you have any additional questions.

Kindly confirm receipt.

Thank you,
Leah

Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

From: Jody L Roth [mailto:roth_jody_l@lilly.com]
Sent: Thursday, May 05, 2016 4:27 PM
To: Maduro, Ruth
Cc: Her, Leah
Subject: RE: Clinical comment and information request 5-5-2016 #2 (BLA 761038)

Dear Ruth,

Lilly has reviewed the questions you have asked for our response by Tuesday. We have a few clarifying questions before we can provide FDA with a response. We would like to be sure we are addressing your questions accurately. Thanks in advance for passing this along to the clinical reviewers.

Could FDA please clarify question 2, what patients were you specifically referencing with the wording “*following patients*” in question 2?

Question 2: Please provide rationale for not including the **following patients** in the listing of ToSNP 5.3.5.3 for patients who completed control arm chemo and elected not to receive olaratumab as the reason listed in DSTHRS1D is completed therapy.

The “following patients” refers to patients:

- a. CP15-0806/002-1006
- b. CP15-0806/003-1001
- c. CP15-0806/003-1012

The reason for end of therapy for these patients on the control arm (DSTHRS1D) is completed therapy, but they are not listed in the referenced table.

Could FDA please clarify question #4, what is specific information you are looking for under the term “treatment disposition”?

Question 4: Provide a line listing of all of the patients who were censored by central review that includes patient ID, treatment arm, site, **treatment disposition**, and the reasons for censoring.

“Treatment disposition” refers to patient disposition at the end of study treatment as per Table 10.2 of the CSR.

Regards,

Jody

Jody Roth, RAC, PMP
Advisor, Global Regulatory Affairs – Oncology
Eli Lilly and Company

Office: 317-277-6016

Mobile: (b) (6)

Fax: 317-276-1652

Email: roth_jody_l@lilly.com | Web: <http://www.lilly.com>

From: Maduro, Ruth [<mailto:Ruth.Maduro@fda.hhs.gov>]
Sent: Thursday, May 05, 2016 3:09 PM
To: Jody L Roth
Cc: Her, Leah
Subject: Clinical comment and information request 5-5-2016 #2 (BLA 761038)
Importance: High

Dear Jody –

In addition to the Clinical comment and information request forwarded to you earlier today (5-5-2016) at 2:42pm, please find the attached Clinical comments and information requests #2, dated 5-5-2016 for BLA 761038.

Provide an electronic response to the above comment and requested information to Ruth.Maduro@fda.hhs.gov and Leah.Her@fda.hhs.gov by **3:00pm EST on Tuesday, May 10, 2016**, or sooner if possible. Please follow with a formal amendment submission to BLA 761038.

Kindly confirm receipt of this communication and attached Clinical information requests #2.

Regards,
Ruth

From: Jody L Roth [mailto:roth_jody_l@lilly.com]
Sent: Thursday, May 05, 2016 3:02 PM
To: Maduro, Ruth
Cc: Her, Leah
Subject: RE: Clinical comment and information request 5-5-2016 (BLA 761038)

Dear Ruth

I have received the incoming requests. We will work to get you a response by 3pm tomorrow.

Thanks
Jody

Regards,
Jody Roth, RAC, PMP
Advisor, Global Regulatory Affairs – Oncology
Eli Lilly and Company

Office: 317-277-6016

Mobile: (b) (6)

Fax: 317-276-1652

Email: roth.jody.l@lilly.com | Web: <http://www.lilly.com>

From: Maduro, Ruth [<mailto:Ruth.Maduro@fda.hhs.gov>]
Sent: Thursday, May 05, 2016 2:42 PM
To: Jody L Roth
Cc: Maduro, Ruth; Her, Leah
Subject: Clinical comment and information request 5-5-2016 (BLA 761038)
Importance: High

Dear Jody –

Please find the attached clinical comment and information request, dated 5-5-2016, for BLA 761038.

Provide an electronic response to the above comment and requested information to Ruth.Maduro@fda.hhs.gov and Leah.Her@fda.hhs.gov by **3:00pm EST on Friday, May 6, 2016**, or sooner if possible. Please follow with a formal amendment submission to BLA 761038.

Kindly confirm receipt of this communication and attached Clinical information request.

Regards,
Ruth

Ruth Maduro

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: (240)402-4232

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/s/

LEAH S HER
05/24/2016



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

Memorandum

Date: May 23, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: BLA 761038 – Eli Lilly and Company
Statistical Review Comments and Information Request

Eli Lilly and Company
 Attention: Jody Roth, M.S., P.M.P., R.A.C.
 Director, Global Regulatory Affairs – U.S.
 Lilly Corporate Center
 Drop Code 2543
 Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

The Statistical Reviewer has the following request for information. Please provide a response via email correspondence **by 4 PM (EST) on Tuesday, May 31, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Comments:

- The re-randomization calculations provided to the BLA on April 1, 2016 in response to comment 4 of the FDA’s March 25, 2016, information request were conducted on the mITT population using a pre-specified randomization seed. Please provide a summary of results based on the combination of the listed stratification factors and randomly assigned randomization seeds.

Population	Endpoint	Stratification Factors Records				P value
		PDGFR alpha	ECOG	# line of therapy	Histology	
ITT	BIRC PFS	IVRS	IVRS	IVRS	IVRS	
		N/A	N/A	IVRS	CRF	
		N/A	N/A	CRF	Path	
	INV PFS	IVRS	IVRS	IVRS	IVRS	
		N/A	N/A	IVRS	CRF	
		N/A	N/A	CRF	Path	
	Final OS	IVRS	IVRS	IVRS	IVRS	
		N/A	N/A	IVRS	CRF	
		N/A	N/A	CRF	Path	

2. Provide a summary of interim analyses for PFS and OS on the ITT population. The April 1, 2016 submission to the BLA containing responses to FDA’s March 25, 2016, information request, and the May 17, 2016 emailed response to FDA’s May 17, 2016, information request, did not include this information. In addition, provide the final alpha for OS analysis using O’Brien-Fleming boundaries, adjusted for the actually conducted OS interim analyses (at interim PFS and final PFS analyses and any unreported OS interim analysis).

Table 4.1. Interim Analysis of Efficacy Study JGDG

Cut-off Date	Total number of events ^a		HR (95% CI) ^a		P-value ^a	
	PFS	OS	PFS	OS	PFS	OS
31 July 2013	94	55	0.597 (0.387, 0.920)	0.460 (0.263, 0.804)	0.0184	0.0052

Abbreviations: CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; OS = overall survival.

a. Based on the randomized and treated population (modified intent-to-treat).

3. Provide the following SAS programs: %subgroup3, aasetupkg.sas, and aasetup2.sas
4. Provide the location of the following data and variables: CMGRP, disgrp, and aldrp

If these have not been submitted, please provide related data, program(s), and reviewer’s guide on how to derive 1) duration of disease and 2) duration of most recent prior systemic treatment as provided on Slide 19 in the March 14, 2016, Application Orientation Meeting.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
05/23/2016



BLA 761038

INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) presubmission dated and received December 17, 2015, submitted under section 351(a) of the Public Health Service Act for Olaratumab, Injection for Intravenous Infusion.

We are reviewing your submission and have the following request for information. We request a prompt written response by June 7, 2016 in order to continue our evaluation of your application.

S.2.2

1. To support the licensure of olaratumab manufacturing process, include the following process parameters and the operating ranges or control limits supported by data in the BLA and update section S.2.2 and S.2.4 with this information.

(b) (4)

2. The information provided on MCB and WCB stability protocol is not sufficient to assess the adequacy of the MCB and WCB stability. Provide information on, but not limited to,

(b) (4)

S.2.5. Process Validation and/or Evaluation

3. Provide an extractable / leachable risk assessment

(b) (4)

18. We note that in the validation of [REDACTED] (b) (4) the assay ranges exceed the linearity ranges. Provide justification for the proposed assay ranges for these assays.

Drug Product

19. Provide information on the age of the drug product lots used in the clinical studies.

If you have questions, call me, at (301) 796-0906.

Sincerely,

Melinda J.
Bauerlien -S

Digitally signed by Melinda J.
Bauerlien -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300178
565, cn=Melinda J. Bauerlien -S
Date: 2016.05.18 15:11:32 -04'00'

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



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

Memorandum

Date: May 17, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

The Clinical Reviewer has the following request for information. Please provide a response via email correspondence **by 12 PM (EST) on Thursday, May 19, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Clinical Comments:

1. Please confirm if patient CP15-0806/008-1007 had any first line therapy as only second line therapy is listed.
2. Confirm the reason for discontinuation of olaratumab for patient I5B-IE-JGDG-008-1001 Olaratumab + Doxorubicin. The narrative states that “the patient was discontinued from study drug treatment on [REDACTED] (b) (6) due to an AE of left ventricular systolic dysfunction”; however, the narrative states that the echo which showed a Gr 2 AE of LV dysfunction (53% from baseline 64%) was [REDACTED] (b) (6), 14 days after the final dose of doxorubicin, and that the patient received the last dose of olaratumab on [REDACTED] (b) (6). The CRF also states that study therapy was discontinued for LV dysfunction but that no action was taken with olaratumab as a result of this AE.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
05/17/2016



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

Memorandum

Date: May 13, 2016

From: Leah S. Her, Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Review Comments and Information Request

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act for “olaratumab injection for intravenous use.”

The Clinical Reviewer has the following request for information. Please provide a response via email correspondence **by 4 PM (EST) on Tuesday, May 17, 2016 or sooner if possible**, and follow with a formal submission to the BLA.

Clinical Comment:

1. Provide narratives for the following patients:
 - a. 001-1008: pleural effusion Grade 3
 - b. 002-1009: enterocolitis Grade 3
 - c. 004-1007: gastrointestinal hemorrhage and upper gastrointestinal hemorrhage

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

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/s/

LEAH S HER
05/13/2016



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

Memorandum

Date: May 10, 2016
From: Claire Myers, Ph.D., DOP2/OHOP/CDER
Subject: BLA 761038 Information Request

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for “Olaratumab, Injection for Intravenous Infusion.”

Please respond to the following Clinical information request via email to Leah.Her@fda.hhs.gov (copying Claire.Myers@fda.hhs.gov), followed by a formal submission to your BLA.

Response due: Noon Eastern Time on Thursday, **May 12, 2016**

1. For Table JGDG 12.28, provide the USUBJID for the following:
 - a. Pts with AE Leading to Modification of olaratumab
 - b. ...of olaratumab only
 - c. AE related to olaratumab only leading to modification of olaratumab
 - d. AE related to doxorubicin only leading to modification of olaratumab
 - e. AE related to both olaratumab and doxorubicin leading to modification of olaratumab
2. Provide the USUBJID for the all the patients in the Investigational Arm who received dexrazoxane
3. For Table JGDG 12.32, provide the USUBJID for the following:
 - a. Patients who received antihistamines, corticosteroids and other treatment for Phase 1b, Phase 2 Investigational Arm, Phase 2 Control Arm: olaratumab monotherapy.
 - b. Provide the name of the Other Treatments each patient received

4. For Table JGDG 12.33, provide the USUBJID for the following:
 - a. Patients who were redosed after first IRR for Phase 1b, Phase 2 Investigational Arm, Phase 2 Control Arm: olaratumab monotherapy
 - b. IRR upon rechallenge for Phase 1b, Phase 2 Investigational Arm, Phase 2 Control Arm: olaratumab monotherapy
5. Provide the USUBJID for the patients in the Investigational Arm who went on to receive monotherapy with olaratumab and experienced the preferred term musculoskeletal pain.

Please confirm receipt.

Thanks,
Claire

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

CLAIRE E MYERS
05/10/2016



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

Memorandum

Date: May 5, 2016
From: Ruth Maduro, Regulatory Health Project Manager-CDER/OHOP/DOP2
Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Comment and Information Request

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for “Olaratumab, Injection for Intravenous Infusion.”

The Clinical reviewer has the following comment and request for information:

Clinical

1. For the row Lowest Post-Baseline in Table JGDG 12.35 Summary of Abnormal LVEF, provide the USUBJID for the 6 patients in the investigational arm and the 3 patients in the control arm that had EF <50%.

Provide an electronic response to the above comment and requested information to Ruth.Maduro@fda.hhs.gov and Leah.Her@fda.hhs.gov by **3:00pm EST on Friday, May 6, 2016**, or sooner if possible. Please follow with a formal amendment submission to BLA 761038.

If you have any questions, please feel free to contact me at Ruth.Maduro@fda.hhs.gov (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RUTH L MADURO
05/05/2016



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

Memorandum

Date: May 5, 2016
From: Ruth Maduro, Regulatory Health Project Manager-CDER/OHOP/DOP2
Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Comments and Information Requests #2

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for “Olaratumab, Injection for Intravenous Infusion.”

The Clinical reviewer has the following comments and requests for information:

Clinical

1. Please provide the status of the following patients who do not have a last survival follow up status
 - a. CP15-0806/003-1012
 - b. CP15-0806/004-1003
 - c. CP15-0806/005-1009
 - d. CP15-0806/003-1014
2. Please provide rationale for not including the following patients in the listing of ToSNP 5.3.5.3 for patients who completed control arm chemo and elected not to receive olaratumab as the reason listed in DSTHRS1D is completed therapy.
3. Provide a by-patient listing of discordant PFS response assessments between the investigator and blinded independent central review.
4. Provide a line listing of all of the patients who were censored by central review that includes patient ID, treatment arm, site, treatment disposition, and the reasons for censoring.

5. Provide a listing of the cases and diagnosis by each reviewer and the adjudicator for which reviewer #1 and #2 did not agree and for which adjudication was required for the pathology report review process.
6. Provide justification for not counting patient CP15-0806/010-1005 on the control arm with chondroblastic osteosarcoma as having had a protocol violation for ineligible histology.
7. Please explain the following protocol deviations included in the DV.xpt
 - a. The pharmacy is missing temp-logs to confirm 'fit for use' of IP after shipping: 2/24/11 5/4/11 6/15/11 8/17/11 8/31/11 9/21/11.
 - b. The site has approximately 324 PK samples stored in the (b) (4) refrigerator that have not been shipped. Many of these samples date back to 2011 and 2012. No samples for subject 004 and 015 have been shipped.

Provide an electronic response to the above comments and requested information to Ruth.Maduro@fda.hhs.gov and Leah.Her@fda.hhs.gov by **3:00pm EST on Tuesday, May 10, 2016**, or sooner if possible. Please follow with a formal amendment submission to BLA 761038.

If you have any questions, please feel free to contact me at Ruth.Maduro@fda.hhs.gov (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RUTH L MADURO
05/05/2016



BLA 761038

INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) presubmission dated and received December 17, 2015, submitted under section 351(a) of the Public Health Service Act for Olaratumab, Injection for Intravenous Infusion.

We are reviewing your submission and have the following request for information. We request a prompt written response by May 9, 2016 in order to continue our evaluation of your application.

Section 3.2.P.2.6, Compatibility

[Redacted] (b) (4)

Section 3.2.P.3.3, Description of the Manufacturing Process and Process Controls

[Redacted] (b) (4)

Please update ***Section 3.2.P.3.3*** with the following information:

- [Redacted] (b) (4)
- [Redacted]

Section 3.2.P.3.4, Control of Critical Steps and Intermediates

1) [Redacted] (b) (4)

- b. Please justify the use of three clinical lots instead of commercial lots for BET method verification.
2. (b) (4)
Please explain how such standardization was performed.

Section 3.2.P.5.6, Justification of Specifications

Please provide a detailed endotoxin limit calculation for the drug product and justification for the drug product endotoxin specification. Justification should be based on the maximum proposed commercial dose for the drug product (15 mg/kg) and consider the impact of endotoxin from the diluent. In addition, a minimum 2-fold safety factor based on the maximum tolerance limit allowed by USP is recommended.

If you have questions, call me, at (301) 796-0906.

Sincerely,

Melinda J.
Bauerlien -S

Digitally signed by Melinda J.
Bauerlien -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130017
8565, cn=Melinda J. Bauerlien -S
Date: 2016.05.02 09:24:49 -04'00'

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



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

Memorandum

Date: April 29, 2016
From: Ruth Maduro, Regulatory Health Project Manager-CDER/OHOP/DOP2
Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Comments and Information Requests

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for “Olaratumab, Injection for Intravenous Infusion.”

The Clinical reviewer has the following comments and requests for information:

Clinical

1. Provide the USUBJID for the 8 patients in the Investigational Arm and the 12 patients in the Control arm that make up Table JGDG 12.25 Adverse Events Leading to Discontinuation of Study Therapy. There is a discrepancy between these numbers and the list of patients in the Integrated Summary of Safety Table 3.1 Listing of Significant Notable Patients Safety Population Discontinuation due to Adverse Event which list 5 patients in the Investigational Arm and 13 patients in the Control Arm. Provide a rationale for this discrepancy.
2. Provide a table for the subjects in Tables 12.26 and Table 12.27 that includes each subject’s USUBJID for the rows dose delay, dose reduced, dose held and infusion interrupted. For the subjects in the Investigational arm, state whether olaratumab or doxorubicin was held or both drugs. Provide a rationale for the modification.

Provide an electronic response to the above comments and requested information to Ruth.Maduro@fda.hhs.gov by **3:00pm EST on Tuesday, May 3, 2016**, or sooner if possible. Please follow with a formal amendment submission to BLA 761038.

BLA 761038 – Eli Lilly and Company
Clinical IR – 4/29/2016

If you have any questions, please feel free to contact me at Ruth.Maduro@fda.hhs.gov
(240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RUTH L MADURO
04/29/2016



BLA 761038

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Eli Lilly and Company
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

ATTENTION: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated and received February 24, 2016, submitted under section 351(a) of the Public Health Service Act, for Olaratumab, 10 mg/mL.

We acknowledge receipt of your correspondence, dated and received February 24, 2016, requesting a review of your proposed proprietary name, Lartruvo.

We have completed our review of the proposed proprietary name, Lartruvo and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your February 24, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Ruth Madura, Regulatory Project Manager, in the Office of New Drugs at (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
04/28/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761038

INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) presubmission dated and received December 17, 2015, submitted under section 351(a) of the Public Health Service Act for Olaratumab, Injection for Intravenous Infusion.

We are reviewing your submission and have the following request for information. We request a prompt written response by May 12, 2016 in order to continue our evaluation of your application.

FDA Information Request:



(b) (4)

If you have questions, call me, at (301) 796-0906.

Sincerely,

**Melinda J.
Bauerlien -S**

Digitally signed by Melinda J. Bauerlien -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300178565,
cn=Melinda J. Bauerlien -S
Date: 2016.04.28 11:43:55 -0400'

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



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

Memorandum

Date: April 27, 2016
From: Ruth Maduro, Regulatory Health Project Manager-CDER/OHOP/DOP2
Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Comments and Information Requests

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for “Olaratumab, Injection for Intravenous Infusion.”

The Clinical reviewer has the following comments and requests for information:

Clinical

1. For the following PTs, provide a table that includes USUBJID, AEDOCOD, AETOXGR, start and stop date of the event:
 - a. Alopecia: control arm only
 - b. Diarrhea: investigational arm only
 - c. Cardiac dysfunction: investigation and control arm
2. In the Control Arm, patient 012-1013 had Grade 4 hypokalemia. In table 12.16 there is no patient listed under Grade 4 with the PT hypokalemia in the Control Arm. Provide a rationale for this discrepancy.

Provide an electronic response to the above comments and requested information to Ruth.Maduro@fda.hhs.gov by **3:00pm EST on Friday, April 29, 2016**, or sooner if possible. Please follow with a formal amendment submission to BLA 761038.

BLA 761038 – Eli Lilly and Company
Clinical IR – 4/27/2016

If you have any questions, please feel free to contact me at Ruth.Maduro@fda.hhs.gov
(240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RUTH L MADURO
04/27/2016



BLA 761038

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, received February 24, 2016, submitted under section 351(a) of the Public Health Service Act for olaratumab, injection for intravenous use.

We also refer to your Rolling Review presubmissions received on December 10, and 17, 2015, January 18, and 27, 2016, and your subsequent amendments submitted on February 11, 19, 22, and 29, 2016, March 4, 10, 11, and 23, 2016, April 1, 7, 12, 15, and 18, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is October 24, 2016. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 26, 2016

In addition, the planned date for our internal mid-cycle review meeting is May 20, 2016. We are currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. Address the issues in the attached, annotated label.
2. In the Highlights section, 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.
3. In the Initial U.S. Approval in Highlights, Initial U.S. Approval must be bolded, and include the verbatim statement “Initial U.S. Approval:” followed by the 4-digit year.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by May 7, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the PI and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Ruth Maduro, Regulatory Health Project Manager, at (240) 402-4232.

Sincerely,

{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

ENCLOSURE:
Content of Labeling

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

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/s/

PATRICIA KEEGAN
04/22/2016



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

Memorandum

Date: April 18, 2016
From: Ruth Maduro, Regulatory Health Project Manager-CDER/OHOP/DOP2
Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Comments and Information Requests

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for “Olaratumab, Injection for Intravenous Infusion.”

The Clinical reviewer has the following comments and requests for information:

Clinical

1. For the AE term dry mouth for the Control Arm only, provide each of the six patients who experienced Dry Mouth by USUBJID, AEDECOD, AETOXGR.
2. For the preferred term rash pustular, patient 012-1027 is counted in AE term Infection/Infestations and rash. Please confirm this finding and provide rationale for counting this patient in both AE terms of Infection/Infestations and Rash.
3. Investigational Arm patient 017-1001 was included under PT lymphocyte count decreased under AE lymphopenia. This patient’s AESTDTC was 06/12/13 and TR01EDT was 05/08/13. It appears that this AE occurred beyond the 30 days after date of dc therapy (05/8/13). Please confirm this finding and provide rationale for including this AE as a treatment-emergent AE.
4. Clarify if the following AEs were included in the Summary of Treatment-Emergent Adverse Events (Any Grade) Occurring in $\geq 10\%$ of Patients. If they have not been included, provide a rationale.
 - a. Control Arm patient 008-1003 with PT arthralgia Grade 1 under AE Musculoskeletal Pain
 - b. Control Arm patient 012-1019 with PT stomatitis Grade 1 under AE Mucositis

- c. Control Arm patient 010-1005 with PT urinary tract infection Grade 2 under AE infections and infestations
- d. Control Arm patient 002-1009 with PT dermatitis acneiform Grade 1 under AE Rash

Provide an electronic response to the above comments and requested information to Ruth.Maduro@fda.hhs.gov by **3:00pm EST on Wednesday, April 20, 2016**, or sooner if possible. Please follow with a formal amendment submission to BLA 761038.

If you have any questions, please feel free to contact me at Ruth.Maduro@fda.hhs.gov (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RUTH L MADURO
04/18/2016

From: [Maduro, Ruth](#)
To: [Jody L Roth](#)
Cc: [David A Rhein](#); [Maduro, Ruth](#)
Subject: Request for information (BLA 761038)
Date: Monday, April 11, 2016 4:24:44 PM
Importance: High

Dear Jody –

In addition to your 3-18-2016 below response, we have the following request:

1. Please provide the ECG core lab name, method used to measure ECGs (manual, semi-automatic, automatic), and what ECG readers were blinded to for Study I5B-EW-JGDI. Please submit the all related ECG waveform files with annotations to the ECG Warehouse at: www.ecgwarehouse.com.

Kindly complete as soon as possible (i.e. by 3:00pm EST Tuesday, April 12, 2016) and return to me via Ruth.Maduro@fda.hhs.gov. Please follow with a formal submission to BLA 761038. Kindly confirm receipt of this email communication.

Regards,
Ruth

From: Maduro, Ruth
Sent: Friday, March 18, 2016 2:57 PM
To: Jody L Roth
Cc: David A Rhein; Maduro, Ruth
Subject: RE: Request for completion of attached form (Highlights of Clinical Pharmacology and Cardiac Safety) BLA 761038

Dear Jody –

I am in receipt of your below response (with attachment) of 3-18-2016 at 1:29pm.. I have forwarded your response to the respective reviewer(s), and I will inform you if additional information is needed.

Thank you for your courtesy update, as I will work alongside David in your absence.

Regards,
Ruth

From: Jody L Roth [mailto:roth_jody_l@lilly.com]
Sent: Friday, March 18, 2016 1:29 PM
To: Maduro, Ruth
Cc: David A Rhein
Subject: RE: Request for completion of attached form (Highlights of Clinical Pharmacology and Cardiac Safety) BLA 761038

Dear Ruth,

Lilly is enclosing the response to FDA's request for information from March 15, 2016. We have attached a word version and will proceed to have a subsequent submission of this document to the

BLA next week.

Please let us know if you have any questions. I will be away from the office on Monday and Tuesday, please continue to copy both David and I on emails. David will take point for me on Monday and Tuesday, as I will have intermittent email access.

Regards,
Jody

*Jody Roth, RAC, PMP
Advisor, Global Regulatory Affairs – Oncology
Eli Lilly and Company*

Office: 317-277-6016

Mobile: (b) (6)

Fax: 317-276-1652

Email: roth.jody.l@lilly.com | Web: <http://www.lilly.com>

From: Maduro, Ruth [<mailto:Ruth.Maduro@fda.hhs.gov>]

Sent: Tuesday, March 15, 2016 4:09 PM

To: Jody L Roth

Cc: David A Rhein; Maduro, Ruth

Subject: Request for completion of attached form (Highlights of Clinical Pharmacology and Cardiac Safety) BLA 761038

Importance: High

Dear Jody –

Please find the attached form (Highlights of Clinical Pharmacology and Cardiac Safety) for completion. Kindly complete as soon as possible (i.e. by **3:00pm EST Friday, March 18, 2016**) and return to me via Ruth.Maduro@fda.hhs.gov. Please forward as MS Word version.

Please follow with a formal submission to BLA 761038.

Kindly confirm receipt of this email communication.

Regards,
Ruth

Ruth Maduro

Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Phone: (240)402-4232

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/s/

RUTH L MADURO
04/12/2016



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

Memorandum

Date: April 8, 2016
From: Ruth Maduro, Regulatory Health Project Manager-CDER/OHOP/DOP2
Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Comment and Information Request

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for “Olaratumab, Injection for Intravenous Infusion.”

The Clinical reviewer has the following comment and request for information:

Clinical

1. For Table 2.7.4.9 provide a by patient breakdown for each of the following AE terms for the Investigational Arm and Control Arm for both Any Grade and Grade ≥ 3 . This should include each patient’s USUBJID, TRT01AD, AEDECOD and AETOXGR. As an example for the AE term fatigue, provide a table of all 44 patients in the investigational arm and all 45 patients in the Control arm using their USUBJID and include the PT (fatigue or asthenia) used for each patient (AEDECOD) and the accompanying AETOXGR.
 - a. Fatigue
 - b. Musculoskeletal Pain
 - c. Neutropenia
 - d. Mucositis
 - e. Infections and Infestations
 - f. Thrombocytopenia
 - g. Headache
 - h. Lymphopenia
 - i. Rash

Provide an electronic response to the above comment and requested information to Ruth.Maduro@fda.hhs.gov by **5:00pm EST on Wednesday, April 13, 2016**, or sooner if possible. Please follow with a formal amendment submission to BLA 761038.

BLA 761038 – Eli Lilly and Company
Clinical IR – 4/8/2016

If you have any questions, please feel free to contact me at Ruth.Maduro@fda.hhs.gov
(240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RUTH L MADURO
04/08/2016

From: [Maduro, Ruth](#)
To: roth_jody_l@lilly.com
Cc: [David A Rhein \(david.rhein@lilly.com\)](#); [Maduro, Ruth](#)
Subject: Clinical comments for 4-7-2016 teleconference (BLA 761038)
Date: Wednesday, April 06, 2016 4:57:36 PM
Attachments: [image004.png](#)
[image003.png](#)
[image007.png](#)
Importance: High

Dear Jody –

Please see the below comments from the clinical team for the 4-7-2016 Teleconference

- 1 In the annotated CRF under code AEACN (Action Taken with Study Treatment) it is unclear what “delayed/modified” means in regards to study drug (IMC-3G3) and chemotherapy (doxorubicin or dexrazoxane) Provide an explanation as to whether the drug was either delayed or was modified, and what the modification was Table 2 7 4 18 page 53 of the summary of clinical safety does not provide details
- 2 There are several date inconsistencies for the DSTERM “death” in DS and AE data sets (see example below) Clarify if the DSSTDTC end of treatment is the last day of treatment and the reason for this is “death” and the end of study and AE “death” represents the actual date of death

(b) (4)

- 3 There are 18 records in the AE domain that have no seriousness qualifiers set to ‘Y’ when AE is serious (AESER = ‘Y’) Please provide the reasons that these were considered serious events (e.g. life-threatening, hospitalization, disability, congenital anomaly, required intervention, or “other” serious event)
- 4 Please verify that AEs that occurred on the day of crossover were counted in the crossover group
- 5 There are several discrepancies within the TEAE tables in regards to the use of preferred terms in Table 2 7 4 9 Summary of Treatment Emergent Adverse Events (any Grade) Occurring in $\geq 10\%$ of patients, with corresponding Grade ≥ 3 Incidence on page 36 of the summary of clinical safety and Table JGDG 12 15 Summary of Overall TEAEs and Consolidated TEAE Categories Occurring in $\geq 10\%$ of Patients page 171 of the Clinical Study Report Body
 - a The AE fatigue included the PT fatigue and asthenia It does not appear that the PT asthenia was used to determine the total subjects in both the investigational arm and control arm Verify and revise the table
 - b The AE term neutropenia used four PTs: neutropenia, low neutrophil count, leukopenia and white blood cell decreased However, the terms leukopenia and white blood cell count decreased are different from neutropenia and low neutrophil count Those two terms should be removed from the total number of patients experiencing neutropenia in the table
 - c Toxicity Grade is missing for alopecia on patient 003-1004 Please confirm the grade and add this subject to the table
 - d The AE term Neuropathy has 4 PTs It does not appear that the PT hypoesthesia was counted to determine the total number of patients Please verify and update the table
 - e For the AEs dry eye and dry mouth, there are no subjects in the Control Arm with these AEs Verify that this is accurate as it does not agree with our analysis
 - f Verify which PTs for musculoskeletal terms were used to define the total number of patients
- 6 There are several discrepancies in Table JGDG 12 16 Summary of Overall TEAEs and Consolidated TEAE Categories (Grade 3 and Grade ≥ 4 , Including AESI) on page 173 of the Clinical Study Report Body and in Table 2 7 4 9 Summary of Treatment Emergent Adverse Events (any Grade) Occurring in $\geq 10\%$ of patients, with corresponding Grade ≥ 3 Incidence on page 36 of the summary of clinical safety
 - a The AE term neutropenia included four PTs: neutropenia, low neutrophil count, leukopenia and white blood cell decreased However, leukopenia and white blood cell count decreased are different from neutropenia and low neutrophil count and those should be removed from the total number of patients
 - b The AE fatigue included the PTs fatigue and asthenia It does not appear that the PT asthenia was used to determine the total number in the Grade 3 category Verify and revise
 - c The AE term musculoskeletal pain used different PT terms in the two tables If you use all the PTs from table 2 7 4 9, then the total number in Table JGDG 12 16 for the Investigational Arm will increase by 2 subjects if you include the PT term for pain in extremity
- 7 Please provide additional justification for the attribution of death due to progressive disease for the following patient:
 - a 011-1006: death is attributed to progressive disease with pneumonia as a confounding factor The CT scan for this patient showed diffuse pneumonia and stable lung disease

Provide an electronic response to the above comments and requested information to Ruth.Maduro@fda.hhs.gov by **9:00am EST on Thursday, April 7, 2016**, or sooner if possible Please follow with a formal amendment submission to BLA 761038

If you have any questions, please feel free to contact me at Ruth.Maduro@fda.hhs.gov
(240) 402-4232

Regards,
Ruth

Ruth Maduro
Regulatory Health Project Manager

Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: (240)402-4232

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/s/

RUTH L MADURO
04/08/2016



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

Memorandum

Date: March 25, 2016
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: BLA 761038 – Eli Lilly – Olaratumab – FDA request for additional information

Dear Ms. Roth,

Please refer to your Biologics License Application (BLA) for the product Olaratumab.

Currently your submission is under review and we have the following comments and requests for information.

1. Provide DSMB meeting minutes and data.
2. Provide the rationale of using only two out of four stratification factors in the stratified log-rank test. As noted, the histology (STRHISR2) used in the analysis was derived per STRHISR.
3. Resubmit executive SAS code for PFS and OS analysis. Per PFS ADRG, the PFS primary analysis result was based on tpfbsm_itt.pdf. This file called data set ADTTEM, which was not submitted in ADAM PFS subfolder. Instead, this reviewer found adtte, which measures time to event endpoints in weeks.

(b) (4)

4. Provide SAS code and results of post hoc sensitivity analyses of PFS and OS, where p-values for the stratified PFS and OS HR estimates were calculated using re-randomization to generate empirical distribution functions for the associated stratified log-rank statistics.
5. The imputation method proposed in the ADRG Section 3.4 for death date for AE is not acceptable for time to event endpoint. Provide a list of patient and summary of missing date imputed for time to event endpoints, if imputation method was applied to them.
6. Resubmit the entire SAS program in the .txt or .sas format
7. Provide SAS program and document on how to merge supplement domain to respective main domain. Otherwise, please confirm the following SAS code to merge SUPPTU to TU domain. Can I apply the same algorithm to the other domains?



8. Please clarify the location of randomization Code and document as stated in the Appendix I5B-IE-JGDG CSR Appendix Randomization:
Program Location: p:\projects\ (b) (4) \cp15-0806\csr_os\pgm\listings\lrand.sas
Output Location: p:\projects\ (b) (4) \cp15-0806\csr_os\output\listings\lrand.rtf

Please provide a response to the aforementioned requests as soon as possible. If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
03/25/2016

From: [Maduro, Ruth](#)
To: roth_jody_l@lilly.com
Cc: [David A Rhein \(david.rhein@lilly.com\)](mailto:David.A.Rhein@lilly.com); [Maduro, Ruth](#)
Subject: Request for completion of attached form (Highlights of Clinical Pharmacology and Cardiac Safety) BLA 761038
Date: Tuesday, March 15, 2016 4:09:03 PM
Attachments: [BLA 761038 Highlights ClinPharm and Cardiac Safety.doc](#)
Importance: High

Dear Jody –

Please find the attached form (Highlights of Clinical Pharmacology and Cardiac Safety) for completion. Kindly complete as soon as possible (i.e. by **3:00pm EST Friday, March 18, 2016**) and return to me via Ruth.Maduro@fda.hhs.gov. Please forward as MS Word version.

Please follow with a formal submission to BLA 761038.

Kindly confirm receipt of this email communication.

Regards,
Ruth

Ruth Maduro

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: (240)402-4232

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) C_{max} and AUC at the single maximum proposed clinical dose Mean (%CV) C_{max} and AUC at the steady state with the maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C _{max} and AUC
	Multiple Dose	Mean (%CV) C _{max} and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	T _{max}	• Median (range) for parent • Median (range) for metabolites
Distribution	V _d /F or V _d	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC
	Sex	Specify mean changes in C _{max} and AUC
	Race	Specify mean changes in C _{max} and AUC
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/

RUTH L MADURO
03/24/2016



IND 121500

MEETING MINUTES

Eli Lilly and Company
Attention: David Rhein, Pharm D.
Manager, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Rhein:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Olaratumab."

We also refer to the meeting between representatives of your firm and the FDA on March 4, 2015. The purpose of the meeting was to discuss the acceptability of the randomized portion of Study JGDG for regulatory approval and to discuss and confirm the acceptability in terms of the proposed study, I5B-MC-JGDJ (JGDJ), to serve as a confirmatory trial and support labeling claims.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2
Meeting Date and Time: March 4, 2015 at 10:00AM
Meeting Location: White Oak Building 22, Room 1421
Application Number: 121500
Product Name: Olaratumab
Indication: Advanced soft tissue sarcoma
Sponsor/Applicant Name: Eli Lilly and Company
Meeting Chair: Patricia Keegan, M.D.
Meeting Recorder: Ruth Maduro

FDA ATTENDEES

Division of Oncology Products 2 (DOP 2)

Patricia Keegan, M.D., Director
Marc Theoret, M.D., Medical Team Lead
Jennie Chang, Pharm.D., Senior Clinical Analyst
Ruth Maduro, Regulatory Project Manager

Division of Biostatistics (DB-V)

Kun He, Ph.D., Statistical Team Leader
Emmanuel Sampene, Ph.D., Statistical Reviewer

Division of Hematology Oncology Toxicology (DHOT)

Whitney Helms, Ph.D., Supervisor
Dubravka Kufirin, Ph.D., Nonclinical Reviewer

Division of Biotechnology Review and Research II (DBRR II)

Joel Welch, Ph.D., CMC Team Leader
Jun Park, Ph.D., CMC Reviewer

Office of Clinical Pharmacology (OCP)

Hong Zhao, Ph.D., Clinical Pharmacology Team Lead
Jun Yang, Ph.D., Clinical Pharmacology Reviewer

Study Endpoints and Labeling Development (SEALD)

Elektra Papadopoulou, M.D., Acting Associate Director

Selena Daniels, Pharm.D., Study Endpoints Reviewer

SPONSOR ATTENDEES

Richard Gaynor, M.D., Sr. VP, Clinical Research, Oncology

Robert Ilaria, M.D., Sr. Medical Director, Oncology

Ilaria Conti, M.D., Medical Advisor, Oncology

Byran Litton, MBA, Product Team Leader

Patrick Peterson, Ph.D., Research Advisor, Statistics

Amy Qin, Ph.D., Director, Biostatistics

Damien Cronier, Ph.D., Research Scientist, Pharmacokinetics

Ashwin Shahir, M.D., Medical Advisor, Global Product Safety

Vijay Reddy, Ph.D., Sr. Medical Advisor, Toxicology

Larry Starke, Ph.D., Sr. Director, CM&C

Robert Metcalf, Ph.D., Vice President, Global Regulatory Affairs

Katherine Sugarman, M.D., Sr. Director, Global Regulatory Affairs – US

Jody Roth, MS Director, Global Regulatory Affairs -US

David Rhein, Pharm.D., Manager, Global Regulatory Affairs – US

1.0 BACKGROUND

Eli Lilly and Company (Lilly) submitted IND 121500 for olaratumab for the treatment of advanced soft tissue sarcoma for Study 15B-IE-JGDG (IMCL CP15-0806; Study JGDG), “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,” (b) (4) on February 21, 2014, to the Division of Oncology Products 2. A 30-day waiver was granted to Lilly on March 17, 2014.

On March 21, 2014, Lilly submitted a preliminary Breakthrough Therapy Determination Request for review, and a teleconference between Lilly and FDA was held on April 14, 2014. FDA provided comments and recommendations to Lilly, via memorandum dated April 25, 2014, advising Lilly that their submission was premature, and that Lilly should “wait until the results of the final progression-free survival analysis are available to support Breakthrough Therapy Designation Request for olaratumab for advanced soft tissue indication.” Subsequently, Lilly submitted a request for Fast Track Designation on June 23, 2014, which was granted on August 21, 2014, for the investigation of olaratumab in combination with doxorubicin, for the treatment of patients with advanced soft tissue sarcoma not amenable to treatment with radiotherapy or surgery to demonstrate improved progression-free survival and overall survival.

On August 21, 2014, FDA provided comments and recommendations regarding the development program of olaratumab for treatment of patients with advanced soft tissue sarcoma. Key comments and recommendations were:

- FDA noted that investigator assessment of progression-free survival (PFS) and objective response rate (ORR) in an open-label trial may be subject to bias. In an open-label trial

intended to support registration based on analysis of these tumor-based endpoints, FDA recommended that the analysis utilize disease status as assessed by a blinded independent committee review. FDA also stated that Eli Lilly may propose a detailed auditing plan that includes a strategy to detect potential assessment bias.

- FDA stated that a single trial to support licensure requires results that show a highly statistically significant effect on survival that is internally consistent across relevant subgroups, sufficiently robust, and so compelling that it would be unethical to repeat the trial.
- FDA discouraged Eli Lilly from using interim PFS analysis results from Trial JGDG for a superiority claim because observed “positive” treatment effects on PFS are more likely to be overestimated an observed effects may not be robust and are rarely reproducible due to the immaturity of the analysis.

On October 9, 2014, the Office of Orphan Products Development granted Orphan Drug status to olaratumab for the treatment of patients with soft tissue sarcoma.

On February 20, 2015, FDA granted Eli Lilly’s December 23, 2014, request for breakthrough designation for olaratumab, in combination with doxorubicin, for the treatment of patients with advanced or metastatic soft tissue sarcomas that are not amenable to curative treatment with radiotherapy or surgery. The preliminary clinical data submitted by Eli Lilly to support this request for Breakthrough Therapy Designation consisted of the final PFS results and a mature interim analysis of OS from the randomized portion of Trial JGDG.

Non-Clinical

The nonclinical pharmacology/toxicology package proposed by Eli Lilly to support the safety of olaratumab consists of 5-week, 13-week and 39-week repeat-dose toxicology studies in cynomolgus monkeys administered IMC-3G3 weekly by intravenous injection. Cross-reactivity studies using a surrogate anti-PDGFR α antibody against selected human and cynomolgus monkey tissues have also been performed. Eli Lilly has submitted an initial assessment of the potential for olaratumab-mediated reproductive activity to support their position that a dedicated embryofetal development study in cynomolgus monkeys is not warranted to support a future marketing application.

Clinical

Trial JGDG Design and Results

Trial JGDG is an open-label, sequential, two-part, multicenter trial:

- Part 1: a non-randomized single-arm cohort of approximately 10 patients with advanced STS to evaluate the initial safety of olaratumab administered in combination with doxorubicin
- Part 2: a randomized, active-comparison, activity-estimating study of doxorubicin with or without olaratumab in the treatment of patients with advanced unresectable or metastatic soft tissue sarcoma

In the randomized portion of the study, 133 patients with advanced STS with documented disease progression, whose disease was not amenable to treatment with surgery or radiotherapy, were randomized (1:1) to receive:

- Doxorubicin 75 mg/m² administered intravenously on Day 1 and olaratumab 15 mg/kg administered intravenously on Day 1 and Day 8 of each 21-day cycle for up to eight cycles followed by single-agent olaratumab 15 mg/kg administered intravenously on Day 1 and Day 8 on an every 21-day cycle (Arm A)
- Doxorubicin 75 mg/m² administered intravenously on Day 1 of each 21-day cycle for up to eight cycles (Arm B)

Randomization was stratified according to PDGFR α expression (positive vs. negative), number of previous lines of treatment (0 vs. 1 or more prior lines of chemotherapy), histological tumor type (i.e., leiomyosarcoma vs. synovial sarcoma vs. other tumor type), and ECOG performance status (0-1 vs. 2).

Tumor response was assessed every 6 weeks. Patients randomized to Arm B were permitted, at the time of disease progression, to receive single-agent olaratumab 15 mg/kg intravenously on Day 1 and Day 8 on a 21-day cycle.

The primary endpoint was PFS as assessed by the investigator per RECIST v1.1 in the modified intent-to-treat (mITT) population defined as patients who are randomized and received any dose of study medication. Secondary endpoints were 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.

A planned sample size of 130 patients for the randomized, activity-estimating 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 and the alpha level allocated to the final analysis was 0.1999 (two-sided). The 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; under protocol-defined censoring rules, PFS was censored at the last radiographic assessment if:

- Death or disease progression was observed after two consecutive missed visits after last assessment or
- The patient began a new systemic anticancer therapy prior to documented disease progression.

Among the 129 randomized and treated patients (mITT population), 20 were censored for one of these two 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.

Of the 133 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). Thirty (45%) patients in the doxorubicin arm received single-agent olaratumab at the time of investigator-determined disease progression.

According to the Eli Lilly, the study met the protocol-defined, significance level for PFS (i.e., two-sided alpha 0.1999) at the final analysis, thereby demonstrating a statistically significant improvement in investigator-assessed PFS in the olaratumab plus doxorubicin arm compared to the doxorubicin arm, with a hazard ratio (HR) of 0.67 (95% CI: 0.44, 1.02) $p=0.062$ and a median of 6.6 months versus 4.1 months, respectively. Lilly further states, "there was no evidence of any systematic bias in the investigators' assessments of PFS, and the independent review thus confirmed the validity of the investigator-based statistical results and conclusions with respect to PFS." As summarized in the briefing package, the IRC analysis of PFS yielded a hazard ratio of 0.67 (95% CI: 0.40, 1.12), with a p -value of 0.12, and the rate of censoring in the IRC analysis (approximately 45%) was substantially higher than the 23% of patients censored in the investigator-determined PFS analysis.

An interim analysis of OS was pre-planned to occur at the time of the final PFS analysis, assuming 91 events would have occurred. At the database lock date on August 15, 2014, 84 events were reported (49% censoring). For the interim analysis of OS conducted in the intent-to-treat (ITT) population with 84 events, 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 analysis of overall survival is projected to occur in the first half of 2015.

Eli Lilly also presented subgroup analyses of PFS and OS according to the randomized, histological subtype of STS, leiomyosarcoma or non-leiomyosarcoma, and in both subgroups, the hazard ratios favor the combination arm for both PFS and OS; however, the treatment effects appear to be greater for the leiomyosarcoma subgroup than for the non-leiomyosarcoma subgroup. Thus, the effects in the ITT population appear to be driven by the leiomyosarcoma subgroup based on the point estimates (hazard ratio) and Kaplan-Meier curves. Additional exploratory analyses of OS indicate a consistent effect favoring the olaratumab plus doxorubicin arm across multiple subgroups defined by PDGFR α status (positive vs. negative), number of previous lines of treatment (0 vs. ≥ 1), ECOG performance status (0-1 vs 2), gender, and race (White vs. Other).

Proposed Trial Design (15B-MC-JGDJ)

Study 15B-MC-JGDJ

(b) (4)

(b) (4)

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Meeting Objectives:

Eli Lilly states the objectives of the meeting are to:

- Provide FDA with final results and discussion of safety and efficacy data from Trial JGDG
- Discuss the acceptability of the randomized Phase 2 portion of Study JGDG for regulatory approval
- Discuss and confirm the acceptability in terms of trial design of Trial JGDJ of olaratumab in combination with doxorubicin to support labeling claims

2.0 DISCUSSION**INTRODUCTORY FDA COMMENT:**

The meeting briefing document does not contain sufficient information to allow FDA to comment on the adequacy of the results of Trial IMCL CP15-0806 (hereafter referred to as Trial JGDG) to provide substantial evidence of efficacy or of a treatment effect reasonably likely to predict efficacy for olaratumab, in combination with doxorubicin, sufficient to support a filing of a proposed BLA.

FDA acknowledges that the high-level results of the final PFS analysis and a relatively mature interim analysis of OS from Trial JGDG are interesting; however, interpretation of the results from Trial JGDG are limited by the trial's design (open-label) and lack of pre-specified statistical criteria around important efficacy endpoints. In addition, for a single trial intended to support approval, the observed effect should be statistically robust, be internally consistent across relevant subgroups and individual study sites, and the trial must be considered adequate and well-controlled (e.g., a limited number of minor protocol deviations, limited missing data). FDA strongly encourages Eli Lilly to provide information regarding the conduct of the clinical trial demonstrating that it was well-conducted, a discussion of the potential sources of bias and Lilly's plan to address them, and justification for why the totality of the results would be considered statistically robust as soon as possible. Upon receipt of this information, FDA will advise whether a request for a pre-BLA meeting with this Division to discuss the contents of a complete application that would be primarily supported by the results of Trial JGDG would be appropriate.

Potential sources of bias in the design, conduct, analysis, and interpretation of the results of Trial JGDG would need to be identified and adequately addressed within a proposed BLA submission.

Potential sources of bias may include:

- Unknown type I error and type II error considerations for secondary efficacy variables because the pre-specified hypothesis is limited to progression-free survival
- Effect of multiple comparisons on the estimate of the size and determination of a treatment effect, e.g., multiple comparisons between treatment arms, multiple efficacy variables, and multiple analyses of the data
- Insufficient description of the process and procedures for examining data, including informal and formal analyses

- Measures taken to minimize bias in the conduct of the trial and assessment of the efficacy parameters
- Heterogeneous trial population with potential imbalance in important prognostic factors

Please refer to 21 CFR 314.126, and International Conference on Harmonization (ICH) Guidelines E3 and E9, for further discussion of the principles of adequate and well controlled trials that would need to be satisfied in order for the results from Trial JGDG to serve as the basis of formal proof of efficacy. ICH Guideline E3 may be accessed at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/Step4/E3_Guideline.pdf and ICH Guideline E9 may be accessed at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf.

Non-clinical

1. Does the Agency agree that the olaratumab nonclinical studies (ADME and toxicology) will be adequate to support registration of olaratumab (Appendix 4)?

FDA Response: The general toxicology studies listed in Appendix 4 appear sufficient to support the submission of a future marketing application. In addition to the studies listed, include any pharmacology studies that have been performed with olaratumab to date that support the proposed mechanism of action and pharmacodynamics activity of the antibody.

Eli Lilly and Company March 3, 2015 Response: Lilly acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

2. Based on a scientific assessment of the PDGFR α target (Appendix 5), does the agency agree that an embryo-fetal development study with olaratumab (b) (4)?

FDA Response: No, FDA does not agree (b) (4)

(b) (4)

(b) (4)

Eli Lilly and Company March 3, 2015 Response: Lilly intends to provide additional data if available to bridge the gap between the knockout data and role of PDGFR α signaling in the maintenance of pregnancy including placental effects and any available non-product specific data resulting from the use of surrogate anti-PDGF pathway antibodies. If the bridging data are not available, then Lilly would like to discuss the design of an embryo/fetal study in non-human primates, to support a marketing application. In addition, if Lilly proceeds to submit the marketing application primarily supported by the Phase 2 study, would FDA be amenable to considering the embryo/fetal study as a post-marketing commitment?

Discussion during the meeting: FDA agreed that the proposal to provide additional literature references to bridge the gap is acceptable; however, if the additional data does not adequately address the issue, an EFD or EPPND study would be required, and at minimum, in-life data should be provided in a proposed BLA.

Clinical

3. Does FDA agree that the current clinical evidence from the randomized Phase 2 Study JGDG (PFS and OS) demonstrate a substantial clinical benefit for treating patients in the proposed indication (see proposed TPP language in Appendix 6)?

FDA Response: No, for the reasons discussed in the FDA Introductory comment.

(b) (4)

. This conclusion would require evidence that this was an adequately conducted and well-controlled clinical trial. In support of a meeting request to discuss the content and format of a proposed BLA under the provisions of accelerated approval, Eli Lilly should provide sufficient information to allow FDA to assess the adequacy of the conduct of the clinical trial and that the results may not be informed by knowledge of the treatment or other biases as discussed in FDA introductory statement.

Eli Lilly and Company March 3, 2015 Response: Lilly acknowledges FDA's introductory comments and response to Question 3, and would like to further discuss Questions 3 and 4 together.

Regarding the conduct of the Phase 2 portion of Study JGDG, Lilly will provide additional information prior to our request for a pre-BLA meeting to demonstrate that it was well-conducted, including more detailed descriptions of the process and procedures for examining and analyzing the data. With respect to potential sources of bias, Lilly performed two analyses for progression-free survival (PFS), one prespecified interim

analysis and one final PFS analysis. Although this was an open label study, the study team did not have access to unblinded aggregate data or individual treatment assignments prior to the first interim analysis of PFS. Lilly also conducted an independent review of PFS and additional sensitivity analyses, which were consistent with the primary analysis of PFS by investigator assessment in the ITT population. Although there was no statistical gatekeeping for the secondary analysis of overall survival (OS), this endpoint is the gold standard in oncology for determining clinical benefit and the highly statistically significant interim results for OS, as determined by a stratified log rank test, are unlikely to be a false positive finding. Treatment arms were well balanced for known prognostic factors, there was no observed imbalance in the selection of post-study therapy between arms, and the doxorubicin arm performed as expected from historical data. Therefore Lilly believes these Phase 2 results are statistically robust and support an interpretation of clinically meaningful benefit in the advanced STS population.

(b) (4)

Please refer to Lilly's response to Question 5 below for further discussion regarding the Phase 3 study design.



Discussion during the meeting: FDA requested that Lilly provide data addressing concerns about possible bias including imbalances in known prognostic factors and informative censoring for PFS and OS within each treatment arm. Lilly agreed to provide these data for FDA assessment prior to seeking a pre-BLA meeting.

With regard to Lilly's response, FDA continues [redacted] (b) (4)
[redacted] as demonstrating substantial evidence of effectiveness.

4. Does FDA agree [redacted] (b) (4)
[redacted], the results of JGDG are appropriate to establish a positive benefit/risk of olaratumab and support submission for regulatory approval in the proposed indication?

FDA Response: No. See response to question 3.

Eli Lilly and Company March 3, 2015 Response: Lilly also references our response to Question 3.

Discussion during the meeting: Questions 4 and 5 were discussed simultaneously. See "Discussion during the meeting" to question 5.

5. Does FDA agree with the design of the planned Phase 3 study (JGDJ) to confirm the clinical benefit of olaratumab in the proposed STS indication, considering in particular the following questions:

Does FDA agree that the inclusion/exclusion criteria are acceptable and identify a well-defined patient population consistent with the proposed indication?

FDA response: Yes, in general, the inclusion/exclusion criteria are acceptable and identify a well-defined patient population; however, the inclusion criteria for hemoglobin should be adjusted to ≥ 9.0 g/dL. Additionally, please capture whether patients have locally advanced unresectable *or* metastatic disease in the Case Report Forms (CRF).

FDA recommends  (b) (4)

 Please also see FDA response to Question 7 regarding FDA's recommended modifications to the proposed design.

Eli Lilly and Company March 3, 2015 Response:  (b) (4)

Discussion during the meeting: FDA requested that Lilly consider hierarchical testing in the proposed confirmatory trial, testing in the LMS subgroup first followed by the ITT population. Lilly agreed to consider this.

6. Does FDA agree with the proposed stratification factors for randomization and primary analysis?

FDA Response: Yes, the proposed stratification factors for randomization and primary analysis appear acceptable.

Eli Lilly and Company March 3, 2015 Response: Lilly acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

7. Does FDA agree with the statistical design of the planned interim analyses for OS (Including the timing, number of events, and proposed alpha spending function)?

FDA Response: No. FDA does not agree because, for the reasons stated in the FDA Introductory Comments, (b) (4)

(b) (4)

Eli Lilly and Company March 3, 2015 Response: Lilly acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

8. If either the first or second interim OS analysis exceeds the O'Brien-Fleming boundary for statistical significance, does FDA agree that such a result could support regulatory approval in this patient population?

FDA Response: Please refer to FDA's response to Question 7.

Eli Lilly and Company March 3, 2015 Response: Lilly acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

9. Does FDA agree that the proposed safety monitoring plans (specifically cardiac, infusion reaction, and immunogenicity testing) for the Phase 3 clinical trial will be adequate to characterize safety for the proposed indication?

FDA Response: Yes, the proposed safety monitoring plans for cardiac toxicity, infusion reactions, and immunogenicity testing appears adequate. For the evaluation of cardiotoxicity, please use the same method of assessment (i.e., echocardiogram or MUGA) per patient for consistency and interpretation of results. However, please ensure that clinical laboratory testing will include bicarbonate.

Eli Lilly and Company March 3, 2015 Response: Lilly acknowledges FDA response. However, Lilly would like to clarify (b) (4)

(b) (4)

Does FDA agree with this updated cardiac toxicity monitoring schedule?

Discussion during the meeting: FDA stated that the proposal as stated in Lilly's March 3, 2015, response is acceptable.

Clinical Pharmacology

10. Does FDA agree that the population pharmacokinetic (PK) modeling strategy using data from studies JGDG, JGDB, JGDE, and JDGH is adequate to support submission based on efficacy data from study JGDG?

FDA Response: Lilly's proposed population PK analysis plan seems reasonable.

Eli Lilly and Company March 3, 2015 Response: Lilly acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

11. Does FDA agree that the population PK modeling strategy supports the sparse PK sampling planned in the Phase 3 study JGDJ and would be adequate to support a confirmatory submission based on data from study JGDJ?

FDA Response: Yes, the proposed sparse PK sampling planned in the Study JGDJ seems acceptable.

Eli Lilly and Company March 3, 2015 Response: Lilly acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

12. Does FDA agree that the proposed immunogenicity and PK sampling and testing in the Phase 3 study JGDJ are adequate to characterize the impact of olaratumab on immunogenicity?

FDA Response: The proposed immunogenicity sampling and testing for Study JGDJ appear acceptable. However, for patients who test positive for anti-drug antibodies (ADAs), please list their ADA titers over time and associated PK information (e.g., plasma concentration) in subsequent cycles for each subject.

Eli Lilly and Company March 3, 2015 Response: Lilly acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

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3.0 ADDITIONAL COMMENTS

Nonclinical Pharmacology/Toxicology

15. FDA requested that Lilly clearly identify future submissions of additional non-clinical data regarding the literature-based reproductive assessment, for the Agency's prioritization.

Clinical Pharmacology

16. Regarding the population PK exposure analysis, please submit a statement of Lilly's plans prior to the submission of BLA.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input

from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

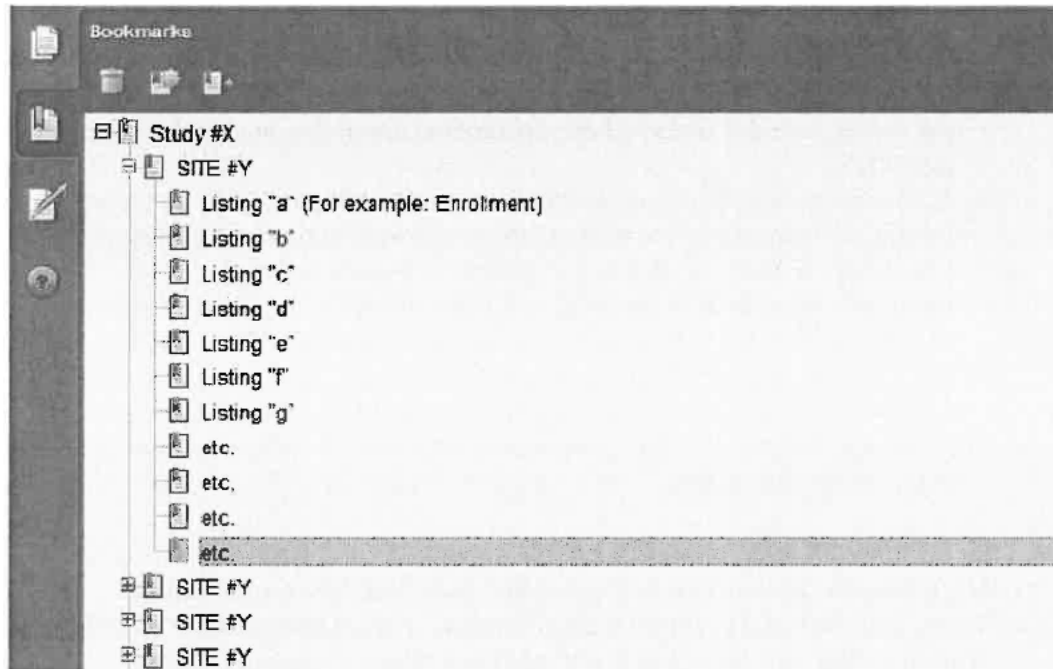
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describes location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

- a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

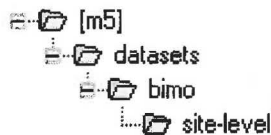
Attachment 1

**Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.thm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

RUTH L MADURO
03/16/2015



BLA 761038

BLA ACKNOWLEDGMENT

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Olaratumab, Injection for Intravenous Infusion

Date of Application: February 24, 2016

Date of Receipt: February 24, 2016

Our Reference Number: BLA 761038

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 24, 2016, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 351 of the PHS Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **BLA 761038** submitted on February 24, 2016, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Ruth Maduro, Regulatory Health Project Manager, at (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MELANIE B PIERCE
03/07/2016



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

Memorandum

Date: March 2, 2016
From: Ruth Maduro, Regulatory Health Project Manager-CDER/OHOP/DOP2
Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Comment and Information Request #2

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for “Olaratumab, Injection for Intravenous Infusion.”

The Clinical reviewer has the following comment and request for information:

Clinical

1. Please submit line-listings of tumor measurement data for the blinded central review as was done for the investigator assessments in the 15B-JGDG CSR Appendix Efficacy Listing.

Provide an electronic response to the above comment and requested information to Ruth.Maduro@fda.hhs.gov by **3:00pm EST on Friday, March 11, 2016**, or sooner if possible. Please follow with a formal amendment submission to BLA 761038.

If you have any questions, please feel free to contact me at Ruth.Maduro@fda.hhs.gov (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RUTH L MADURO
03/02/2016



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

Memorandum

Date: February 26, 2016
From: Ruth Maduro, Regulatory Health Project Manager-CDER/OHOP/DOP2
Subject: **BLA 761038 – Eli Lilly and Company**
Clinical Comment and Information Request

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for “Olaratumab, Injection for Intravenous Infusion.”

The Clinical reviewer has the following comment and request for information:

Clinical

1. Please provide the address of the Imaging Contract Research Organization (CRO).

Provide an electronic response to the above comment and requested information to Ruth.Maduro@fda.hhs.gov and Gina.Davis@fda.hhs.gov by **3:00pm EST on Monday, February 29, 2016**, or sooner if possible. Please follow with a formal amendment submission to BLA 761038.

If you have any questions, please feel free to contact me at Ruth.Maduro@fda.hhs.gov (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RUTH L MADURO
02/26/2016



BLA 761038

INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) presubmission dated and received December 17, 2015, submitted under section 351(a) of the Public Health Service Act for Olaratumab, Injection for Intravenous Infusion.

We are reviewing your submission and have the following request for information. We request a prompt written response in order to continue our evaluation of your application.

Please provide a schedule for planned manufacturing of Olaratumab at (b) (4)
(b) (4) site during the months April, May and June.

If you have questions, call me, at (301) 796-0906.

Sincerely,

Melinda J.
Bauerlien -S

Digitally signed by Melinda J.
Bauerlien -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=13001785
65, cn=Melinda J. Bauerlien -S
Date: 2016.02.09 15:08:22 -05'00'

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



IND 121500

ADVICE/INFORMATION REQUEST

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Olaratumab."

We also refer to your amendment dated January 29, 2016 (eCTD sequence Number 0078), received January 29, 2016, requesting FDA's response concerning the content of the data for the unblinded studies for the 120-day safety profile for olaratumab, Study 15B-MC-JGD (Study JGDJ). Specifically, you requested a response to the below question:

Does FDA agree with the information supplied on the blinded Phase 3 study (Study JGDJ) for the 120-day safety update, and is this sufficient to complete the evaluation of the safety of olaratumab?

We have completed our review of your January 29, 2016, submission and have the following request and comment:

Clinical

1. FDA requests that Lilly not submit blinded safety data from patients treated on Study JGDJ as part of the safety update. It is unlikely that this limited blinded additional information will affect the assessment of the safety profile of olaratumab in combination with doxorubicin. The proposal to submit the IDMC recommendations for Study JGDJ from the April/May meeting is acceptable.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

Since your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. Since your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Since your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, contact Ruth Maduro, Regulatory Health Project Manager, at (240) 402-4232.

Sincerely,

{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
02/03/2016



BLA 761038

ACKNOWLEDGE PRESUBMISSION

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

We have received Biologics License Application (BLA) under the program for step-wise submission of sections of a marketing application under 351 of the Public Health Service Act) for the following:

Name of Drug Product: Olaratumab, Injection for Intravenous Infusion

Date of Submission: January 27, 2016

Date of Receipt: January 27, 2016

Our Reference Number: BLA 761038

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the application number listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call, Regulatory Health Project Manager, Ruth Maduro at (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MELANIE B PIERCE
02/01/2016



BLA 761038

ACKNOWLEDGE PRESUBMISSION

Eli Lilly and Company
Attention: David Rhein, Pharm D.
Manager, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Rhein:

We have received Biologics License Application (BLA) under the program for step-wise submission of sections of a marketing application under 351 of the Public Health Service Act) for the following:

Name of Drug Product: Olaratumab, Injection for Intravenous Infusion

Date of Submission: January 18, 2016

Date of Receipt: January 19, 2016

Our Reference Number: BLA 761038

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the application number listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call, Regulatory Health Project Manager, Ruth Maduro at (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MELANIE B PIERCE
01/29/2016



BLA 761038

ACKNOWLEDGE PRESUBMISSION

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

We have received Biologics License Application (BLA) under the program for step-wise submission of sections of a marketing application under 351 of the Public Health Service Act) for the following:

Name of Drug Product: Olaratumab, Injection for Intravenous Infusion

Date of Submission: December 17, 2015

Date of Receipt: December 17, 2015

Our Reference Number: BLA 761038

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the application number listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call, Regulatory Health Project Manager, Ruth Maduro at (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NORMA S GRIFFIN

12/22/2015

Norma Griffin, Lead Regulatory Project Manager, signing for Melanie Pierce, CPMS.



BLA 761038

ACKNOWLEDGE PRESUBMISSION

Eli Lilly and Company
Attention: Jody Roth, MS, PMP, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Roth:

We have received the Biologics License Application (BLA) under the program for step-wise submission of sections of a marketing application under 351 of the Public Health Service Act) for the following:

Name of Drug Product: Olaratumab, Injection for Intravenous Infusion

Date of Submission: December 10, 2015

Date of Receipt: December 10, 2015

Our Reference Number: BLA 761038

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the application number listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call, Regulatory Health Project Manager, Ruth Maduro at (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NORMA S GRIFFIN

12/22/2015

Norma Griffin, Lead Regulatory Project Manager, signing for Melanie Pierce, CPMS.



IND 121500

GRANT ROLLING REVIEW

Eli Lilly and Company
Attention: David Rhein, Pharm D.
Manager, Global Regulatory Affairs - Oncology
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Rhein:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "olaratumab."

We also refer to the October 16, 2015, preBLA meeting, in which we advised, and you agreed, to modify your draft proposal for the schedule for rolling submission of portions of your planned BLA, and to your November 6, 2015, request for rolling submission and review of portions of your planned Biologics License Application (BLA) for olaratumab, in combination with doxorubicin, which was designated as a breakthrough therapy for the treatment of patients with advanced or metastatic soft tissue sarcomas that are not amenable to curative treatment with radiotherapy or surgery.

We have reviewed and accept your request and plan for submitting portions of the proposed application.

If the breakthrough therapy designation for for olaratumab, in combination with doxorubicin, which was designated as a breakthrough therapy for the treatment of patients with advanced or metastatic soft tissue sarcomas that are not amenable to curative treatment with radiotherapy or surgery is rescinded, submission of portions of the BLA will not be permitted under this program. However, if you still have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

For further information regarding breakthrough therapy designations, please refer to the FDA *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*¹.

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

If you have any questions, contact Ruth Maduro, Regulatory Health Project Manager, at (240) 402-4232.

Sincerely,

{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
12/09/2015



IND 121500

MEETING MINUTES

Eli Lilly and Company
Attention: David Rhein, Pharm D.
Manager, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Rhein:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Olaratumab."

We also refer to the meeting between representatives of your firm and the FDA on October 16, 2015. The purpose of the meeting was to discuss the content and format of a planned BLA submission for olaratumab.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
OSI pre-BLA Request
CMC Final Meeting Minutes
DOP2 CDISC Guidance



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: October 16, 2015 at 11:00am
Meeting Location: White Oak 22, Room 1309

Application Number: 121500
Product Name: Olaratumab (proposed propriety name: (b) (4))
Indication: Advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery
Sponsor/Applicant Name: Eli Lilly and Company

Meeting Chair: Patricia Keegan, M.D.
Meeting Recorder: Ruth Maduro

FDA ATTENDEES

Division of Oncology Products 2 (DOP 2)

Patricia Keegan, M.D., Director
Marc Theoret, M.D., Clinical Team Leader
Meredith Chuk, M.D., Clinical Reviewer
Ruth Maduro, Regulatory Project Manager

Division of Biostatistics (DB-V)

Kun He, Ph.D., Statistical Team Leader
Pallavi Mishra-Kalyani, Ph.D., Statistical Reviewer

Division of Hematology Oncology Toxicology (DHOT)

Whitney Helms, Ph.D., Supervisor
Dubravka Kufrin, Ph.D., Nonclinical Reviewer

Office of Biotechnology Products (OBP)

Rashmi Rawat, Ph.D., Drug Quality Team Lead
Chikako Torigoe, Ph.D., Drug Quality Assessment Reviewer

Office of Clinical Pharmacology (OCP)

Hong Zhao, Ph.D., Clinical Pharmacology Team Lead
Ruby Leong, Pharm.D., Clinical Pharmacology Reviewer
Yaning Wang, Ph.D., Division of Pharmacometrics, Deputy Director
Jingyu (Jerry) Yu, Ph.D., Pharmacometrics Reviewer

SPONSOR ATTENDEES

Richard Gaynor, M.D., Sr. VP, Product and Clinical Development, Oncology
Robert Ilaria, M.D., Sr. Medical Director, Oncology
Ilaria Conti, M.D., Sr. Medical Advisor, Oncology
Byran Litton, MBA, Product Team Leader, Olaratumab
Jon Denne, Ph.D., Sr. Director, Statistics
Patrick Peterson, Ph.D., Research Advisor, Statistics
Damien Cronier, Ph.D., Principal Research Scientist, Global PK&PD, Pharmacometrics
Ashwin Shahir, M.D., Medical Advisor, Global Patient Safety
Vijay Reddy, Ph.D., Sr. Research Advisor, Non-clinical Safety Assessment
Larry Starke, Ph.D., Sr. Director, CMC
Bruce Meiklejohn, Ph.D., Sr. Research Fellow, Global Regulatory CM&C Biotechnology
Katie Sugarman, M.D., Sr. Director, Global Regulatory Affairs – Oncology
Jody Roth, MS, Director, Global Regulatory Affairs – Oncology
David Rhein, PharmD, Manager, Global Regulatory Affairs – Oncology

1.0 BACKGROUND

IND 121500, which cross-references IND (b)(4), became active on March 17, 2014, for the clinical development program for olaratumab for the treatment of patients with (b)(4). Fast Track Designation was granted on August 21, 2014, for the investigation of olaratumab, in combination with doxorubicin, for the treatment of patients with advanced soft tissue sarcoma not amenable to treatment with radiotherapy or surgery to demonstrate improved progression-free survival and overall survival. Breakthrough Therapy Designation was granted on February 20, 2015, for olaratumab, in combination with doxorubicin, for the treatment of patients with advanced or metastatic soft tissue sarcomas that are not amenable to curative treatment with radiotherapy or surgery. Olaratumab received Orphan Drug Designation on October 9, 2014, for the treatment of soft tissue sarcoma.

On May 5, 2015, Lilly submitted a request for propriety name review, which was conditionally accepted on July 19, 2015, for the proposed propriety name for (b)(4). On July 24, 2015, Lilly submitted a Type B meeting to seek general advice regarding the content of their proposed BLA submission for olaratumab. Lilly has been scheduled to meet with, or has met with, FDA to discuss various aspects of the development program for olaratumab under IND 121500 as follows:

- End of Phase 2 meeting – March 4, 2015
- CMC Program development meeting – June 9, 2015
- Breakthrough Therapy Multidisciplinary meeting – June 18, 2015 (meeting cancelled by Lilly upon acceptance of FDA's Preliminary Meeting Comments)
- August 18, 2015, General Advice meeting gain preliminary agreement with FDA on the proposed contents of the BLA, present a preliminary plan for a rolling submission, and to provide a summary of technical information and proposed dataset structure and gain FDA's alignment with the information and structure on the proposed BLA
- CMC pre-BLA meeting – October 6, 2015

According to Lilly, they intend to submit the BLA in two components: the first component is to be submitted in December 2015, containing clinical, clinical pharmacology, and nonclinical modules and the second component, containing quality information, is to be submitted in January 2016. Lilly states they will be requesting priority review designation. Lilly proposes to have two separate Application Orientation meetings, with the first to occur within 30 days of the December 2015 submission and the second to occur within 30 days of the January 2016 submission module.

Chemistry, Manufacturing, and Controls

Olaratumab is a human monoclonal antibody (IgG₁) that binds to a platelet-derived growth factor receptor alpha (PDGFR α), blocking binding of the ligand to the receptor. A pre-BLA CMC meeting was held on October 6, 2015 to discuss the proposed comparability assessment between drug product lots manufactured at (b) (4) (clinical material manufacturing site) and (b) (4) (commercial manufacturing site), to be provided in the BLA; to discuss the approach for process validation to be included in the BLA, to discuss the timing of submission of stability data from process validation to the BLA, and to discuss the content of Module 3. A copy of these minutes with the agreements reached are appended to these meeting minutes.

Nonclinical

Lilly states that pharmacology, PK, tissue cross-reactivity, and single and multiple dose toxicology studies in mice and monkeys with olaratumab have been completed to date. Lilly's September 16, 2015, briefing document indicates that a complete list of all nonclinical pharmacology studies will be included in a rolling BLA; however, only study reports that directly relate to the mechanism of action and relevant disease indications will be submitted in the BLA.

Reproductive and developmental toxicity studies with olaratumab have not been conducted in monkeys. Instead, as discussed at a prior meeting with FDA, Lilly planned to use a murine monoclonal antibody surrogate (IMC-1E10; LSN3338786) of olaratumab in a pilot embryo-fetal developmental study in combination with non-product specific data from the scientific literature to support the assessment of reproductive toxicity of olaratumab. Based on the September 16, 2015, meeting package, issues such (b) (4) in the results from the pilot EFD study using the surrogate antibody; however, preliminary data from this study do not show the severe developmental hazards anticipated based on knockout mouse data. Lilly is initiating a definitive GLP mouse embryo-fetal study with IMC-1E10 in the last quarter of 2015 with estimated finalization date in April 2016. Additionally, (b) (4), with a consultation with the Agency once it obtains after the data from the definitive mouse embryo-fetal study with the surrogate antibody IMC-1E10 becomes available.

Clinical Pharmacology

The clinical pharmacology section of the proposed BLA submission for olaratumab will include olaratumab pharmacokinetic (PK) characterization, the effects of olaratumab on doxorubicin PK and cardiac electrophysiology (trial JGDI), population pharmacokinetic (popPK) and exposure-response analyses for efficacy. PK characterization by noncompartmental methods will be provided as SAS-transported WinNonlin[®] datasets. Data included in the popPK/pharmacodynamic (PK/PD) analysis (including data from trial JGDG) will be provided as SAS-transported NONMEM[®] datasets. NONMEM[®] input, output, and summary files in ASCII text format with a “.txt” extension will be included for the base model, significant covariate runs, and final and validation models. The effects of organ (renal and hepatic) impairment, concomitant doxorubicin administration (drug-drug interaction), and immunogenicity (positive anti-drug antibodies [ADA]) on olaratumab PK will be evaluated via popPK analysis. The impact of positive ADAs on the pharmacokinetics, safety and efficacy of olaratumab will also be evaluated.

Clinical

Lilly states that Trial I5B-MC-JGDG (JGDG) will serve as the sole trial providing evidence of effectiveness for olaratumab in support of the proposed indication “olaratumab, in combination with doxorubicin, is indicated for the treatment of patients with advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery”.

Trial JGDG is a two-stage, open-label, multicenter trial designed to evaluate the anti-tumor activity of olaratumab, when administered in combination with doxorubicin, as compared with single-agent doxorubicin for the treatment of patients with advanced soft tissue sarcoma (STS) with documented disease progression whose disease was not amenable to treatment with surgery or radiation. The first stage of the trial was a single-arm assessment of the tolerability of olaratumab, given in combination with doxorubicin, that was conducted in 15 patients with advanced STS. The second stage of this trial was an open-label, randomized, two-arm, active-controlled study. There were 133 patients randomized (1:1) to:

- Experimental (Arm A): doxorubicin 75 mg/m² followed by olaratumab 15 mg/kg on day 1 and olaratumab 15 mg/kg on day 8 of each 21-day cycle or
- Control (Arm B): doxorubicin 75 mg/m² on day 1 of each 21-day cycle

Randomization was stratified by PDGFR- α expression (positive vs. negative), prior lines of treatment (0 vs. ≥ 1), histological tumor type (leiomyosarcoma vs. synovial sarcoma vs. other), and ECOG performance status (0-1 vs. 2). Treatment continued for up to eight cycles or until disease progression, unacceptable treatment-related toxicity, patient or physician decision to discontinue, or death. Patients who completed eight cycles could continue to receive olaratumab at the same dose and schedule until progression, death, intolerable toxicity, or other discontinuation criteria were met. Patients on Arm B were eligible to receive single-agent olaratumab upon disease progression.

The primary endpoint of the trial was progression-free survival (PFS) as determined by the investigator. A planned sample size of 130 patients for the second stage of the trial 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. No sample size calculations or pre-specified assumptions were provided in the analysis plan for the secondary endpoints of OS or ORR.

Lilly states that the data cutoff dates for the efficacy analyses were August 15, 2014, for the final PFS and tumor response analyses and May 16, 2015, for final overall survival (OS) and safety and drug exposure analyses. At the time of the data cutoff date for the final PFS analysis, 103 PFS events had occurred. The median PFS was 6.6 months on the olaratumab plus doxorubicin arm and was 4.1 months on the single-agent doxorubicin arm, a 2.5 month improvement in median PFS (. This effect met the protocol-specified criteria for evidence of anti-tumor activity ($P < 0.2$) but is not considered statistically robust [stratified HR = 0.67 ((0.4, 1.02); $p = 0.06$].

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Number of events	55 (83)	48 (72)
Median PFS in months (95% CI)	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
Stratified long-rank p-value	0.06	
Stratified HR (95% CI)	0.67 (0.4, 1.02)	

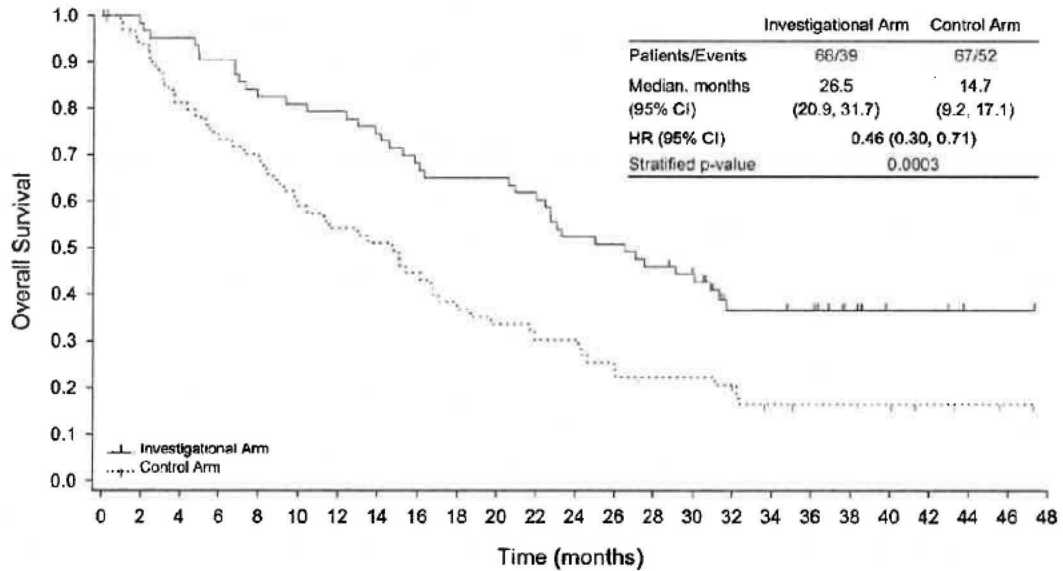
Objective response rates, which may include both confirmed and unconfirmed responses as assessed by the investigator per RECIST v1.1, were similar between arms. The overall response rate (ORR) was 18% in the olaratumab plus doxorubicin arm and 12% in the single-agent doxorubicin arm. Two patients (3%) in the olaratumab plus doxorubicin arm and one (2%) in the control arm were reported as having a complete response (CR).

An interim analysis of OS was performed at the time of the final PFS analysis. At that time, 84 deaths had occurred. The median OS was 25.0 months on the olaratumab plus doxorubicin arm and was 14.7 months on the single-agent doxorubicin arm, a 10.3-month improvement in median OS (HR = 0.44, $p = 0.0004$).

The results of the final OS analysis based on a data cutoff date of May 16, 2015, with a total of 91 deaths, are summarized in the table below.

	Olaratumab + Doxorubicin N=66 (%)	Doxorubicin N=67 (%)
Number of deaths	39 (59)	52 (78)
Median OS in months (95% CI)	26.5 (20.9, 31.7)	14.7 (9.2, 17.1)
Stratified long-rank p-value	0.0003	
Stratified HR (95% CI)	0.46 (0.30, 0.71)	

The Kaplan-Meier curve for final OS results in the intent-to treat (ITT) population is shown in the figure below:



Number at Risk

Investigational Arm	66	62	60	57	52	51	50	47	43	41	41	39	33	32	29	26	16	16	15	8	3	3	1	1	0
Control Arm	67	61	51	46	43	37	34	32	28	23	21	19	19	15	13	13	10	7	6	6	5	3	2	1	0

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

(Source: Lilly preBLA briefing document of Sept 16, 2015)



(b) (4)

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Safety

Lilly states that safety data for 485 patients treated with olaratumab, either as a single agent or in combination with chemotherapy, in nine clinical trials will be included in the initial BLA submission to support the evaluation of the safety of olaratumab. This includes 96 patients receiving olaratumab monotherapy in 4 studies (I5B-IE-JGDC [JGDC], I5B-IE-JGDF [JGDF], I5B-IE-JGDE [JGDE], and I5B-IE-JGDH [JGDH]); 95 patients initially randomized to receive chemotherapy only, in Studies JGDA, JGDB, JGDD, or JGDG, who received olaratumab monotherapy after discontinuation of chemotherapy; and 294 patients receiving olaratumab in combination with chemotherapy in 5 studies (I5B-IE-JGDA [JGDA], I5B-IE-JGDB [JGDB], I5B-IE-JGDD [JGDD], JGDG and JGDI). Lilly estimates that approximately 90 patients with advanced STS will have received olaratumab in combination with doxorubicin at the proposed dose and schedule at the time of filing: 79 from trial JGDG and 11 from trial JGDI (non-randomized drug interaction study). Lilly plans to submit the safety update 120 days after the BLA submission is complete; the 120-day safety update will include safety data from ongoing studies not included in the initial BLA submission.

Confirmatory Trial JGDJ



2.0 DISCUSSION

1. Does FDA agree that the content and format for the Summary of Clinical Efficacy, Integrated Summary of Efficacy, Summary of Clinical Safety, and Integrated Summary of Safety support the filing of the olaratumab BLA?

FDA Response: As stated in the minutes of the August 18, 2015, meeting, the proposal to cross-reference the Summary of Clinical Efficacy (Module 2.7.3) for the Integrated Summary of Efficacy (Module 5.3.5.3) is acceptable as Trial JGDG is the single trial submitted to support the efficacy of olaratumab. The proposal to cross-reference the Summary of Clinical Safety (Module 2.7.4) for the Integrated Summary of Safety (Module 5.3.5.3) is acceptable provided that the text portion consists of comprehensive, integrated analyses that are sufficiently detailed to qualify for the text portion of the ISS. The Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) should also include key tables, listings, and graphs to support the discussions of efficacy and safety. It is acceptable and may be necessary to place additional tables, listings, and graphs in Module 5.3.5.3 with working links to tables if space limitations prohibit inclusion of all supportive data in the SCS or SCE.

FDA expects that the clinical data submitted as part of the initial BLA to support the safety and efficacy of olaratumab is from databases that have been locked and adequately cleaned. Lilly should provide a definitive statement that the data provided in the BLA have been audited by Lilly for accuracy and completeness. In addition, a complete audit trail should be available IVRS and eCRF data which have “corrected” as a result of on-site monitoring and auditing.

A filing determination will be made within 60 days of receipt of the complete BLA.

See FDA response to Question 4.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA’s response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

2. Does FDA agree with the proposal and date for the 120-day safety cut off?

FDA Response: Lilly proposed to submit a 120-day safety update for the 485 patients treated with olaratumab, either as a single agent or in combination with chemotherapy, in nine clinical trials, containing narrative summaries for all new serious adverse events observed in clinical experience and updated safety information for clinical trials included in the original BLA as well as safety data for clinical trials not provided in the original BLA, as follows:

(b) (4)

The proposal is acceptable provided that all data have been audited and verified by Lilly for accuracy and that the data is limited to patients with adequate exposure to olaratumab to permit an adequate assessment for safety (e.g., at least 2 cycles of treatment with submission of safety data on case report forms). In addition, Lilly should provide a brief summary of the new safety information, identifying any significant changes in the safety profile for olaratumab between the original ISS and the 120-day safety update.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response, however additional discussion or clarification is needed.

Discussion during the meeting: No discussion occurred during the meeting.

3. Does FDA agree that the updated results of the Phase 2 registration Study JGDG provide sufficient safety and efficacy information on the use of olaratumab plus doxorubicin for treatment of patients with advanced STS, to support review of the olaratumab BLA and inform labeling?

FDA Response: The final results of the Study JGDG as presented in the pre-meeting briefing package, appear sufficient to support filing of a BLA for the proposed indication from a clinical perspective.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

4. Does FDA agree that the proposed analyses for infusion-related reactions from Study JGDG are acceptable to support review of the olaratumab BLA?

FDA Response: No, the proposed analyses for infusion-related reactions from Study JGDG are not acceptable. Include the following in the analysis of infusion-related reactions:

- A time-frame for identifying AEs thought to be related to infusion-related reactions (i.e., 24 hours following infusion)
- Preferred terms (PT) for adverse events commonly observed as infusion-reactions, including fever, rigors, flushing, hypotension, dyspnea, back pain, and abdominal pain Analysis of the incidence of infusion reactions by treatment cycle
- Analysis of interventions for management of infusion reactions, including mediations administered, alterations of infusion rate, etc.
- Analysis of the incidence of infusion reactions in patients with a previous infusion reaction (i.e., re-challenge)

Provide similar analyses for all patients receiving olaratumab in the BLA.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

5. Does FDA agree that the proposed clinical pharmacology data package will be adequate to support FDA review of the BLA for olaratumab (see Section 7 [Drug Interactions] and Section 12 [Clinical Pharmacology] of the Target Product Profile (TPP); Appendix 12)?

FDA Response: In addition to the proposed exposure-response (E-R) analyses for efficacy, FDA expects the inclusion of exploratory E-R analyses for safety in the proposed BLA submission. FDA recommends the use of olaratumab trough concentration at the end of Cycle 1 ($C_{min,1}$) and steady-state exposure measures in the safety E-R analysis. Refer to the additional clinical pharmacology comments conveyed in the responses provided for the Type B Administrative meeting scheduled for August 18, 2015.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response, however additional discussion or clarification is needed.

Discussion during the meeting: Lilly stated that they will include an exposure-safety analysis based on exposure at the end of cycle one and exposure over the entire course of treatment. FDA acknowledged Lilly's response.

6. Does FDA agree that the proposed immunogenicity data package will be adequate to support FDA review of the olaratumab BLA?

FDA Response: FDA generally agrees with the proposed plan to evaluate the impact of anti-drug antibodies, as determined by analytically validated assays with acceptable drug

tolerance, on the pharmacokinetics, safety and efficacy of olaratumab. Please note that FDA has not had an opportunity to evaluate the immunogenicity assay validation reports.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

7. Are the proposed safety data package and analyses acceptable to FDA for review of the olaratumab BLA?

FDA Response: The proposed safety data package and analyses as agreed to in the responses provided for the Type B Administrative meeting scheduled for August 18, 2015, are acceptable.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

8. Does FDA agree that the olaratumab nonclinical studies (pharmacology, ADME, and toxicology) are adequate to support review of the BLA and inform labeling for olaratumab (see Section 8.1, 8.2, 8.3, and 13.1 of the TPP; Appendix 12)?

FDA Response: In general, the proposed studies appear adequate to support the filing of a BLA with the exception of the data (b) (4)

Lilly will need to submit the finalized study for the application to be considered complete from a nonclinical perspective. If an additional EFD study in monkeys is warranted, then a monkey study may be requested as a PMR.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response, however additional discussion or clarification is needed.

Discussion during the meeting: FDA stated that inclusion of a draft report of the definitive mouse EFD study, in addition to the items described Section 8.1, 8.2, 8.3, and 13.1 of the TPP; Appendix 12 of the meeting package, would constitute a complete nonclinical package, sufficient to support filing of the BLA. Considering the newly proposed timeline, if it is impossible to complete this draft study report by the time of submission of the final component of the BLA, FDA agreed to accept the draft report for the mouse EFD study as a late submission of a minor component of the BLA. This late submission must be received within 30 days of submission of the last major component of the complete application.

9. Does FDA have any comments on Lilly's plans to provide the definitive mouse developmental and reproductive toxicology report during the course of the application review?

FDA Response: Please see response to Question 8.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

10. Does FDA agree with Lilly's plan to include only those nonclinical pharmacology study reports that directly relate to the mechanism of action and relevant disease indications in the BLA?

FDA Response: FDA agrees.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

11. Does FDA have any comments on Lilly's plan [REDACTED] (b) (4)
[REDACTED] (b) (4)

FDA Response: FDA does not agree with Lilly's plan [REDACTED] (b) (4)
[REDACTED] (b) (4) Under the PDUFA V program, FDA cannot agree to accept an application that does not contain complete information to allow for a comprehensive review of and decision on the application, with exception of the required safety update. [REDACTED] (b) (4)

As during the October 6, 2015, meeting with Lilly, FDA provided the following comment regarding the submission of a complete CMC module for the proposed NDA:

"Submit the BLA component under rolling submission where a specific CMC unit (e.g. 3.2.S, 3.2.R etc.) can be submitted as available and the final data from the initial PPQ batch be submitted when available as the final component to the complete license application."

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response, however additional discussion or clarification is needed.

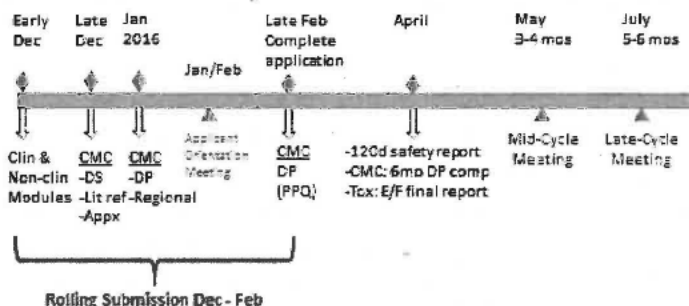
Discussion during the meeting: Lilly agreed to provide the process validation data for the initial drug product PPQ lot and clarified that the final component of CMC submission will be the release data from the first PPQ lot.

12. Does FDA agree with the proposed content and timeline for the rolling submission, such that the BLA would be considered complete following the final module submission in January 2016?

FDA Response: No. See FDA's responses to Questions 8 and 11 and provide a revised schedule for the rolling BLA submission.

Eli Lilly and Company October 16, 2015 Response:

Sponsor Proposed BLA Submission/Review



Discussion during the meeting: In general the proposed timeline appears acceptable, however Lilly stated their intent to revise to reflect the discussion during the meeting (See Questions 8, 11, and 15).

13. Does FDA have any comments regarding the draft carton labeling for olaratumab?

FDA Response: Preliminary FDA review of the proposed container labels and carton labeling in the meeting package did not identify any major issues. However, a more comprehensive review of the container labels and carton labeling will be completed as part of the BLA review, which will include the proposed Prescribing Information. Thus, FDA reserves the opportunity to further comment and provide recommendations on container labels and carton labeling during BLA review.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

3.0 ADDITIONAL COMMENTS

Clinical/Statistical

14. As previously noted by FDA during the March 4, 2015, meeting, "interpretation of the results from Trial JGDG is limited by the trial's design (open-label) and lack of pre-specified statistical criteria around important efficacy endpoints. In addition, for a single trial intended to support approval, the observed effect should be statistically robust, be internally consistent across relevant subgroups and individual study sites, and the trial must be considered adequate and well-controlled (e.g., a limited number of minor protocol deviations, limited missing data). FDA strongly encourages Eli Lilly to provide information regarding the conduct of the clinical trial demonstrating that it was well-conducted, a discussion of the potential sources of bias and Lilly's plan to address them, and justification for why the totality of the results would be considered statistically robust as soon as possible."

While the results of JGDG may be sufficient to support approval, the BLA must contain a detailed discussion of the potential sources of bias in the design, conduct, analysis, and interpretation of the results of Trial JGDG, which include type I error and type II error considerations for secondary efficacy variables because the pre-specified hypothesis was limited to progression-free survival; the effect of multiple comparisons on the estimate of the size and determination of a treatment effect; descriptions of the process and procedures for examining data, including informal and formal analyses; measures taken to minimize bias in the conduct of the trial and assessment of the efficacy parameters; and heterogeneous trial population with potential imbalance in important prognostic factors.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

15. In addition, FDA notes that there are substantial differences in the results based on the stratified analysis per IVRS and the stratified analysis based on case report forms. All differences between the IVRS stratification variables and case reports forms for each patient should be provided in the BLA, together with the Lilly's determination of which variable was incorrect and the basis for this conclusion.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response, however additional discussion or clarification is needed.

Discussion during the meeting: Lilly stated that they would provide a tabular line listing for each patient with any discrepancy for stratification variables between that captured in the IVRS and recorded on the CRF (with the exception of PDGFR which is only in the IVRS). The line listings will also contain a column denoting which result is considered by Lilly to be most accurate for each stratification variable where discrepancies exist and the basis for that conclusion. This information should also be included in a stand-alone dataset. The dataset will also contain a separate variable for histology as categorized based on the pathology report collected from the study site. In addition, a stand-alone report will be provided which contains efficacy analyses based upon stratification variables as captured in the IVRS and as recorded in the CRFs, and, for histology, as categorized based on the pathology report collected from the study site.

16. For the reasons discussed in items 14 and 15, above, together with the wide confidence interval [HR 0.52 (95% CI: 0.34, 0.79); $p=0.002$, unstratified log-rank test] observed for the overall survival analysis, there is uncertainty regarding the magnitude of the treatment effect on overall survival. Therefore, approval may be granted under the provisions of 21 CFR 601.41 subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the observed clinical benefit to ultimate outcome. Please also refer to the FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, found at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response, however additional discussion or clarification is needed.

Discussion during the meeting: Lilly expressed understanding that the evaluation of overall survival will include an assessment of robustness and magnitude of effect in the final dataset, noting the agreement to submit additional information as discussed during the meeting with regard to Question 15.

17. Efficacy claims (either in labeling or promotional materials) for overall response rate, response duration, and progression-free survival must be based on tumor status according to blinded independent central review. In addition, claims for overall response rate and response duration should be limited to responses with a confirmed duration by radiographic imaging obtained at least 4 weeks after initial determination of tumor response.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response, however additional discussion or clarification is needed.

Discussion during the meeting: Discussed in conjunction with question 16.

18. In the datasets submitted in the BLA, ensure that information is included from the blinded independent central radiology review necessary to confirm the results for

analyses of tumor response-based endpoints (individual lesion measurements, non-target lesion evaluation, etc.).

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

19. In the initial BLA submission, provide subgroup analyses of confirmed ORR and durations of confirmed responses based on histologic subtype using the most accurate assessment of that subtype (i.e., histopathologic report, if available).

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

20. Provide a strategy for the completion of trial JGDJ, in the event that this is considered necessary to confirm the clinical benefit of olaratumab in combination with doxorubicin, if olaratumab is licensed prior to full enrollment of trial JGDJ.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed. Lilly will address as an IND submission following October 16, 2015 meeting.

Discussion during the meeting: No discussion occurred during the meeting.

Risk Evaluation and Mitigation Strategy

21. At this time, the FDA has insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of olaratumab outweigh its risks, and if a REMS is necessary, what the required elements will be. It will be important to consider the benefit-risk profile of olaratumab for the proposed treatment of patients with advanced or metastatic soft tissue sarcomas that are not amendable to curative treatment with surgery or radiotherapy.

Eli Lilly and Company October 16, 2015 Response: Eli Lilly and Company acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The timing of the submission of all components of a complete application was discussed. Based on discussions during the

meeting, the proposed content of each submission and the timing of the submissions will be revised in order to accommodate the additional data requested by FDA during the meeting (see discussion during meeting for Questions 11 and 15).

- Lilly confirmed that a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for a REMS was held. Refer to FDA comment 21.
- Agreement was reached on the late submission of one minor component of the BLA (see discussion during meeting for Question 8. Specifically, FDA agreed that the draft EFD study report may be submitted within 30 days after submission of the final component of the original BLA.

Information on PDUFA V and the Program is available at

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities

associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is

intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

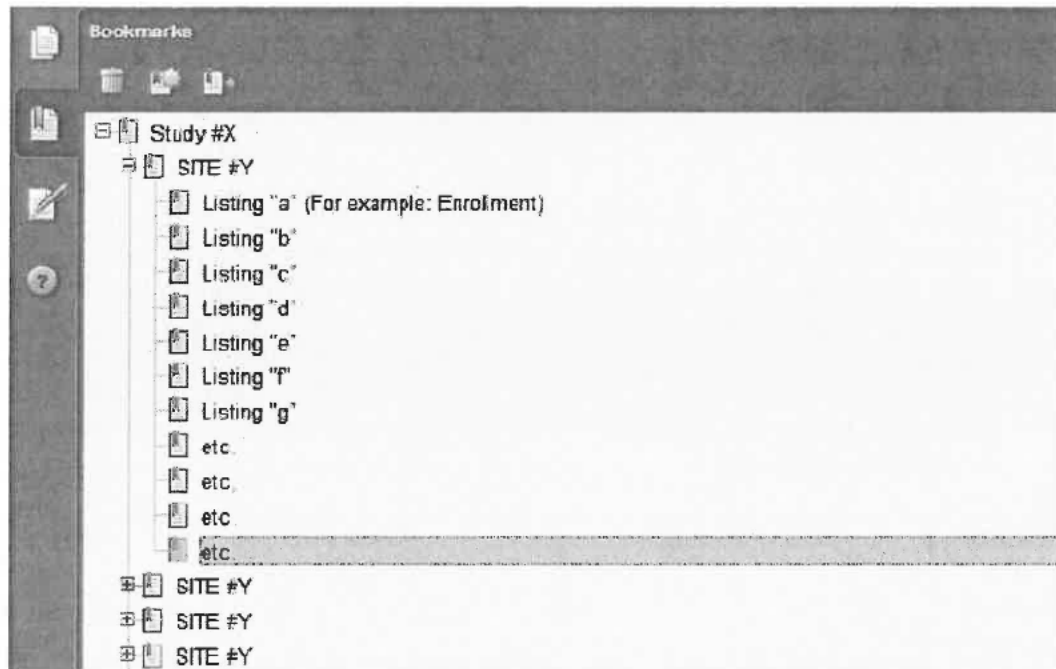
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- A. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov



IND 121500

MEETING MINUTES

Eli Lilly and Company
Attention: David Rhein, Pharm.D.
Manager, Global Regulatory Affairs
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Rhein,

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for olaratumab.

We also refer to the meeting between representatives of your firm and the FDA on October 6, 2015. The purpose of the meeting is to gain concurrence with the Agency on our proposed plan to submit Eli Lilly & Company [REDACTED] ^{(b) (4)} as the sole manufacturing site for Olaratumab drug product in the initial BLA.

A copy of the official minutes is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me.

Sincerely,

{See appended electronic signature page}

Rashmi Rawat, Ph.D.
Team Leader
Division of Biotechnology Products Research and Review II
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: CMC Only

Meeting Date and Time: October 6, 2015 at 10:00 A.M.
Meeting Format: Face to Face

Application Number: 121500
Product Name: olaratumab
Sponsor/Applicant Name: Eli Lilly and Company

Meeting Chair: Rashmi Rawat
Meeting Recorders: Andrew Shiber

FDA ATTENDEES:

Center for Drug Evaluation and Research

Office of Pharmaceutical Quality

Office of Biotechnology Products (OBP)/Division of Biotechnology Review and Research II

Rashmi Rawat Team Leader
Juhong Liu Review Chief
Chikako Torigoe Product Quality

Office of Process and Facilities

Division of Microbiology Assessment

Colleen Thomas Team Leader
Natalia Pripuzova Microbiology

Division of Inspection Assessment

Zhihao Qiu Branch Chief
Wayne Seifert Consumer Safety

Office of Program and Regulatory Operations

Andrew Shiber Project Manager
Kristine Leahy Project Manager

SPONSOR ATTENDEES

Eli Lilly and Company

David Maclaren Regulatory Affairs, CMC
Bruce Meiklejohn Sr. Research Fellow, Regulatory CMC
Lawrence Starke AVP, Regulatory CMC
Lisa Wenzler Regulatory Affairs, CMC
David Allen Tech Services
Austin Kuo Tech Services
Jacques Zimmowitch Product Quality

1.0 BACKGROUND

Name of drug: 121500

Objectives: To discuss CMC program development plans to support the timely registration.

2.0 DISCUSSION

Question 1:

Does the Agency agree with our detailed protocol to demonstrate comparability between drug product manufactured at our clinical (b) (4) site versus our planned commercial (Lilly) site?

FDA Response to Question 1:

We have following comments for the proposed comparability assessment between the drug product lots manufactured at (b) (4) and (b) (4)

(b) (4)

(b) (4). *This statistical assessment is designed to assure that the differences (or ratio) in means are smaller than a predefined maximum acceptable difference (comparability band) with 95% confidence.*

In addition, Lilly commits to providing the requested summaries (means, standard deviations and ranges) as well as control charts of the historical (b) (4) and (b) (4) commercial scale lots in Section 3.2.P.2.3.

(b) (4)

Meeting Discussion: No discussion

- c. Comparability assessment of the stability analysis should also include analysis of (b) (4) under long term and accelerated storage conditions.

Sponsor Response:

Lilly acknowledges the FDA's comments and no further discussion is needed.

- d. It is not clear if the comparability would be established between the manufacturing process used for the commercial scale DP lots and the proposed commercial DP process. The comparability data to demonstrate that the commercial scale process is fully representative of the proposed commercial process at Lilly will be needed to support the use the stability data from commercial scale lots manufactured at Lilly, to establish the shelf life of the commercial DP. These data should include the comparison of these two manufacturing process with respect to the process steps and the in-process controls, operating parameters and in process testing along with their acceptable and target ranges used in the manufacture. Additionally the lot release data from the commercial-scale lots and the validation lots should be compared.

Sponsor Response:

The Lilly comparability lots are representative of the commercial manufacturing process as described in the Lilly response to Question 4. The comparability assessment included in the BLA application will address the transition in manufacturing from (b) (4) to (b) (4). Lilly agrees with the data outline for this comparison of the two manufacturing processes described in the FDA response. The data will include the comparison with respect to the process steps and the in-process control, operating parameters and in-process testing along with the target and acceptable ranges used in the manufacture.

The PPQ batches will be fully representative of the intended commercial manufacturing process. Lilly would like clarification if this satisfies the FDA question regarding the difference in the commercial scale DP lots and the proposed commercial DP process.

Meeting Discussion:

The Agency acknowledged Lilly's response and noted that determination of the process comparability between the processes for Lilly (b) (4) comparability lots and the final proposed commercial product will be a review issue.

Question 2:

Does the Agency agree with our approach to process validation at Lilly as described in the process validation summary?

FDA Response to Question 2:

Your approach for the DP process validation at Lilly appears reasonable.

Sponsor Response:

Lilly agrees with FDA's comments and no further discussion is needed.

Question 3:

Does the Agency agree with our approach to submission of stability data from process validation lots manufactured at Lilly based on the FDA "Guidance for Industry Process Validation: General Principles and Practices"?

FDA Response to Question 3:

Your proposal may be acceptable if the execution of the DP-PPQ protocol is not completed at the time of the BLA approval. Provide information on what part(s) of the PPQ protocol will not be executed at the time of the concurrent release.

To evaluate the suitability of the PPQ lots for the concurrent release, the following information should be provided in the BLA:

- a. Process validation protocol and interim process validation report for at least one PPQ batch.

Sponsor Response:

Lilly would like to discuss this topic in the meeting to gain additional clarity on the FDA expectations relative to the following Lilly proposal. While the DP-PPQ protocol will not be fully executed prior to potential BLA approval, Lilly will include the process validation protocol in the initial Module 3 submission. Lot release data, including in-process data, from the first PPQ batch and the interim process validation report will be provided within 30 days of initial Module 3 submission. Also see Lilly's response to FDA comments for Question 4a.

Meeting Discussion:

The Agency asked Lilly to clarify its plan to submit the data from the remaining two PPQ batches. Lilly stated that they expect the PPQ activities of two PPQ batches to be completed. The PPQ data from these two batches would be available for review during the DP facility inspection. Regarding the rolling submission of the BLA, the Agency stated that complete 3.2.S, 3.2R, and 3.2A sections can be submitted in December/January as available. Section 3.2.P will be submitted in two parts. The first part will contain all of the Drug Product information except for the process qualification data from the first PPQ lot, which will be submitted later as the last CMC component of the BLA submission.

- b. Post-approval stability commitment to place validation lots under long term and accelerated stability studies. Information on how the trend analysis will be performed and what action will be taken should data be out of trend.

Sponsor Response:

Lilly agrees with FDA's proposal to place validation lots on stability under long term and accelerated conditions as a post-approval stability commitment. Trend analysis will be performed based on analysis of stability indicating results using the (b) (4)

which includes the following:

(b) (4)

• [REDACTED] (b) (4)
[REDACTED] (b) (4)

Meeting Discussion:

The Agency noted that the sponsor's approach is reasonable.

Question 4:

Does the Agency agree with Lilly's plan to:

- a. [REDACTED] (b) (4)

FDA Response to Question 4a

No. Under the PDUFA V program, FDA cannot agree to accept an application that does not contain complete information to allow for a comprehensive review of and decision on the application, with exception of the required safety update. [REDACTED] (b) (4)

[REDACTED]

Sponsor Response:

Lilly would like to discuss this question during the meeting to gain clarity on FDA expectations and discuss the following Lilly proposal based on the FDA preliminary response to this question and Question 3a.

Lilly recognizes the PDUFA requirement for inclusion of PPQ data in the BLA in order for FDA to complete a substantive review of the application. Lilly will include information and data for one Drug Product process validation lot in the BLA and will not submit any information on additional validation lots during the BLA review. Lilly will provide the PPQ protocol and information on the execution of this validation lot including process parameters relative to the validation criteria, in the initial Module 3 submission. Lilly proposes to submit the lot release data including the microbial testing results within 30 days of submission of Module 3.

Lilly wishes to provide further clarification to its position that [REDACTED] (b) (4) comparability lots are representative of process validation. A comparison of [REDACTED] (b) (4) demonstrates similarity between comparability batches and PPQ batches as described in the tables below.

[REDACTED] (b) (4)

Based on the similarity between the comparability and intended PPQ batches, Lilly proposes to include information and data for one Drug Product PPQ lot in the BLA and will not submit any information on additional validation lots during the BLA review. Lilly will provide the PPQ protocol and information on the execution of this validation lot including process parameters relative to the validation criteria in the initial Module 3 submission. Lilly will submit lot release data including the microbial testing results within 30 days of the initial Module 3 submission.

Meeting Discussion:

The Agency reiterated that the PPQ data from at least one PPQ lot need to be in the BLA to constitute a substantially complete submission. The Agency expressed their concern that not having any PPQ lot data for the final proposed commercial process creates uncertainty regarding the commercial DP process performance and product quality. Therefore the PPQ data from one PPQ lot will be needed before the BLA can be filed. The Agency stated that the stability data from the first PPQ lot can be submitted during the review cycle upon the Agency's request. Thus, the Agency asked the sponsor to follow the approach for submitting the CMC data discussed under question 3a. The PPQ data from first PPQ DP lot (which would include in-process and release testing data), would be provided as the last component of the BLA submission. This approach would allow the Agency to review CMC information in a timely manner. Lilly agreed with this approach.

- b. Provide additional comparability data (6 month stability time point) from the commercial (Lilly) and clinical (b)(4) manufacturing sites as a simple update in tabular format during BLA review.

FDA Response to Question 4b:

Yes.

Sponsor Response:

Lilly agrees with the FDA recommendation and no further discussion is needed.

Question 5:

To facilitate a timely review of the BLA, does the Agency agree with Lilly's proposals regarding a pre-approval inspection of the (Lilly) commercial facility?

FDA Response to Question 5:

We acknowledge receipt of the planned manufacturing dates for the drug substance and drug product facilities. The proposed drug substance and product production schedules appear to be appropriate to support the PLI at the drug substance and drug product sites based on your current submission timeframe. The decision and dates for pre-approval inspections will be made upon receipt of the application and the facility's compliance status at that time.

Sponsor Response:

Lilly acknowledges the FDA's comments and no further discussion is needed.

Question 6:

Lilly intends to submit Olaratumab as a rolling BLA submission with the last section, Module 3, to be provided in January 2016. Does the Agency agree that the content of Module 3 to be provided in January 2016 to support our proposed commercial drug product manufacturing site (Eli Lilly and Company (b)(4)) will allow for a substantive review and to establish a PDUFA filing date for the BLA?

FDA Response to Question 6:

No. Please refer to our response to Q4.

Sponsor Response:

Lilly recognizes the PDUFA requirement for inclusion of PPQ data in the BLA in order for FDA to complete a substantive review of the application. Lilly will include information and data for one Drug Product PPQ lot in the BLA and will not submit any information on additional PPQ lots during the BLA review. Lilly will provide the PPQ protocol and information on the execution of this PPQ lot including process parameters relative to the validation criteria, in the Module 3 submission. Lilly proposes to submit the lot release data including the microbial testing results within 30 days of submission of Module 3.

Based on Lilly's proposal, does the Agency agree that the content of Module 3 to support our proposed commercial drug product manufacturing site (Eli Lilly and Company (b) (4)) will allow for a substantive review and to establish a PDUFA filing date for the BLA?

No Meeting Discussion.

In addition, insufficient information was provided in the meeting package regarding the contents of the January 2016 submission. Please refer to the additional product quality microbiology comments. Aside from the analytical testing results, it is not clear which items would be provided in Section 3.2.P.3.5.2 (Sterilization Process and Validation) in January 2016 and which items would be provided in April 2016. Please clarify.

Sponsor Response:

With the exception of Section 3.2.P.3.5, complete content including Sterilization Process and Validation will be provided in the initial Module 3 submission. Section 3.2.P.3.5 will be updated with release data from the first PPQ lot within 30 days of the initial Module 3 submission. Stability data supporting commercial (Lilly) and clinical ((b) (4)) manufacturing sites will be provided as a simple update in tabular format during BLA review.

Meeting Discussion: See the response to question 4a.

Additional FDA CMC Quality Microbiology Comments:

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your BLA submission.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support (b) (4) sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products” at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>

The following information related to microbial control (b) (4), should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:

(b) (4)

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- (b) (4)



The following method validation information should be provided:



Sponsor Response:

Lilly acknowledges FDA comments. This information will be provided in the BLA.

Because Lilly is proposing the inclusion of one PPQ batch in the BLA, Lilly seeks clarity on the requirement for the following comment as part of the initial Module 3:

-  (b) (4)

(b) (4)

Meeting Discussion:

The Division of Microbiology Assessment (DMA) agreed that data from one PPQ lot will be sufficient for the Agency to take a review action on the BLA.

(b) (4)

(b) (4)

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

/s/

RASHMI RAWAT
10/14/2015

APPENDIX I

Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this SDTM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (<http://www.cdisc.org/sdtm>) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--

CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)
CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE, ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)

DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601
DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null

RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601
RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRES, NTGRES & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601

TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials⁽¹⁾. RECIST (Response Evaluation Criteria in Solid Tumors)⁽²⁾ has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification⁽³⁾ in the assessment lymphomas, or, MacDonald Response⁽⁴⁾ in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:

--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

(1) E.A. Eisenhauer*, P. Therasse, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER* 45 (2009) 228-247

(2) RECIST Criteria - <http://www.eortc.be/recist/>

(3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology*. Vol 25 Number 5 Feb 10 2007

(4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology*, Vol 8, 1277-1280

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3..x.x One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2.. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5. SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.
2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

- a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".
- b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).
- c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.
4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.
7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..x.x One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.
2. TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. "Percent Change From Nadir") if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..x.x One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRES, BESTRESP, SYMTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSBTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.
2. RSTESTCD / RSTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRES	Target Response	
NTRGRES	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. *TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.*
5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEVALID="RADIOLOGIST 1". The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

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/s/

RUTH L MADURO
11/06/2015



IND 121500

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Eli Lilly and Company
Attention: David Rhein, Pharm D.
Manager, Global Regulatory Affairs - Oncology
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Rhein:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “Olaratumab.”

We also refer to your December 23, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that olaratumab, in combination with doxorubicin, for the treatment of patients with advanced or metastatic soft tissue sarcomas that are not amenable to curative treatment with radiotherapy or surgery, meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of olaratumab to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics, Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting. Please refer to the Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants for procedures on requesting a meeting. If you feel

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the Breakthrough Therapy designation for olaratumab, in combination with doxorubicin, for the treatment of patients with advanced or metastatic soft tissue sarcomas that are not amenable to curative treatment with radiotherapy or surgery, is rescinded, submission of portions of the BLA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Ruth Maduro, Regulatory Health Project Manager, at (240) 402-4232.

Sincerely,

{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
02/20/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121500

GRANT FAST TRACK

Eli Lilly and Company
Attention: David Rhein, Pharm.D.
Manager, Global Regulatory Affairs – Oncology
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Rhein:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “Olaratumab.”

We also refer to your June 23, 2014, request for Fast Track designation. In addition, we refer to our information requests sent to you on August 5, August 6, August 7, August 13, and August 14, 2014 and to your responses received via electronic mail (email) communications on August 7, August 8, August 13, and August 15, 2014, subsequently submitted to the IND on August 13 and 19, 2014.

We have reviewed your request and concluded that it meets the criteria for the Fast Track designation. Therefore, we are designating as a Fast Track development program the investigation of olaratumab, in combination with doxorubicin, for the treatment of patients with advanced soft tissue sarcoma not amenable to treatment with radiotherapy or surgery to demonstrate improved progression-free survival and overall survival. Please note that if the clinical development program you pursue does not continue to meet the criteria for Fast Track designation, the application will not be reviewed under the Fast Track program.

For further information regarding Fast Track Drug Development Programs, please refer to the FDA document "Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics". This document is available on the internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf> or may be requested from the Office of Communications, Division of Drug Information at 301-796-3400 or 1-888-463-6332.

If you have any questions, contact Ruth Maduro, Regulatory Health Project Manager, at (240) 402-4232.

Sincerely,

{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/

JOSEPH E GOOTENBERG on behalf of PATRICIA KEEGAN
08/21/2014



IND 121500

ADVICE/INFORMATION REQUEST

Eli Lilly and Company
Attention: David Rhein, Pharm.D.
Manager, Global Regulatory Affairs – Oncology
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Rhein:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “Olaratumab.”

We also refer to your February 21, 2014 submission containing Protocol I5B-IE-JGDG (IMCL CP15-0806) titled “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,” your June 23, 2014 request for Fast Track designation which included preliminary results from Trial I5B-IE-JGDG, our August 14, 2014 information request, and your response sent via electronic mail on August 15, 2014, submitted to the IND on August 19, 2014, clarifying the design of the proposed Phase 3 trial I5B-MC-JGDJ in patients with advanced soft tissue sarcoma.

We have the following comments and recommendations:

1. If Eli Lilly seeks approval based on the final analysis of progression-free survival (PFS) and objective response rate (ORR) in an open-label trial, we strongly recommend that the analysis of tumor-based endpoints utilizes disease status as determined by an independent radiologic review committee blinded to treatment assignment. Alternatively, Eli Lilly may propose a detailed auditing plan that includes a strategy to detect potential assessment bias and minimize selection bias. This auditing plan should include the percentage of patients to be audited, method used to identify the subset of images to be audited, method for comparing the PFS/ORR results obtained by local review with the PFS and ORR results of the audit, and criteria for determining whether all images need to be audited. All images should be archived and easily accessible. If bias cannot be excluded based upon the audit, then we will consider an independent evaluation of all radiographic images to be necessary for assessments of PFS and ORR.

2. Please be advised that two phase 3 trials are required for licensure; however, we would accept a single pivotal trial to support licensure if results show a highly statistically significant effect on survival that is internally consistent across relevant subgroups. The results of the single pivotal trial must be sufficiently robust and so compelling that it would be unethical to repeat the trial. For further information please refer to the FDA document "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" at <http://www.fda.gov/cder/guidance/index.htm>.

Regarding Protocol 15B-IE-JGDG (Trial JGDG):

3. If the minimization technique was used in the randomization, a re-randomization test (not a stratified log-rank test) on the intent-to-treat (ITT) population should be the primary analysis. For discussions about the issues of dynamic randomization, please refer to Guidance for Industry--Adaptive Design Clinical Trials for Drugs and Biologics (Section VI. B) found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf>.
4. Clarify if the patients enrolled in the phase 1b portion were included in the primary analysis.
5. Any stratified analysis result should be interpreted with caution if there are few events/patients in some strata. Given 133 patients enrolled in Trial JGDG with 94 PFS events, there may be few events/patients in some strata as the result of four randomized stratified factors with 24 strata.
6. We strongly discourage using an interim PFS analysis result for a superiority claim because observed "positive" treatment effects on PFS are more likely to be overestimated and observed effects may not be robust and are rarely reproducible due to the immaturity of the data.

Regarding the Proposed Phase 3 Study 15B-MC-JGDJ (Trial JGDJ):

7. Specify what randomization method will be used in Trial JGDJ.
8. Results of secondary endpoints will generally not be considered for labeling claims unless the analysis of the primary endpoint OS shows statistical significance. A statistical analysis plan controlling the overall false positive rate for those secondary endpoints (e.g., PFS, ORR) to be potentially included in the label at a level of two-sided 0.05 should be specified.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

Since your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, contact Ruth Maduro, Regulatory Health Project Manager, at (240) 402-4232.

Sincerely,

{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/

JOSEPH E GOOTENBERG on behalf of PATRICIA KEEGAN
08/21/2014

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 761038

LATE-CYCLE MEETING MINUTES

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for “olaratumab injection, for intravenous use.”

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 7, 2016.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Leah Her, Regulatory Project Manager at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Marc Theoret, M.D.
Cross Discipline Team Lead (CDTL)
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: Wednesday, September 7, 2016 / 12:00 - 1:00 PM (EST)
Meeting Location: Teleconference

Application Number: BLA 761038
Product Name: Olaratumab
Applicant Name: Eli Lilly and Company

Meeting Chair: Marc Theoret
Meeting Recorder: Leah Her

FDA ATTENDEES

Patricia Keegan	Director, OHOP/DOP2
Marc Theoret	Clinical Team Lead, OHOP/DOP2 & Cross Discipline Team Leader (CDTL)
Meredith Chuk	Clinical Reviewer, OHOP/DOP2
Anuja Patel	Senior Regulatory Health Project Manager, OHOP/DOP2
Leah Her	Regulatory Health Project Manager, OHOP/DOP2
Whitney Helms	Nonclinical Supervisor, OHOP/DHOT
Emily Wearne	Nonclinical Reviewer, OHOP/DHOT
Kun He	Statistical Team Lead, OB/DBV
Huanyu (Jade) Chen	Statistical Reviewer, OB/DBV
Rashmi Rawat	Product Quality Branch Chief, OPQ/OBP/DBRRII
Chikaka Torigoe	Product Quality Reviewer, OPQ/OBP/DBRRII
Ruby Leong	Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Mei-Yean Chen	Medical Officer, OSE/OMEPRM/DRISK
Sarah Thomas	Medical Officer, OSE/OMEPRM/DMEPA
Leyla Sahin	Medical Officer, OND/DPMH

EASTERN RESEARCH GROUP ATTENDEES

Christopher Sese, Independent Assessor

APPLICANT ATTENDEES

Jody Roth	Director, Global Regulatory Affairs - Oncology
Allen S Melemed	Sr. Director, Global Regulatory Affairs - Oncology
(b) (4)	Consultant-Regulatory Affairs-Oncology
Lawrence Carl Starke	Associate Vice President Regulatory CMC
Edward A Saltus	Director-Regulatory CMC
Lisa A Wenzler	Research Advisor Global Regulatory CMC Biotechnology
(b) (4)	Consultant-Regulatory Global Labeling
Raffael Kurek	Sr. Director Global Patient Safety Medical and Benefit-Risk

Ashwin Shahir	Medical Advisor, Global Patient Safety
Robert L Ilaria	Sr. Medical Director, Oncology
Ilaria Conti	Sr Medical Advisor-Olaratumab
Gary Mo	Research Scientist-Pharmacometrics
Michael A Turik	Sr Medical Director-Oncology Clinical Pharmacology-
Kelley J Fisher	Consultant-Data Sciences
Patrick M Peterson	Research Advisor Statistics-Oncology
Chirag Jani	Manager-Statistical Programming Global Statistics
Jonathan Shane Denne	Sr. Director, Statistics
Vijayapal R Reddy	Sr. Research Advisor, Non-clinical Safety Assessment
Symantha Ann Melemed	Product Team Leader, Olaratumab
Richard Brian Gaynor	Sr. VP, Product and Clinical Development, Oncology
Stephanie Roberson	Consultant-Clinical Project Management-Oncology

BACKGROUND

BLA 761038 was submitted on February 24, 2016, for olaratumab.

Proposed indication(s): 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.

PDUFA goal date: October 24, 2016

FDA issued a Background Package in preparation for this meeting on August 30, 2016.

DISCUSSION

1. Introductory Comments

Discussion: FDA provided ground rules and objectives for the discussion as stated in the Late Cycle Meeting Background Package issued on August 30, 2016. No discussion occurred.

2. Discussion of Substantive Review Issues

Discussion: FDA reiterated the uncertainty regarding the magnitude of the clinical effect of olaratumab for patients with soft tissue sarcoma given the data submitted in support of the BLA. FDA stated that while no action is expected from Eli Lilly at this point, this is an outstanding issue. Eli Lilly expressed understanding and no further discussion occurred.

3. Postmarketing Requirements/Postmarketing Commitments

Discussion: FDA stated that Eli Lilly's proposed timelines for the clinical postmarketing requirement (PMR) and the two product quality postmarketing commitments (PMC) were acceptable. FDA also communicated that no additional PMR/PMC has been identified to date. Regarding the product quality PMC (b) (4)

Eli Lilly expressed understanding and agreed to contact the RPM prior to the submission.

4. Labeling issues

Discussion: FDA stated that review of the proposed labeling revisions from Eli Lilly is ongoing. FDA also stated that further discussion may be needed regarding the following: (1) the identification of adverse reactions and laboratory abnormalities for inclusion in the labeling and (2) (b) (4)

Eli Lilly expressed understanding and had no further questions.

5. Review Plans

Discussion: FDA stated that clearance of the special government employees (SGE) is ongoing. FDA also stated that the labeling review and finalization of the PMR/PMCs are ongoing. Lastly, FDA communicated that an internal Wrap-Up meeting is scheduled for September 23, 2016. Eli Lilly inquired whether FDA will be able to provide labeling comments before the Wrap-Up meeting. FDA stated the date that FDA will send labeling comments to Lilly is uncertain as FDA would also like to receive input from the SGEs being consulted for this application. FDA confirmed that the targeted action date is still set for October 24, 2016. Eli Lilly expressed understanding and no further discussion occurred.

6. Wrap-up and Action Items

Discussion: None.

Please note that this application has not yet been fully reviewed by the signatory authority, division director, and cross-discipline team leader and, therefore, this meeting did not address the final regulatory decision for the application.

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/s/

MARC R THEORET
10/11/2016



BLA 761038

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Eli Lilly and Company
Attention: Jody Roth, M.S., P.M.P., R.A.C.
Director, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Roth:

Please refer to your Biologics License Application (BLA) dated February 24, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act) for “olaratumab injection, for intravenous use.”

We also refer to the Late-Cycle Meeting (LCM) scheduled for **Wednesday, September 7, 2016**. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Leah Her, Regulatory Project Manager, at (240) 402-6611.

Sincerely,

{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

ENCLOSURE:

Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: Wednesday, September 7, 2016 / 12:00 - 1:00 PM (EST)
Meeting Location: Teleconference

Application Number: BLA 761038
Product Name: olaratumab injection, 500 mg/50 mL (10 mg/mL) single use vials
Proposed Indication: 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.

Applicant Name: Eli Lilly and Company

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

Discipline Review Letters

No Discipline Review letters have been issued to date and none are expected at this time.

Substantive Review Issues

The following substantive review issue has been identified to date:

1. Clinical/Statistics:
 - There is substantial uncertainty regarding the magnitude of the clinical effect of olaratumab for patients with soft tissue sarcoma given the data submitted in support of

this BLA, which consists of the results from a single small trial in a heterogeneous patient population. As a result, although overall survival is generally a measure of clinical benefit, this BLA is being considered for accelerated approval because there is uncertainty regarding the magnitude of the treatment effect and whether the treatment effect is similar across the variety of sarcoma subtypes included within this heterogeneous population.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned; however, three Special Government Employees (SGEs), comprising two medical oncologists and a patient advocate, will be separately consulted with regard to the following aspects of the olaratumab application:

- The level of evidence supporting the efficacy of olaratumab, administered in combination with doxorubicin, for the treatment of patients with soft tissue sarcoma given the results of a single trial in a heterogeneous disease.
- The adequacy of the proposed product label to inform patients and physicians of the potential risks and benefits of olaratumab treatment.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

Late Cycle Meeting (LCM) AGENDA

1. Introductory Comments – 5 minutes

Welcome, Introductions, Ground rules, Objectives

2. Discussion of Substantive Review Issues – 25 minutes

- Review issue will be introduced by FDA and followed by a discussion.

3. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

- Clinical Post Marketing Requirement:
 - 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 Milestone Dates:

Final Protocol Submission Date:	June 8, 2015
Interim Analysis Submission Date:	June 2018
Clinical Trial Completion Date:	August 2019
Final Report Submission Date:	January 2020

- Chemistry, Manufacturing and Controls Post Marketing Commitment:

-  (b) (4)

- 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 Milestone Dates:

Final Protocol Submission Date:	Not applicable at this time
Study Completion Date:	Not applicable at this time
Final Report Submission Date:	December 2019

4. Major labeling issues – 15 minutes

- Further discussion is required in regards to identification of adverse reactions and laboratory abnormalities for inclusion in the labeling  (b) (4)

5. Review Plans – 5 minutes

- Clearance and discussion with SGEs - ongoing
- Labeling discussions- ongoing
- Finalization of above PMR/PMC - ongoing
- FDA Wrap-Up meeting planned for September 23, 2016

6. Wrap-up and Action Items – 5 minutes

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/s/

PATRICIA KEEGAN
08/31/2016