CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761038Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Memo	
BLA	761038
Link to EDR	\\CDSESUB1\evsprod\BLA761038\
Submission Date	Part 1: December 9, 2015; Part 2: December 17, 2015; Part 3: January 18, 2016; Part 4: January 27, 2016; Part 5: February 22, 2016; Part 6: February 24, 2016
Submission Type	NME (Priority)
Brand Name	LARTRUVO
Generic Name	Olaratumab (LY3012207, IMC-3G3)
Dosage Form and Strength	500 mg/50 mL (10 mg/mL) solution in single-dose vials
Route of Administration	Intravenous infusion over 60 minutes
Proposed Indication	In combination with doxorubicin for the treatment of patients with advanced soft tissue sarcoma not amenable to curative treatment with surgery or radiotherapy
Applicant	Eli Lilly and Company
Associated INDs	121,500; (b) (4)
OCP Review Team	Ruby Leong, Pharm.D., Hong Zhao, Ph.D., Fang Li, Ph.D., Jingyu (Jerry) Yu, Ph.D., Rosane Charlab Orbach, Ph.D., Michael Pacanowski, Pharm.D.
OCP Final Signatory	NAM Atiqur Rahman, Ph.D. (Division Director)

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. The proposed dosing regimen of 15 mg/kg administered by intravenous infusion over 60 minutes on days 1 and 8 of 21-day cycles has demonstrated clinical efficacy with a tolerable safety profile; therefore the proposed dosing regimen is acceptable. From a Clinical Pharmacology standpoint, the BLA is acceptable to support approval provided that the Applicant and the FDA reach an agreement regarding the labeling language.

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

/s/

RUBY LEONG
07/28/2016

FANG LI
07/28/2016

JINGYU YU
07/28/2016

ROSANE CHARLAB ORBACH
07/28/2016

MICHAEL A PACANOWSKI
07/28/2016

HONG ZHAO
07/28/2016
I concur.

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	761038	**SDN**	8
Applicant	Eli Lilly and Company	**Submission Date**	02/24/2016
Generic Name	Olaratumab	**Brand Name**	Lartruvo
Drug Class	Monoclonal antibody targeting platelet-derived growth factor alpha (PDGFRα)		
Indication	In combination with doxorubicin for the treatment of patients with advanced soft tissue sarcoma not amenable to curative treatment with surgery or radiotherapy		
Dosage Regimen	15 mg/kg on days 1 and 8 of 21-day cycles		
Dosage Form	500 mg/50 mL solution	**Route of Administration**	Intravenous
OCP Division	DCPV	**OND Division**	DOP2

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Ruby Leong, Pharm.D.	Hong Zhao, Ph.D.
Pharmacometrics	Fang Li, Ph.D.	Jingyu (Jerry) Yu, Ph.D.
Genomics	N/A	N/A

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	4/24/2016	**74-Day Letter Date**	5/8/2016
Review Due Date	7/28/2016	**PDUFA Goal Date**	8/24/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		

Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	11	I5B-IE-JGDG, I5B-EW-JGDI, I5B-MC-JGDJ, I5B-JE-JGDK, I5B-IE-JGDC, I5B-IE-JGDF, I5B-IE-JGDA, I5B-IE-JGDB, I5B-IE-JGDD, I5B-IE-JGDE, I5B-IE-JGDH
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☑ Race			Population pharmacokinetic (popPK) analyses
☑ Sex			PopPK analyses
☑ Geriatrics			PopPK analyses
☐ Pediatrics			Exempt from PREA due to orphan drug designation
☑ Hepatic Impairment			PopPK analyses
☑ Renal Impairment			PopPK analyses
☐ Genetics			
Extrinsic Factors			
☑ Effects on Primary Drug			PopPK analyses
☑ Effects of Primary Drug			Potential PK interaction between olaratumab and doxorubicin evaluated in Trial JGDI
Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients			Exposure-response analyses
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients			
☑ QT		1	I5B-EW-JGDI
Pharmacometrics			
☑ Population Pharmacokinetics		1	
☑ Exposure-Efficacy		1	
☑ Exposure-Safety		1	

Total Number of Studies	**In Vitro**	0	**In Vivo**	15
Total Number of Studies to be Reviewed		0		15

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	Potential PK interaction between olaratumab and doxorubicin evaluated in Trial JGDI
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	Report 178103, VR1776 , 183259, ARDOXM2
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

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

/s/

RUBY LEONG
04/19/2016

HONG ZHAO
04/19/2016
I concur.