

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761035Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

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

NDA/BLA#: 761035 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DHP PDUFA Goal Date: 2/29/16 Stamp Date: 6/29/2015

Proprietary Name: EMPLICITI

Established/Generic Name: elotuzumab

Dosage Form: Injection

Applicant/Sponsor: Bristol-Myers Squibb

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

- (1) _____
(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: In combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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 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 †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	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

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

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?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	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?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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}

Natasha Kormanik, MSN, RN, OCN® / 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/

NATASHA L KORMANIK
11/09/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA # 761035	BLA Supplement # N/A	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: elotuzumab Established/Proper Name: EMPLICITI Dosage Form: Injection		Applicant: Bristol-Myers Squibb Company Agent for Applicant (if applicable):
RPM: Natasha Kormanik		Division: Division of Hematology Products (DHP)
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> 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) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><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></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action: November 30, 2015 User Fee Goal Date is <u>February 29, 2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> 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 _____		<input type="checkbox"/> 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)

- | | |
|--|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input checked="" type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input checked="" type="checkbox"/> 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 require 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>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	N/A
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>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) 11/30/15
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ 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>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	9/16/15- Acceptable Letter 9/15/15- Review
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 10/5/15 DMEPA: 10/15/15 DMPP/PLT (DRISK): 11/16/15 OPDP: 11/12/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: 11/12/15 Other: DHP 10/26/15
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	8/24/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	N/A
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ 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>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>orphan designation</u> 	N/A
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	Granted 5/12/14
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • 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>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	N/A
<ul style="list-style-type: none"> ❖ 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 previous action letters, as these are located elsewhere in package</i>) 	11/19/15, 11/16/15, 11/9/15 (2), 11/6/15 (2), 11/4/15 (2), 10/26/15, 10/22/15, 10/16/15 (3), 10/15/15, 10/7/15 (2), 9/30/15, 9/28/15, 9/24/15, 9/16/15, 9/9/15, 9/4/15, 9/1/15, 8/28/15, 8/27/15, 8/26/15, 8/19/15, 8/18/15, 8/17/15, 8/11/15, 8/7/15 (2), 7/28/15, 7/27/15, 7/22/15, 7/6/15, 7/2/15
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	11/10/15, 8/11/15
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	3/9/15
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	2/15/11
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	9/28/15
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	10/29/15
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	10/17/12, 1/25/11, 7/12/10

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/29/15
Division Director Summary Review (<i>indicate date for each review</i>)	11/30/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	11/16/15
PMR/PMC Development Templates (<i>indicate total number</i>)	11/20/15, 11/19/15, 11/16/15 (4) ; 6 PMCs
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	11/16/15
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review page 123, dated 11/16/15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	N/A
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	N/A
• 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>)	11/2/15
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	11/18/15, 11/5/15
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review; refer to Cosigned Clinical review dated 11/16/15
Statistical Review(s) (<i>indicate date for each review</i>)	Joint review with clinical; refer to Cosigned Clinical review dated 11/16/15

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review; cosigned 11/2/15 review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review; cosigned 11/2/15 review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	11/2/15 10/9/15 - QT-IRT
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	11/4/15
• Supervisory Review(s) <i>(indicate date for each review)</i>	11/2/15
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	11/2/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	Cosigned 11/9/15 review
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	Cosigned 11/9/15 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>	11/9/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Refer to 11/9/15 Integrated Quality Assessment, OBP Primary Review page 6
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input checked="" type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ 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	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

NATASHA L KORMANIK
11/30/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Thursday, November 19, 2015 6:07 PM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab PI and PPI- due Friday 2:00 PM (ET)
Attachments: BLA761035 elotuzumab_ DHP 11-19-15.doc; EMPLICITI PPI DHP 11-19-15.doc

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. Please find the attached FDA revised version of the label for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with (**do not reject any changes that the FDA proposed**)
- Please address the comments directly to the document in tracked changes

After you have made the changes, please e-mail a revised label (in tracked changes word document) by **2:00 PM (ET) on November 20, 2015**. Be advised that there is a separate word file for the Patient Information. Please also follow up with a formal submission to your BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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

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/s/

NATASHA L KORMANIK
11/19/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Monday, November 16, 2015 4:52 PM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab PI- due 10:00 AM Wednesday
Attachments: BLA761035 elotuzumab_ DHP 16Nov15.doc

Importance: High

Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. Please find the attached FDA revised version of the label for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with (**do not reject any changes that the FDA proposed**)
- Please address the comments directly to the document in tracked changes

After you have made the changes, please e-mail a revised label (in tracked changes word document) by **10:00 AM (ET) on November 18, 2015**. Please also follow up with a formal submission to your BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
11/16/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 10, 2015
Application Number: BLA 761035
Product Name: elotuzumab
Sponsor/Applicant Name: Bristol-Myers Squibb

Subject: Infusion Rate in USPI Discussion

FDA Participants

- Ann Farrell, MD – Division Director
- Albert Deisseroth, MD, PhD –Clinical Team Lead
- Nicole Gormley, MD – Clinical Reviewer
- Virginia Kwitkowski, MS, ACNP-BC – Clinical Team Leader & Associate Director of Labeling
- Gene Williams, PhD – Clinical Pharmacology Team Lead
- Olanrewaju Okusanya, PharmD, MS – Clinical Pharmacology Reviewer
- Natasha Kormanik, MSN – Regulatory Project Manager

Sponsor/Applicant Participants

BMS Participants

- Akintunde Bello, PhD – Executive Director, Clinical Pharmacology & Pharmacometrics
- Eric Bleickardt, MD – Group Director, Oncology, Global Clinical Research
- Julie Dixon, PhD – Group Director, Global Regulatory Sciences – Oncology
- Manish Gupta, PhD, FCP – Director, Clinical Pharmacology & Pharmacometrics
- Jonathan Leith, PhD –Vice President, Global Development Lead - Elotuzumab
- George Manos, PhD –Director, Oncology, Global Biometric Sciences
- Mark Moyer, MS – Vice President, Global Regulatory Sciences - Oncology
- Marie-Laure Papi, PharmD –Director, Global Regulatory Sciences – Oncology
- David Shapiro, MD, PhD –Vice President, Oncology, Global Clinical Research

Abbvie Participants

- Lisa Wax –Director, Global Regulatory Affairs

1.0 BACKGROUND:

Bristol-Myers Squibb (BMS) is filing a Biologics License Application (BLA) for elotuzumab. BMS is seeking approval of elotuzumab in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies. Breakthrough Therapy Designation was granted on May 12, 2014 for elotuzumab in combination with

lenalidomide and dexamethasone for treatment of multiple myeloma (MM) in patients who have received one or more prior therapies.

On October 29, 2015, the Agency requested that the Applicant provide further rationale for the faster infusion rate. On November 9, 2015, the Agency determined a teleconference with the Applicant was needed to discuss the Agency's position and provide guidance for how to proceed. On November 10, 2015, a teleconference was held between the Applicant and Agency.

2.0 DISCUSSION:

The Agency expressed concerns with the rapid infusion rates and noted that current data would not support the increased infusion rates. [REDACTED] (b) (4)

[REDACTED] The Applicant agreed and will modify the label accordingly.

The Agency discussed the clinical pharmacology PMC and requested that the Applicant consider whether, in the event that the interim analysis for Trial CA204006 was negative, it might be possible to fulfill the PMC more rapidly than the applicant has proposed. The Applicant agreed to consider if there is a means to more rapidly fulfill the PMC if the interim analysis for Study X is negative.

3.0 ACTION ITEMS:

- BMS will provide language to add to the label regarding infusion rates from Cycle 4 and on.
- BMS will provide their conclusion regarding the due date proposals for the clinical pharmacology PMC.

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/s/

NATASHA L KORMANIK
11/12/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Monday, November 09, 2015 3:03 PM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab clinical IR- due by COB Today

Importance: High

Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following clinical information request to help facilitate our meeting tomorrow:

The Agency has reviewed the information you have provided regarding CA204112. The Agency continues to have residual concerns regarding the use of a faster infusion rate, particularly in (b) (4). In order to have adequate confidence in the safety of the faster infusion rate, the Agency would need to review the following from study CA204112:

- Statistical Analysis Plan for CA204112
- Initial Protocol for Study CA204112
- All narratives for patients with Grade 2 or greater infusion reactions
- Subject listings of all subjects with any grade infusion reaction
- Vital Signs, SDTM data set
- AE SDTM data set
- Summary description of all development of vital sign abnormalities, infusion reactions, adverse events by cycle
- Listing of all infusions and rates administered by cycle by dose

It would be an aid to tomorrow morning teleconference if you could provide as much of the above information as possible by **5:00 PM (ET) on today, November 9, 2015**. We look forward to discussing this matter during our teleconference scheduled for 9:00 AM (ET), tomorrow, November 10, 2015. In addition to a courtesy copy via e-mail, please formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
11/10/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Monday, November 09, 2015 12:25 PM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab clinical IR- due November 11, 2015

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. Please provide an update on the status of your expanded access treatment protocol. Please provide information detailing the following:

- Number of patients enrolled thus far
- Listing of the centers at which these patients were enrolled
- Number of participating centers
- Status of participating centers
- Listing of all participating centers

We ask for the response by **5:00 PM (ET) on November 11, 2015**. In addition to a courtesy copy via e-mail, please formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
11/09/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Friday, November 06, 2015 3:13 PM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab clinical information request- due November 11, 2015

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following clinical information request:

Please refer to Clinical Study Report for CA204004, section 8.11. The CSR states that "there were no clinically relevant vital sign findings". The Agency review of vitals presented in the ADVS dataset revealed that abnormalities in some vital sign parameters occurred a significantly higher rate in the E-Ld arm when compared to the Ld arm. In some cases, these differences may represent infusion related reactions. The Agency's initial review of vital signs is included in the table below. Please conduct analyses on the vital sign parameters listed in the table below.

	E-Ld (N= 318)		Ld (N=317)	
	n	%	n	%
Systolic BP \geq 160 mm Hg	109	34.2	68	21.4
Systolic BP $<$ 90 mm Hg	92	28.9	26	8.2
Diastolic BP \geq 100 mm Hg	56	17.6	39	12.3
Heart rate \geq 100 bpm	153	48.1	97	30.6
Hear rate \leq 60 bpm	211	66.3	99	31.2

These analyses should address the following questions and any other aspects that you deem relevant:

- Did the vital sign abnormalities occur at the same time points
- Were the abnormalities limited to the time of infusion
- Was there a cycle predominance or any trends over time
- Concurrence of vital sign abnormalities and reporting of an adverse event
- Is there overlap of subjects that had vital sign abnormalities and had documentation of infusion reaction at that visit and/or any visit

We ask for the response by **3:00 PM (ET) on November 11, 2015**. In addition to a courtesy copy via e-mail, please formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP

10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
11/06/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Friday, November 06, 2015 4:24 PM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab PI- due Monday at 2:00 PM
Attachments: BLA761035 elotuzumab_ DHP 6Oct15.doc

Importance: High

Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. Please find the attached FDA revised version of the label for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with (**do not reject any changes that the FDA proposed**)
- Please address the comments directly to the document in tracked changes

After you have made the changes, please e-mail a revised label (in tracked changes word document) by **2:00 PM (ET), Monday, November 9, 2015**. Please also follow up with a formal submission to your BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
11/06/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Wednesday, November 04, 2015 9:12 AM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab PMCs- respond by 3:00 Thursday
Attachments: Elotuzumab PMCs 11-4-15.doc

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab.

As we continue our review of your Application, our normal policy is to consider post-marketing studies and labeling at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing commitments (PMCs), based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated. Most Milestones only require the applicant to provide the month and year for completion of each category. (However, PREA Milestones require month, day, and year.) For milestone calculation purposes only, assume that an approval occurs on the PDUFA date. We are available to discuss by teleconference, if needed.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.

Final PMC designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMR/PMCs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email. Reply with your edits in a WORD document that you submit by email as well as to the document room. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.
2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:
 - a. For any new studies, it is necessary to submit the protocol for DHP review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.
 - b. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

c. It is critical that you advise, prominently, both with the email and cover letter to the EDR that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly. All protocol submissions are made to the IND.

We ask for a response by **3:00 PM (ET) on November 5, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,

Natasha Kormanik, MSN, RN, OCN®

LT, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

FDA/CDER/OHOP

10903 New Hampshire Avenue, Room 2389

Silver Spring, MD 20903

(o) 240-402-4227

Natasha.Kormanik@fda.hhs.gov

BLA 761035/ Elotuzumab
Draft PMCs

Clinical Pharmacology PMC 1:

Conduct elotuzumab exposure-response analysis for efficacy and safety utilizing data from trial CA204006. The result of the exposure-response analyses from both CA204004 and CA204006 will be used to determine whether a post-marketing trial is needed to optimize the dose in patients with multiple myeloma who have low exposure to elotuzumab at the approved dose (10 mg/kg). Submit a final report of the exposure-response analysis based on CA204004 and CA204006.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

CMC PMC 1:

Re-evaluate elotuzumab drug substance lot release and stability specification acceptance criteria for the cell-based ADCC potency assay and cation exchange chromatography (CEX) assay after 30 lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. BMS will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

BLA 761035/ Elotuzumab
Draft PMCs

CMC PMC 2:

Re-evaluate elotuzumab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. BMS will submit corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

CMC PMC 3:

Complete the ongoing studies to support the (b) (4) of the elotuzumab master cell bank (MCB). BMS will submit the results of the (b) (4) using multiple cells from the MCB.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

CMC PMC 4:

To provide additional maximum hold times validation studies for the (b) (4) using a new surrogate solution with microbial growth promotion (b) (4)

Validation report should be submitted per 21CFR601.12 by December, 2016.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>12/31/2016</u>
	Other:	<u>MM/DD/YYYY</u>

BLA 761035/ Elotuzumab
Draft PMCs

CMC PMC 5:

Perform a repeat microbial retention study for the sterilizing filter using a suitable surrogate solution. Alternatively, perform the study using a modified process, a modified formulation (e ^{(b) (4)}), or a reduced exposure time for the challenge organism. Provide the summary data, the associated report, and justification for any modifications to the study. If any filtration parameters are changed as a result of the study, update the BLA file accordingly.

PMC Schedule Milestones:

Final Report Submission:

04/2016

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/s/

NATASHA L KORMANIK
11/04/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Wednesday, November 04, 2015 1:55 PM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab Clinical Information Request- due Tomorrow by 3:00 PM

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following clinical information request:

The Agency acknowledges receipt of your Clinical Safety Update on September 25, 2015. Please submit the following information:

- ADAMs datasets to support the analyses presented in the 90 Day Safety Update.

We ask for the response by **3:00 PM (ET) on November 5, 2015**. In addition to a courtesy copy via e-mail, please formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
11/04/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Monday, October 26, 2015 2:43 PM
To: julie.dixon@bms.com
Cc: Kormanik, Natasha; Boehmer, Jessica
Subject: BLA 761035 elotuzumab Clinical Information Request - due 10/28

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab, BLA 761035. We have the following clinical information request:

[Clinical Information Request:](#)

Please provide the narratives from study CA204004 requested below.

Provide narratives describing the development of neoplasms for the following patients:

- 2407-24
- 3404-565
- 4505-199
- 5505-144
- 6008-60

Provide death narratives for the following patients:

- 1442-667
- 2403-30
- 2407-16
- 3400-161
- 4201-589
- 4414-457
- 4512-59
- 4600-78
- 4601-680
- 4601-689
- 4700-322
- 4700-520
- 4702-460
- 5005-230
- 5014-519
- 5303-141
- 5501-342
- 5801-562
- 5910-588
- 6008-42

Provide narratives describing hepatotoxicity for the following patients:

- 2405-448
- 2407-351
- 4109-367
- 4414-457
- 4600-477
- 4601-691
- 4703-259
- 4901-191
- 5208-566
- 5301-712
- 5504-300
- 5909-606
- 6015-237

Please provide the requested information via email to me and Natasha, by **3:00 PM (ET) on October 28, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Please confirm receipt of this e-mail.

Kind regards,

Jessica on behalf of Natasha Kormanik

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

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/s/

JESSICA L BOEHMER
10/26/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Friday, October 16, 2015 10:56 AM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab PI- Due Thursday 10/22/15
Attachments: BLA 761035 elotuzumab draft-label DHP 10-16-15.doc

Importance: High

Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. Please find the attached FDA revised version of the label for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with (**do not reject any changes that the FDA proposed**)
- Please address the comments directly to the document in tracked changes

After you have made the changes, please e-mail a revised label (in tracked changes word document) by **3:00 PM (ET) on October 22, 2015**. Please also follow up with a formal submission to your BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regard,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
10/16/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Friday, October 16, 2015 10:07 AM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab Carton and Container Information Request- Due Thursday 10/22/15

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following comments regarding your proposed container labels and carton labeling submitted on June 29, 2015:

A. General Comments

1. Confirm there is no text on top of the ferrule and cap overseal of the vials to comply with United States Pharmacopeia (USP) General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, 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).
3. Update the NDC numbers.

B. Carton Labeling

1. [REDACTED] (b) (4)
2. Increase font size of proper name to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2) to increase readability of this important information on the principal display panel (PDP).
3. Revise the dosage form “FOR INJECTION” to appear as “for Injection”.
4. Relocate the dosage form “for Injection” to appear below the proper name. For CDER-regulated biological products, the proper name should not include the finished dosage form. The finished dosage form, for Injection, can appear on the line below the proper name^[1].
5. If space permits, increase the prominence of the route of administration “For Intravenous Infusion Only” by using larger font size.
6. Add the statement “Reconstitute and Further Dilute Prior to Use” to appear under the route of administration.

7. Consider deleting the statement from the side panel “Prior to Use, EMPLICITI must be reconstituted and further diluted.”
8. Revise the statement (b) (4) to read “Single-Dose Vial. Discard Unused Portion”. Note the change from (b) (4) to “Single-Dose”. Single-Dose is the appropriate package term for a container designed for use with a single patient as a single injection or infusion per USP General Chapters: <7> Packaging and Storage Requirements. Therefore the PDP should appear as:

Empliciti
(elotuzumab)
for Injection

300 mg per vial
For Intravenous Infusion Only
Reconstitute and Further Dilute Prior to Use
Single-Dose Vial. Discard Unused Portion

9. Revise the statement of contents to appear as:

Contents: Each single-dose vial delivers 300 mg elotuzumab, citric acid monohydrate (2.44 mg), polysorbate 80 (3.4 mg) sodium citrate (16.6 mg), sucrose (510 mg). After reconstitution with 13 mL of Sterile Water for Injection, USP, the reconstituted solution concentration is 25 mg/mL and the vial contains overfill to allow for withdrawal of 12 mL.

Use a similar format for the 400 mg vial.

C. Vial Container Label

1. See comments B1, B2, B3, B4, B5, B6, and B8.
2. Rotate the orientation of the text on the side panel so that it appears horizontally in the same direction as the information on the PDP to help ensure the safe use of this product.

We ask for the response by **12:00 PM (ET) on October 22, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

^[1] Guidance for Industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft Guidance) April 2013, page 9. Available from:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

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/s/

NATASHA L KORMANIK
10/16/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Thursday, October 15, 2015 10:25 AM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab Clinical Pharmacology Information Request- Due Monday

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following clinical pharmacology information request:

Using your population PK model, for the patients in your exposure-response analysis, simulate the concentration-time profile and the C_{ssav} for the following dosing regimens:

1. 10 mg/kg QW for cycle 1 and 2, followed by 10 mg /kg Q2W thereafter (regimen studied in CA204004)
2. 10 mg/kg QW for all cycles
3. 10 mg/kg QW for cycle 1 and 2, followed by 15 mg /kg Q2W thereafter
4. 10 mg/kg QW for cycle 1 and 2, followed by 20 mg /kg Q2W thereafter

Using your final multivariate cox proportional hazard model, perform simulations to predict the PFS benefit (along with 95% CI) for the above dosing regimens in the following scenarios:

1. In the entire population
2. In patients with high M-protein (i.e. greater than the median),
3. In patients whose C_{ssav} that fall into the lower 25% quartile of your studied dose in Study CA204004.

Also provide the following:

1. Discuss the predicted PFS benefit of the higher dosing regimens for each of the above population
2. A table with the resultant C_{ssav} and predicted PFS for each patient for each dosing regimen. The table should also include each subjects corresponding demographics, covariates included in the population PK and covariates included in the Cox proportional hazard model.
3. The simulation dataset and model run script files used to generate the results.

We ask for the response by **3:00 PM (ET) on October 19, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
10/15/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Wednesday, October 07, 2015 12:16 PM
To: julie.dixon@bms.com
Subject: BLA 761035 Elotuzumab Information Request- Due Friday by Noon

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following information request:

Please clarify how you calculated the individual CavgSS values for the phase2 study HuLu63-1703, in your response dated October 1, 2015.

We ask for the response by **12:00 PM (ET) on October 9, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
10/07/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Wednesday, October 07, 2015 2:50 PM
To: julie.dixon@bms.com
Subject: BLA 761035 Elotuzumab Information Request #2- Due Friday by Noon

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following information request:

The PK values from HuLu63-1703 were not used in the population PK analysis because the bioanalytical assays did not cross-validate. Did you adjust the raw values reported in your pc.xpt tabulations dataset to inform the Cavg values for study HuLu63-1703 in the context of comparison to exposures from study CA204004?

We ask for the response by **12:00 PM (ET) on October 9, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
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10903 New Hampshire Avenue, Room 2389
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Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
10/07/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Wednesday, September 30, 2015 3:04 PM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab Label- Due October 6, 2015
Attachments: BLA 761035 elotuzumab draft-labeling- DHP.doc

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. Please find the attached FDA revised version of the label for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with (**do not reject any changes that the FDA proposed**)
- Please address the comments directly to the document in tracked changes

After you have made the changes, please e-mail a revised label (in tracked changes word document) by **9:00 AM (ET) on October 6, 2015**. Please also follow up with a formal submission to your BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
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Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
09/30/2015



BLA 761035

MID-CYCLE COMMUNICATION

Bristol-Myers Squibb Company
Attention: Julie Dixon, PhD
Group Director, Global Regulatory Safety & Biometrics
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Dixon:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for elotuzumab.

We also refer to the teleconference between representatives of your firm and the FDA on September 28, 2015. 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 Natasha Kormanik, Regulatory Project Manager at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: September 28, 2015 from 2:00-3:00 PM (ET)

Application Number: BLA 761035
Product Name: elotuzumab
Indication: Treatment of multiple myeloma in patients who have received one or more prior therapies, in combination with lenalidomide and dexamethasone (b) (4)

Applicant Name: Bristol-Myers Squibb Company

Meeting Chair: Albert Deisseroth, MD, PhD
Meeting Recorder: Natasha Kormanik, MSN, RN, OCN®

FDA ATTENDEES

Office of Hematology Oncology Products (OHOP)/ Division of Hematology Products

Ann Farrell, MD – Director

Edvardas Kaminskas, MD – Deputy Director

Albert Deisseroth, MD, PhD – Clinical Team Leader

Nicole Gormley, MD – Acting Clinical Team Leader/ Reviewer

Patricia Garvey, RPh – Regulatory Project Manager Team Leader

Natasha Kormanik, MSN, RN, OCN® – Regulatory Health Project Manager

OHOP/ Division of Hematology, Oncology, Toxicology

Christopher Sheth, PhD – Team Lead

Michael Manning, PhD – Pharmacologist

Office of Biotechnology Products/ Division of Biotechnology Review and Research

Linan Ha, PhD – Team Lead

Rachel Novak, PhD – Biologist

Office of Process and Facilities/ Division of Microbiology Assessment

Patricia Hughes, PhD – Team Lead

Maria Jose Lopez-Barragan, PhD – Reviewer

Natalia Pripuzova, PhD – Reviewer

Office of Clinical Pharmacology/ Division of Clinical Pharmacology V

Gene Williams, PhD – Team Leader

Olanrewaju Okusanya, PharmD, MS – Reviewer

Office of Biostatistics/ Division of Biometrics V

Lei Nie, PhD –Biostatistics Team Leader

Chia-Wen Ko, PhD – Biostatistics Reviewer

Office of Surveillance and Epidemiology (OSE)/ Division of Risk Management

Naomi Redd, PharmD – Acting Team Leader

Mona Patel, PharmD – Reviewer

Kevin Wright, PharmD – Safety Regulatory Project Manager

OSE/ Division of Pharmacovigilance II

Tracey Salaam, PharmD – Team Leader

Shaily Arora, PharmD – Safety Evaluator

OSE/ Division of Epidemiology I

Steven Bird, PhD, PharmD, MS –Team Leader

Carolyn McCloskey, MD, MPH –Epidemiologist

Eastern Research Group

Christopher A. Sese – Independent Assessor

APPLICANT ATTENDEES

Bristol-Myers Squibb Company

Akintunde Bello – Executive Director, Clinical Pharmacology & Pharmacometrics

Eric Bleickardt, MD – Group Director, Oncology, Global Clinical Research

Julie Dixon, PhD – Director, Global Regulatory Sciences – Oncology

Manish Gupta, PhD, FCP – Director, Clinical Pharmacology & Pharmacometrics

Dominic Labriola – Vice President, Global Biometric Sciences

Jonathan Leith, PhD – Vice President, Global Development Lead – Elotuzumab

George Manos, PhD – Director, Oncology, Global Biometric Sciences

Mark Moyer, MS – Vice President, Global Regulatory Sciences – Oncology

Marie-Laure Papi, PharmD – Director, Global Regulatory Sciences – Oncology

Jan Racenberg, MD – Medical Director, Global Pharmacovigilance & Epidemiology

David Shapiro, MD, PhD – Vice President, Oncology, Global Clinical Research

Annie Sturgess, PhD – Executive Director, Global Regulatory Sciences – CMC

Cheryl Watson – Associate Director, Global Regulatory Sciences – CMC

Abbvie

Anil Singhal, PhD – Program Director, Clinical Research

Lisa Wax – Director, Global Regulatory Affairs

1.0 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.

2.0 SIGNIFICANT ISSUES

Clinical

(b) (4)



3.0 INFORMATION REQUESTS

Clinical Pharmacology

We would like to bring to your attention our finding regarding the apparent lack of drug effect of elotuzumab in patients with relatively low elotuzumab concentrations at the proposed dosing regimen of 10 mg/kg QW for Cycles 1 and 2 followed by 10 mg/kg Q2WKS thereafter. Your exposure-response analysis for efficacy identified C_{ssavg} as correlated with PFS after controlling for other baseline risk factors. We conducted an independent exposure-response evaluation for PFS using case control analysis to control for all the factors in your final exposure-response model (B2-microglobulin, LDH levels, prior treatment duration, prior iMiD therapy, prior stem cell transplant) as well as M-protein and ECOG score. The active control group was matched to the patients in the lowest quartile of elotuzumab exposure (C_{ssavg}) with respect to these risk factors. The active control group was also matched to the patients in the highest three quartiles of exposure. The case control analysis shows the following:

1. There was no difference in median PFS between patients with C_{ssavg} in the lowest quartile of elotuzumab exposure ($C_{ssavg} < 209$ mg/L) and patients on active control (Patients in the Len/Dex arm) after controlling for all the risk factors as described above. It is worth noting that patients who have lower exposures inherently also have higher risk factors such as high M-protein, higher B2-microglobulin, and higher LDH levels.
2. Patients with elotuzumab concentrations in the higher three quartiles of exposure showed treatment benefit in terms of PFS compared to active control after controlling for other risk factors as described above.

Given that approximately a quarter of the patients administered elotuzumab do not appear to have benefit at the currently proposed dosing regimen, it is possible that these patients may benefit from higher exposures. We are informing you about this issue in order to provide you the opportunity to share your thoughts on this with us, provide us with any analysis that you may have conducted or would now like to conduct to evaluate this issue, and explore strategies that will ensure that patients that can derive some benefit from elotuzumab have an opportunity to do so.

Response expected: September 30, 2015

Clinical

Please provide information about the interference of elotuzumab with response assessments using SPEP and Immunofixation. Specifically, please describe what is known thus far about the interference, the estimated amount of protein expected to be attributable to elotuzumab, the implications for response assessment, and any strategies that may be used to aid physicians in response assessments given the interference.

Please also provide an update on the status of your development of your anti-elotuzumab assay.

Information regarding this interference will need to be included in the label. Further information will be forthcoming as to where to include this information in the label.

Response expected: October 5, 2015.

CMC

Additional CMC information requests will be conveyed.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee (AC) Meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

Late Cycle Meeting: October 29, 2015 from 3:00-4:00 PM (ET)

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for October 29, 2015. We intend to send the briefing package to you approximately 5-7 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

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/s/

ALBERT B DEISSEROTH
09/30/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Monday, September 28, 2015 2:41 PM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab Clinical Information Request- Due October 5, 2015

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following clinical information request:

Please provide information about the interference of elotuzumab with response assessments using SPEP and Immunofixation. Specifically, please describe what is known thus far about the interference, the estimated amount of protein expected to be attributable to elotuzumab, the implications for response assessment, and any strategies that may be used to aid physicians in response assessments given the interference.

Please also provide an update on the status of your development of your anti-elotuzumab assay.

Information regarding this interference will need to be included in the label. Further information will be forthcoming as to where to include this information in the label.

We ask for the response by **3:00 PM (ET) on October 5, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
09/28/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Thursday, September 24, 2015 6:55 AM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab Clinical Pharmacology Information Request- Due September 20 2015

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following clinical pharmacology information request:

We would like to bring to your attention our finding regarding the apparent lack of drug effect of elotuzumab in patients with relatively low elotuzumab concentrations at the proposed dosing regimen of 10 mg/kg QW for Cycles 1 and 2 followed by 10 mg/kg Q2WKS thereafter. Your exposure-response analysis for efficacy identified C_{ssav} as correlated with PFS after controlling for other baseline risk factors. We conducted an independent exposure-response evaluation for PFS using case control analysis to control for all the factors in your final exposure-response model (B2-microglobulin, LDH levels, prior treatment duration, prior iMiD therapy, prior stem cell transplant) as well as M-protein and ECOG score. The active control group was matched to the patients in the lowest quartile of elotuzumab exposure (C_{ssav}) with respect to these risk factors. The active control group was also matched to the patients in the highest three quartiles of exposure. The case control analysis shows the following:

1. There was no difference in median PFS between patients with C_{ssav} in the lowest quartile of elotuzumab exposure ($C_{ssav} < 209$ mg/L) and patients on active control (Patients in the Len/Dex arm) after controlling for all the risk factors as described above. It is worth noting that patients who have lower exposures inherently also have higher risk factors such as high M-protein, higher B2-microglobulin, and higher LDH levels.
2. Patients with elotuzumab concentrations in the higher three quartiles of exposure showed treatment benefit in terms of PFS compared to active control after controlling for other risk factors as described above.

Given that approximately a quarter of the patients administered elotuzumab do not appear to have benefit at the currently proposed dosing regimen, it is possible that these patients may benefit from higher exposures. We are informing you about this issue in order to provide you the opportunity to share your thoughts on this with us, provide us with any analysis that you may have conducted or would now like to conduct to evaluate this issue, and explore strategies that will ensure that patients that can derive some benefit from elotuzumab have an opportunity to do so.

We ask for the response by **3:00 PM (EST) on September 30, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products

FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
09/24/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Wednesday, September 16, 2015 11:51 AM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab Stats Information Request- Due September 22, 2015

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following information request:

For Study CA204004, please provide 3 additional sensitivity analyses for IRC-assessed PFS and investigator-determined PFS, treating any subsequent systemic-therapy as a PFS event with the start of the subsequent therapy as the event date for both treatment groups and for one treatment group but not the other.

We ask for the response by **3:00 PM (ET) on September 22, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
09/16/2015



BLA 761035

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bristol Myers Squibb
5 Research Parkway
Wallingford, CT 06492

ATTENTION: Julie Dixon, Ph.D.
Global Regulatory Safety and Biometrics, Group Director

Dear Dr. Dixon:

Please refer to your Biologics License Application (BLA) dated June 27, 2015, received June 29, 2015, submitted under section 351(a) of the Public Health Service Act for Elotuzumab, 300 mg/vial and 400 mg/vial.

We also refer to your June 27, 2015, correspondence, received June 29, 2015, requesting review of your proposed proprietary name, Empliciti.

We have completed our review of the proposed proprietary name, Empliciti and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your June 27, 2015, 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 Kevin Wright, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Natasha Kormanik, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4227.

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/

TODD D BRIDGES
09/16/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Wednesday, September 09, 2015 8:47 AM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab Clinical IR- Due Tomorrow

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following information request:

Submit copies of the initial protocols CA204004 and CA204009 prior to any amendments.

We ask for the response by **3:00 PM (EST) tomorrow- September 10, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
09/09/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Friday, September 04, 2015 10:10 AM
To: 'Dixon, Julie'
Subject: RE: BLA 761035 elotuzumab Clinical Information Request- Due September 10 2015

Importance: High

This e-mail supersedes the previous e-mail

Julie,

I apologize, but I made a typo. This e-mail supersedes the previous e-mail. The due date for the response is 3:00 PM (EST) on September 10, 2015. I apologize for the confusion!

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

From: Dixon, Julie [<mailto:julie.dixon@bms.com>]
Sent: Friday, September 04, 2015 8:04 AM
To: Kormanik, Natasha
Subject: RE: BLA 761035 elotuzumab Clinical Information Request- Due September 10 2015

Good Morning Natasha,

Confirming receipt of email.

Best regards,
Julie

From: Kormanik, Natasha [<mailto:Natasha.Kormanik@fda.hhs.gov>]
Sent: Friday, September 04, 2015 7:20 AM
To: Dixon, Julie
Subject: BLA 761035 elotuzumab Clinical Information Request- Due September 10 2015
Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab.

The Agency acknowledges receipt of your Responses to the IRs received on August 28 and 31, 2015.

(b) (4)

[Redacted]

[Redacted]

(b) (4)

We ask for a response by **3:00 PM (EST) on September 10, 2015.** ~~October 10, 2015.~~ In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

[Redacted]

(b) (4)

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
09/04/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Tuesday, September 01, 2015 7:55 AM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab Clinical Pharmacology Information Request- Due Tomorrow at 3:00 PM

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following information requests:

Please provide an updated PK dataset that includes the corrected PK parameter values that were recalculated in the file "huluc63-1701_db0110_1st dose AUC calculation for 1611,1612,1613,1708.pdf." You should also clarify why these values were recalculated.

We ask for a response by **3:00 PM (EST) on September 2, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
09/01/2015



BLA 761035

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Bristol-Myers Squibb Company
Attention: Julie Dixon, PhD
Group Director, Global Regulatory Safety & Biometrics
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Dixon:

Please refer to your Biologics License Application (BLA) dated June 27, 2015, received June 29, 2015, submitted under section 351(a) of the Public Health Service Act for elotuzumab.

We also refer to your amendments dated May 27; July 7 and 31; and August 5, 12, 18, and 21, 2015.

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 February 29, 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>.

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

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 December 7, 2015. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for

labeling and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is September 15, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical

1. Reference is made to your August 14, 2015 response regarding our August 7, 2015 Information Requests to submit the following information:
 - Proprietary electronic dataset for studies HuLuc-1701 and HuLuc-1702.
 - Pooled analyses and corresponding CDISC compliant datasets on existing ADaM data from studies CA204009 and HuLuc63-1702 for the select safety domains available.

The Agency will review the datasets and information submitted, and depending on the review, we may request additional datasets.

The Agency acknowledges that you plan to submit this information by September 15, 2015; however, if this information could be provided earlier, it may allow for a more expedited review.

2.



We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded

upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 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.

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) and patient PI (as applicable). 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 package insert (PI) and patient PI (as applicable), 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 Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
08/28/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Thursday, August 27, 2015 1:50 PM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab Information Request- Due Monday

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following information requests:

Please indicate how the time-averaged $C_{avg,SS}$ was calculated for use as an exposure metric in the exposure-response models for Efficacy and Safety. (e.g. was this calculation from the raw PK values directly, using NONMEM output, was an equation such as Dosing Rate/CL used, etc).

We ask for a response by **3:00 PM (EST) on August 31, 2015**. In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,

Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
08/27/2015

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Wednesday, August 26, 2015 3:42 PM
To: julie.dixon@bms.com
Subject: BLA 761035 elotuzumab Information Request- Due Friday and ASAP
Attachments: Highlights_ClinPharm_and_Cardiac_Safety.doc

Importance: High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following information requests:

Please complete/update the attached clinical pharmacology and cardiac safety table. Please provide a response by **COB on Friday, August 28, 2015.**

We noticed in the ECG warehouse that 24% of ECGs for study CA204-004 and 13% of those related to study CA204-011 have no waveforms. Please double check your waveform files and resubmit all of them to the ECG warehouse at www.ecgwarehouse.com. Please provide the resubmission as soon as possible.

In addition to a courtesy copy via e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose	Include 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) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax 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)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t½	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax 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 Cmax 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/

NATASHA L KORMANIK
08/26/2015

Anderson, Alycia

From: Anderson, Alycia
Sent: Wednesday, August 19, 2015 8:24 AM
To: julie.dixon@bms.com
Cc: Kormanik, Natasha
Subject: BLA 761035

Good morning, Dr. Dixon.

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. Our Clinical team has the following information request:

1. Reference is made to the March 9, 2015 pre-BLA meeting, question 1. In review of your proposed indication of elotuzumab "for the treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone." (b) (4)



Please provide a written response to the above information request, by COB, Friday, August 28, 2015. Please formally submit this information to the BLA.

Please confirm receipt of this e-mail.

Best Regards,

Alycia Anderson

~~~~~

Alycia Anderson, CCRP  
Regulatory Project Manager  
CDER/OND/OHOP/DHP  
10903 New Hampshire Avenue  
WO #22, Room 2379  
Silver Spring, MD 20903  
(240) 402-4270 (Desk)  
[alycia.anderson@fda.hhs.gov](mailto:alycia.anderson@fda.hhs.gov)

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/s/  
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ALYCIA C ANDERSON  
08/19/2015

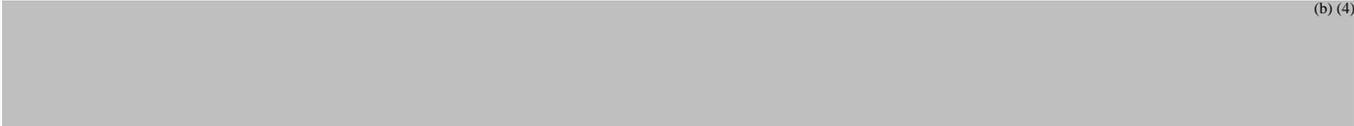
## Anderson, Alycia

---

**From:** Anderson, Alycia  
**Sent:** Tuesday, August 18, 2015 9:22 AM  
**To:** julie.dixon@bms.com  
**Cc:** Kormanik, Natasha  
**Subject:** BLA 761035

Good morning, Dr. Dixon.

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. Our Biometrics team has the following information request:

1.  (b) (4)
2. According to study reports for trials CA204004 and CA204009, the AE-related treatment discontinuation rate was much lower in patients receiving elotuzumab in addition to Ld or Bd compared to receiving Ld or Bd alone. Please provide an explanation to that observation, and assess any potential impacts that the differential AE-related treatment discontinuation rate might have on the determination of study primary efficacy endpoint.

Please provide a written response to the above information request, **by COB, Monday, August 31, 2015**. Please formally submit this information to the BLA.

Please confirm receipt of this e-mail.

Best Regards,

Alycia Anderson  
~~~~~

Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP/DHP
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
(240) 402-4270 (Desk)
alycia.anderson@fda.hhs.gov

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/s/

ALYCIA C ANDERSON
08/18/2015

Anderson, Alycia

From: Anderson, Alycia
Sent: Monday, August 17, 2015 1:22 PM
To: 'julie.dixon@bms.com'
Cc: Kormanik, Natasha
Subject: BLA 761035 - IR

Good afternoon, Dr. Dixon.

I, Alycia Anderson, am covering for Ms. Natasha Kormanik while she is out.

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. Our Clinical team has the following information request:

Reference is made to your response to August 7 2015 Information requests received on August 14, 2015. Please submit the following:

- Proprietary electronic dataset for studies HuLuc-1701 and HuLuc-1702
- Pooled analyses and corresponding CDISC compliant datasets on existing ADaM data from studies CA204009 and HuLuc63-1702 for the select safety domains available.

The Agency will review the datasets and information submitted, and depending on the review may request additional datasets.

The Agency acknowledges that the applicant plans to submit this information by September 15, 2015; however, if this information could be provided earlier, it may allow for a more expedited review. Please respond acknowledging receipt and acceptance with this proposal.

Please also follow up with an official response under the BLA.

Please confirm receipt of this e-mail.

Best Regards,

Alycia Anderson
~~~~~

Alycia Anderson, CCRP  
Regulatory Project Manager  
CDER/OND/OHOP/DHP  
10903 New Hampshire Avenue  
WO #22, Room 2379  
Silver Spring, MD 20903  
(240) 402-4270 (Desk)  
[alycia.anderson@fda.hhs.gov](mailto:alycia.anderson@fda.hhs.gov)

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/s/  
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ALYCIA C ANDERSON  
08/17/2015

# MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** August 11, 2015  
**Application Number:** BLA 761035  
**Product Name:** Elotuzumab  
**Sponsor/Applicant Name:** Bristol-Myers Squibb

**Subject:** Pooled Data Submission

## FDA Participants

- Ann Farrell, MD Division Director
- Albert Deisseroth, MD, PhD Clinical Team Lead
- Nicole Gormley, MD Clinical Reviewer
- Lei Nie, PhD Biostatistical Team Lead
- Theresa Carioti, MPH Chief Project Management Staff
- Natasha Kormanik, MSN Regulatory Project Manager

## Sponsor/Applicant Participants

### BMS

- Eric Bleickardt, MD Group Director, Global Clinical Research, Oncology
- Julie Dixon, PhD Group Director, Global Regulatory Sciences, Oncology
- Jonathan Leith, PhD Vice President, Elotuzumab Development Lead
- George Manos, PhD Director, Global Biometric Sciences
- Mark Moyer, MS Vice President, Global Regulatory Sciences, Oncology

### AbbVie

- Lisa Wax Director, Global Regulatory Affairs

## 1.0 BACKGROUND:

Bristol-Myers Squibb (BMS) is filing a Biologics License Application (BLA) for elotuzumab. BMS is seeking approval of elotuzumab in combination with lenalidomide and dexamethasone (b) (4) for the treatment of patients with Multiple Myeloma who have received one or more prior therapies. Breakthrough Therapy Designation was granted on May 12, 2014 for elotuzumab in combination with lenalidomide and dexamethasone for treatment of multiple myeloma (MM) in patients who have received one or more prior therapies.

On August 7, 2015, the Agency requested a response to the following two Information Requests (IR):

1. Please submit to the NDA ADAMs datasets for the following trials: HuLuc63-1702 and HuLuc63-1701. This information should be submitted no later than

COB August 24, 2015. This may represent a filing review issue if this information is not received in a timely manner.

2. Refer to the meeting minutes from our March 9, 2015 pre-BLA meeting (under IND 100043), question 3a. Provide pooled safety analyses of studies CA204009 and HuLuc63-1702. These analyses should be comparable to the pooled analyses conducted for the E-Ld combination. In addition to the analyses and discussion, please submit pooled datasets. Submit the requested analyses, discussion, and datasets no later than 3:00 PM (EST) on August 24, 2015.

At this time, the Applicant indicated that the sample sizes were too small and that the data was unavailable. BMS requested a teleconference to further discuss the details of the Agency's request.

On August 10, 2015, a filing meeting was held internally and the clinical team determined a teleconference was needed to resolve the pending issue.

## **2.0 DISCUSSION:**

The Agency requested that pooled data from the 204-009 and 1702 studies be provided in addition to the monotherapy data (1701 study). BMS argued that an agreement was made at the pre-BLA meeting in March 2015 and in the July 2014 preliminary comments (cancelled pre-BLA meeting). The Agency explained that the agreement that was made referenced formatting of the submission (EDATA), rather than the content of the submission. The Agency requested that BMS submit their proposal to address the requested information/datasets, including details on timelines. BMS agreed and stated they would provide three proposals within one week for the Agency's consideration.

## **3.0 ACTION ITEMS:**

BMS will provide three proposals of time frames to provide the necessary data.

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/s/  
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NATASHA L KORMANIK  
08/14/2015

## Kormanik, Natasha

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**From:** Kormanik, Natasha  
**Sent:** Tuesday, August 11, 2015 8:44 AM  
**To:** julie.dixon@bms.com  
**Subject:** BLA 761035 elotuzumab Information Request- Due Friday

**Importance:** High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following information request:

Please resubmit "RTR13 - Analysis of ADCC and CDC Activity of HuLuc63" in section 4.2.1.1. The graph on pages 10-11 cannot be read.

We request a response by Friday, **August 14, 2015 at 12:00 PM (EST)**. Please also follow up with an official response under the BLA.

Please confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,  
Natasha Kormanik, MSN, RN, OCN®  
LT, U.S. Public Health Service  
Regulatory Health Project Manager  
Division of Hematology Products  
FDA/CDER/OHOP  
10903 New Hampshire Avenue, Room 2389  
Silver Spring, MD 20903  
(o) 240-402-4227  
[Natasha.Kormanik@fda.hhs.gov](mailto:Natasha.Kormanik@fda.hhs.gov)

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/s/  
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NATASHA L KORMANIK  
08/11/2015

## Kormanik, Natasha

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**From:** Kormanik, Natasha  
**Sent:** Friday, August 07, 2015 3:45 PM  
**To:** julie.dixon@bms.com  
**Subject:** BLA 761035 elotuzumab Information Request- Due 10:00 AM Monday

**Importance:** High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following information request:

Refer to the meeting minutes from our March 9, 2015 pre-BLA meeting (under IND 100043), question 3a. Provide pooled safety analyses of studies CA204009 and HuLuc63-1702. These analyses should be comparable to the pooled analyses conducted for the E-Ld combination. In addition to the analyses and discussion, please submit pooled datasets. Submit the requested analyses, discussion, and datasets no later than 3:00 PM (EST) on August 24, 2015.

We would like a commitment to conduct the requested analyses by Monday, **August 10, 2015 at 10:00 AM (EST)**. Please also follow up with an official response under the BLA and IND.

Please confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,  
Natasha Kormanik, MSN, RN, OCN®  
LT, U.S. Public Health Service  
Regulatory Health Project Manager  
Division of Hematology Products  
FDA/CDER/OHOP  
10903 New Hampshire Avenue, Room 2389  
Silver Spring, MD 20903  
(o) 240-402-4227  
[Natasha.Kormanik@fda.hhs.gov](mailto:Natasha.Kormanik@fda.hhs.gov)

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/s/  
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NATASHA L KORMANIK  
08/07/2015

## Kormanik, Natasha

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**From:** Kormanik, Natasha  
**Sent:** Friday, August 07, 2015 6:06 PM  
**To:** julie.dixon@bms.com  
**Subject:** BLA 761035 Elotuzumab Information Request

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following information request:

Please submit to the NDA ADAMs datasets for the following trials: HuLuc63-1702 and HuLuc63-1701. This information should be submitted no later than COB August 24, 2015. This may represent a filing review issue if this information is not received in a timely manner.

Please confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,  
Natasha Kormanik, MSN, RN, OCN®  
LT, U.S. Public Health Service  
Regulatory Health Project Manager  
Division of Hematology Products  
FDA/CDER/OHOP  
10903 New Hampshire Avenue, Room 2389  
Silver Spring, MD 20903  
(o) 240-402-4227  
[Natasha.Kormanik@fda.hhs.gov](mailto:Natasha.Kormanik@fda.hhs.gov)

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/s/  
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NATASHA L KORMANIK  
08/07/2015

## Kormanik, Natasha

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**From:** Kormanik, Natasha  
**Sent:** Tuesday, July 28, 2015 12:17 PM  
**To:** julie.dixon@bms.com  
**Subject:** BLA 761035 elotuzumab Inspection Information Request- Due August 1 2015

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. BLA 761035 is currently under review and we have the following additional requests for information:

Submit the information request below separately as pdf files, per clinical study investigator site. Provide the following the study subject data listings that should capture the following, as applicable for Meletios Dimopoulos, MD (Athens, Greece Study CA204004 Site 4600), Antonio Palumbo, M.D. (Turin, Italy Study CA204009 Site 4934), Paul Richardson, M.D. (Study CA204004 Site 1414 Boston, MA), and Darrell White, M.D. (Study CA204004 Site 2407, Halifax, Canada):

- a. Subject discontinuations (If applicable application per treatment group: site subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).
- b. Subject assignment per treatment arm (randomization group, as applicable).
- c. Concomitant medication list (non-study medications).
- d. All adverse events (If applicable pretreatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no])).
- e. Primary study efficacy endpoint.

We request a response by **3:00 PM (EST) on August 1, 2015**, via e-mail. Please also follow up with an official response under the BLA.

Please confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,  
Natasha Kormanik, MSN, RN, OCN®  
LT, U.S. Public Health Service  
Regulatory Health Project Manager  
Division of Hematology Products  
FDA/CDER/OHOP  
10903 New Hampshire Avenue, Room 2389  
Silver Spring, MD 20903  
(o) 240-402-4227  
[Natasha.Kormanik@fda.hhs.gov](mailto:Natasha.Kormanik@fda.hhs.gov)

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/s/  
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NATASHA L KORMANIK  
07/28/2015

## Kormanik, Natasha

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**From:** Kormanik, Natasha  
**Sent:** Monday, July 27, 2015 11:36 AM  
**To:** julie.dixon@bms.com  
**Subject:** BLA 761035 Elotuzumab Information Request- Due August 3, 2015

**Importance:** High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following comments and information requests:

### Section 3.2.P.2.5. Container Closure Integrity

1) Please provide summary CCIT results (study date and run number) obtained from the qualification of the (b) (4) and describe the (b) (4) controls (both positive and negative). Please provide the (b) (4) process parameters validated with the CCIT.

### Section 3.2.P.2.5.3. Rabbit Pyrogen Test

1) Please provide justification for the administered dose based on the maximum dose of DP per day per kg of body weight of a human.  
2) Please submit the protocol report for Rabbit Pyrogen Test. (b) (4)

### Section 3.2.P.3.4.1. In-Process Test Methods: Bioburden

Please provide the sample volume for the bioburden test performed for the (b) (4). Please clarify, if the bioburden samples are taken at the (b) (4) step.

### Section 3.2.P.3.5.2.4. Validation of Sterile Filtration

1) There is no information provided in the submission about the (b) (4) used during validation and for production.  
2) Please provide the filter validation report, containing the following information: the viability results that demonstrated that the DP has (b) (4).  
It appears that the microbial retention study was conducted by (b) (4).  
We recommend that the challenge study be conducted with a surrogate DP formulation with (b) (4) or other modification which allow (b) (4) growth. A placebo solution could be used.

(b) (4)  
Please provide a time frame for conducting these studies.

3) Provide a description of the (b) (4) with validation data.  
The microbial retention study should be done with the filters sterilized (b) (4)

### Section 3.2.P.3.5.2.5. Process Simulation and Media Fills

(b) (4)

**Section 3.2.P.5.3. Validation of Analytical Procedures**

Please provide CCIT method validation data.

We request a response by **12:00 PM (EST) on August 3, 2015** via e-mail. Please also follow up with an official response under the BLA.

Please confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,  
Natasha Kormanik, MSN, RN, OCN®  
LT, U.S. Public Health Service  
Regulatory Health Project Manager  
Division of Hematology Products  
FDA/CDER/OHOP  
10903 New Hampshire Avenue, Room 2389  
Silver Spring, MD 20903  
(o) 240-402-4227  
[Natasha.Kormanik@fda.hhs.gov](mailto:Natasha.Kormanik@fda.hhs.gov)

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/s/  
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NATASHA L KORMANIK  
07/27/2015

## Kormanik, Natasha

---

**From:** Kormanik, Natasha  
**Sent:** Wednesday, July 22, 2015 1:02 PM  
**To:** julie.dixon@bms.com  
**Cc:** Wall, Laura  
**Subject:** BLA 761035 elotuzumab Information Request- Due by 3:00 Friday

**Importance:** High

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab. We have the following information requests:

For Study CA204004, please provide the SAS codes for the two different protocol-specified mixed-effect models:

- A longitudinal mixed model for the analysis of HRQoL data
- A random intercept and slope mixed model for the QT/QTc analyses

We request a response by **3:00 PM (EST) on July 24, 2015 (Friday)**. I will be out of the office on Friday, so please forward the response to my colleague Laura Wall (who I have CC'd) and keep me CC'd. Please also follow up with an official submission under the BLA. Please confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,

Natasha Kormanik, MSN, RN, OCN®  
LT, U.S. Public Health Service  
Regulatory Health Project Manager  
Division of Hematology Products  
FDA/CDER/OHOP  
10903 New Hampshire Avenue, Room 2389  
Silver Spring, MD 20903  
(o) 240-402-4227  
[Natasha.Kormanik@fda.hhs.gov](mailto:Natasha.Kormanik@fda.hhs.gov)

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/s/  
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NATASHA L KORMANIK  
07/22/2015



BLA 761035

**BLA ACKNOWLEDGMENT**

Bristol-Myers Squibb Company  
Attention: Julie Dixon, PhD  
Group Director, Global Regulatory Safety & Biometrics  
5 Research Parkway  
Wallingford, CT 06492

Dear Dr. Dixon:

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: Elotuzumab

Date of Application: June 27, 2015

Date of Receipt: June 29, 2015

Our Reference Number: BLA 761035

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 August 28, 2015, 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).

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 Hematology Products  
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](mailto: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 me at (240) 402-4227.

Sincerely,

*{See appended electronic signature page}*

Natasha Kormanik, MSN, RN, OCN<sup>®</sup>  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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NATASHA L KORMANIK  
07/06/2015

## **Kormanik, Natasha**

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**From:** Kormanik, Natasha  
**Sent:** Thursday, July 02, 2015 2:20 PM  
**To:** julie.dixon@bms.com  
**Subject:** BLA 761035 elotuzumab Information Request

Dear Dr. Dixon,

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for elotuzumab.

We also refer to your submission dated June 29, 2015. We have the below information request.

**Information Request:**

The Division of Risk Management notes that a risk management plan was not submitted with this application. Please submit as an amendment to your application a copy of your most recent EU Risk Management plan and a U.S. risk management plan if you have one available.

Please do so with an official response under the BLA and provide me a courtesy copy. Please confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,  
Natasha Kormanik, MSN, RN, OCN®  
LT, U.S. Public Health Service  
Regulatory Health Project Manager  
Division of Hematology Products  
FDA/CDER/OHOP  
10903 New Hampshire Avenue, Room 2389  
Silver Spring, MD 20903  
(o) 240-402-4227  
[Natasha.Kormanik@fda.hhs.gov](mailto:Natasha.Kormanik@fda.hhs.gov)

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/s/  
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NATASHA L KORMANIK  
07/02/2015



IND 100043

**MEETING MINUTES**

Bristol-Myers Squibb Company  
Attention: Julie Dixon, PhD  
Director, Global Regulatory Safety & Biometrics  
5 Research Parkway  
Wallingford, CT 06492

Dear Dr. Dixon:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for elotuzumab (BMS-901608).

We also refer to the meeting between representatives of your firm and the FDA on March 9, 2015. The purpose of the meeting was to discuss various elements of your planned BLA based on two randomized controlled trials, CA204004 and CA204009, including the adequacy of the clinical data to support submission of the BLA and potential approval.

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 Natasha Kormanik, Regulatory Project Manager at (240) 402-4227.

Sincerely,

*{See appended electronic signature page}*

Albert Deisseroth, MD, PhD  
Clinical Team Leader  
Division of Hematology Products  
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**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** March 9, 2015 at 1:00 PM to 2:00 PM (EST)  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1315  
Silver Spring, Maryland 20903

**Application Number:** IND 100043  
**Product Name:** Elotuzumab (BMS-901608)  
**Indication:** (b) (4) Multiple Myeloma  
**Sponsor/Applicant Name:** Bristol-Myers Squibb Company

**Meeting Chair:** Albert Deisseroth, MD, PhD  
**Meeting Recorder:** Natasha Kormanik, MSN, RN, OCN<sup>®</sup>

**FDA ATTENDEES**

OHOP/ Division of Hematology Products

Albert Deisseroth, MD, PhD – Clinical Team Leader  
Theresa Carioti, MPH – Chief, Project Management Staff  
Natasha Kormanik, MSN, RN, OCN<sup>®</sup> – Regulatory Health Project Manager

OHOP/ Division of Hematology, Oncology, Toxicology

Ramadevi Guidi, PhD – Acting Team Lead  
Brenda Gehrke, PhD – Pharmacologist  
Michael Manning, PhD – Pharmacologist

Office of Biotechnology Products/ Division of Monoclonal Antibodies

Linan Ha, PhD – Team Lead  
Rachel Novak, PhD – Biologist

Office of Clinical Pharmacology/ Division of Clinical Pharmacology V

Bahru Habtemariam, PharmD – Acting Clinical Pharmacology Team Leader  
Vicky Hsu, PhD – Clinical Pharmacology Reviewer

Office of Biostatistics/ Division of Biometrics V

Lei Nie, PhD – Biostatistics Team Leader

Chia-Wen Ko, PhD – Biostatistics Reviewer

Office of Surveillance and Epidemiology/ Division of Risk Management

Naomi Redd, PharmD – Acting Team Leader

Mona Patel, PharmD – Reviewer

Kevin Wright, PharmD – Safety Regulatory Project Manager

Eastern Research Group

Patrick Zhou – Independent Assessor

## **SPONSOR ATTENDEES**

Bristol-Myers Squibb Company

Akintunde Bello – Executive Director, Clinical Pharmacology & Pharmacometrics

Eric Bleickardt, MD – Group Director, Oncology, Global Clinical Research

Julie Dixon, PhD – Director, Global Regulatory Sciences – Oncology

Rana Ezzeddine, PhD – Associate Director, Oncology, Global Biometric Sciences

Manish Gupta, PhD, FCP – Director, Clinical Pharmacology & Pharmacometrics

Jessica Katz, MD, PhD – Medical Director, Oncology, Global Clinical Research

Jonathan Leith, PhD – Vice President, Global Development Lead – Elotuzumab

George Manos, PhD – Director, Oncology, Global Biometric Sciences

Mark Moyer, MS – Vice President, Global Regulatory Sciences – Oncology

Marie-Laure Papi, PharmD – Director, Global Regulatory Sciences – Oncology

David Shapiro, MD, PhD – Vice President, Oncology, Global Clinical Research

Penelope Sinanian, MPH – Global Regulatory Manager, Global Regulatory Science-  
Oncology

Jean Viallet, MD – Vice President, Oncology, Global Clinical Research

Abbvie

Lisa Wax – Director, Global Regulatory Affairs

## **1.0 BACKGROUND**

Elotuzumab is humanized monoclonal immunoglobulin G1 (IgG1) antibody product directed to human SLAMF7 (Signaling Lymphocyte Activation Molecule, Family 7, also known as CS1). The proposed mechanism of action of elotuzumab involves NK cell-mediated antibody dependent cellular cytotoxicity (ADCC).

On February 15, 2011, there was an end-of-Phase 2 meeting to discuss the Phase 3 study CA204006 for first line treatment of multiple myeloma in combination with lenalidomide and low-dose dexamethasone.

(b) (4)

On January 8, 2014, there was a guidance meeting to discuss a proposed interim analysis of ongoing study CA204004 Phase 3 trial and to receive a preliminary assessment from FDA on the adequacy of the results from the HuLuc63-1703 (Phase 1/2) study to support a Breakthrough Designation for elotuzumab.

As an outcome of the January 8, 2014 Type C meeting, FDA agreed that an interim PFS analysis after completion of patient accrual and the majority of event occurrence is acceptable. However, they requested a minimum of 2 years follow-up on all study subjects. In addition, FDA proposed that an analysis of overall response rate (ORR) as a primary endpoint could be used to support an accelerated approval. A revised CA204004 statistical analysis plan (SAP) which included ORR as a co-primary endpoint and one interim analysis of PFS at 70% of the events and 2 years follow-up on all subjects was reviewed and agreed upon with FDA.

On September 1, 2011, elotuzumab was designated orphan status for the treatment of multiple myeloma.

On May 12, 2014, elotuzumab was granted Breakthrough Therapy Designation.

On December 9, 2014, the Sponsor requested a Pre-BLA meeting to discuss various elements of the planned BLA based on two randomized controlled trials, CA204004 and CA204009, including the adequacy of the clinical data to support submission of the BLA and potential approval.

The purpose of this meeting is to gain feedback from the Agency and to reach agreement on the planned BLA based on two completed, randomized, controlled studies demonstrating consistent results in relapsed/refractory multiple myeloma subjects.

FDA sent Preliminary Comments to Bristol-Myers Squibb Company on March 3, 2015.

## 2. DISCUSSION

***Question 1:*** Does FDA agree that the results from the two randomized, controlled trials, CA204004 and CA204009, with data from supporting studies, are adequate to support a filing to enable regulatory decision making for the proposed indication of elotuzumab for the treatment of MM in patients who have received one or more prior therapies: in combination with lenalidomide and dexamethasone

(b) (4)

**FDA Response to Question 1:** A filing decision will be made at the time of initial review of the BLA submission.

(b) (4)

(b) (4)

**Discussion:** The Agency acknowledges that the elotuzumab combinations are active.

(b) (4)

The Sponsor offered to provide information relating to other combination trials under development and as well as a mechanism based discussion of elotuzumab combinations being developed.

**Question 2:** Does FDA have any comments on the proposed approach to determine adverse drug reactions?

**FDA Response to Question 2:** It is premature to discuss labelling at this point. The BLA submission should include data for and discussion of all adverse events that occurred in the clinical trials. The adequacy of your approach for the determination of which adverse events should be included as adverse drug reactions in labeling will be a review issue at the time of BLA review.

**Discussion:** There was no discussion pertaining to this question.

**Question 3:**

a) *Is the proposed format and content of the BLA acceptable to FDA?*

**FDA Response to Question 3a:** No, given the relatively large number of studies that are planned for inclusion in this BLA, the application should include an Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS). The ISE and ISS are not summaries, but detailed integrated analyses of all relevant data from the clinical studies. We refer you to the FDA Guidance “Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document” at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm136174.pdf> and “Guidance for Industry: Integrated Summary of Effectiveness” at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079803.pdf>.

The ISS and ISE should address combinations of elotuzumab with lenalidomide and dexamethasone (b) (4)

**Discussion:** The Sponsor plans to provide an overall integrated safety and efficacy analysis.

- b) *Does FDA agree that the draft TOC, which includes the contents of the application, is complete for FDA review in support of a BLA submission and potential BLA approval?*

**FDA Response to Question 3b:** No. See response to question 3a.

**Discussion:** There was no discussion pertaining to this question.

**Question 4:** *Does FDA agree with the updated data submission plans as described above and outlined in Appendix 6)?*

**FDA Response to Question 4:** No. The safety update should be provided at 120 days for a standard review, and a 90 day update should be provided in the event of priority review. Furthermore, please clarify why you do not intend to submit data for the following trials in the safety update: HuLuc63-1701, CA204011, HuLuc63-1702, CA204010. Additionally, please clarify if information for trials CA204006 and CA204112 will be included in the initial BLA submission and what information from these trials will be provided in the safety update.

**Discussion:** The Sponsor will provide a safety update at 120 days if standard review is given and at 90 days in the vent a priority review is granted.

**The Agency agrees with the Sponsors proposed plan.**

**Question 5:** *Based on the preliminary study results from the two randomized, controlled trials, CA204004 and CA204009, and the safety profile from the additional elotuzumab studies, does FDA agree with the current proposed Risk Management Strategy?*

**FDA Response to Question 5:** Your proposed Risk Management Strategy appears acceptable, however, additional comments will be provided during the BLA review.

**Discussion:** There was no discussion pertaining to this question.

**Question 6:** *The proposed clinical pharmacology package at the time of BLA submission will be comprised of the following: single-dose PK, multiple-dose PK, PPK (CA204004, CA204005, CA204007, CA204011), E-R analysis with safety/efficacy endpoints from the CA204004 study, PD, cytokine modulation data, ECG analysis, and immunogenicity. BMS proposes to submit the results of the supplementary PPK* (b) (4)

*from the CA204009 study during review of the BLA submission. Does the FDA agree with this proposal?*

**FDA Response to Question 6:** It is the Agency's expectation that the BLA submission should be complete at the time of original BLA submission. Submission of data/reports during the review cycle should be avoided and is subject to extension of the review clock. If you commit to submitting the population PK [REDACTED] (b) (4) within 30-days after the date of original BLA submission, the reports will be reviewed and the review clock will not be extended.

**Discussion:** There was no discussion pertaining to this question.

**Question 7:** *Does FDA agree that during the review process CMC responses can be provided in Module 1 in a question & response format, with corresponding updates to Module 3 provided once agreement on responses is reached? BMS proposes to provide this update within one week after the late-cycle review meeting. Is this proposal acceptable?*

**FDA Response to Question 7:** It is acceptable to provide CMC responses in Module 1 in a question and response format during the review process. However, be aware that the timeline to which the product quality reviewer will adhere is different from the PDUFA V deadline. Your BLA should be updated in a timely manner to allow sufficient time for the product quality reviewer to ensure that changes to Module 3 have been implemented adequately. Please refer to the CDER 21<sup>st</sup> Century Review Process Desk Reference Guide (<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.htm>).

**Discussion:** There was no discussion pertaining to this question.

**Additional Comment:**

In the BLA please provide an assessment on the reproductive and developmental toxicity of elotuzumab which may be based on non-product specific literature or data for which BMS has right of reference.

**3.0 OTHER IMPORTANT INFORMATION**

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed. The Sponsor will plan to formally request a rolling submission. The Sponsor plans to submit the quality and non-clinical modules by the end of May 2015. A full application is expected by the end of June

2015, with the exception of the clinical pharmacology population PK studies from study CA204009.

All applications are expected to include 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 and it was concluded that REMS will not be applied to the application, based upon the current safety information for elotuzumab.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
  1. Clinical Pharmacology population PK (b) (4) studies from study CA204009.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

**BLA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY**

In addition, we note that a chemistry pre-submission meeting is planned. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

### **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.

## **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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

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<br>(Person, Title) | Phone and<br>Fax<br>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).**

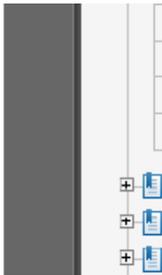
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - 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.

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

No issues identified at the meeting.

#### **5.0 ACTION ITEMS**

| <b>Action Item/Description</b>               | <b>Owner</b> | <b>Due Date</b>                 |
|----------------------------------------------|--------------|---------------------------------|
| Formally submit rolling submission proposal. | Sponsor      | Date not identified at meeting. |

#### **6.0 ATTACHMENTS AND HANDOUTS**

Sponsor's PowerPoint presentation.

**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.”

| <b>DSI Pre-NDA Request Item<sup>1</sup></b> | <b>STF File Tag</b>          | <b>Used For</b>                                  | <b>Allowable File Formats</b> |
|---------------------------------------------|------------------------------|--------------------------------------------------|-------------------------------|
| 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.

<sup>1</sup> 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](mailto:ESUB@fda.hhs.gov)

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ALBERT B DEISSEROTH  
03/12/2015



IND 100043

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

Bristol-Myers Squibb Company  
Attention: Julie Dixon, PhD  
Director, Global Regulatory Sciences  
5 Research Parkway  
Wallingford, CT 06492

Dear Dr. Dixon:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Elotuzumab (BMS-901608).

We also refer to your March 21, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that Elotuzumab indicated for Elotuzumab in combination with lenalidomide and dexamethasone for treatment of multiple myeloma in patients who have received one or more prior therapies 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 Elotuzumab indicated for Elotuzumab in combination with lenalidomide and dexamethasone for treatment of multiple myeloma in patients who have received one or more prior therapies 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 draft *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.<sup>1</sup>

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. Attachment 1 lists 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*<sup>2</sup> for procedures on requesting a meeting. If you feel that submitting a meeting request

<sup>1</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

<sup>2</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

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 Elotuzumab indicated for Elotuzumab in combination with lenalidomide and dexamethasone for treatment of multiple myeloma in patients who have received one or more prior therapies 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, please contact Patricia Garvey, Senior Regulatory Project Manager, at (301) 796-8493.

Sincerely,

*{See appended electronic signature page}*

Ann Farrell, MD  
Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

**Attachments:**

Attachment 1: Breakthrough Designated Product, Initial Multidisciplinary Comprehensive Meeting between FDA/Sponsor, Potential Topics for Discussion

**Attachment 1: Breakthrough Designated Product**  
**Initial Multidisciplinary Comprehensive Meeting between FDA/Sponsor**  
**Potential Topics for Discussion**

**General/Regulatory:**

- Planned target date for NDA/BLA submission, including plans for rolling review
- Other indications in development
- Expanded access plans, including intent to communicate these plans publicly
- Plans to seek accelerated approval
- Regulatory status with non-U.S. regulatory agencies
- Plans to defer or waive studies or trials, including those to be conducted as postmarketing commitments/postmarketing requirements (PMC/PMRs)
- Rationale for proposed flexibility in study and trial design
- Plans for submission of a proprietary name request
- If a drug/device combination product, device development information and plan
- In-vitro diagnostic development plan with the Center for Device and Radiologic Health (CDRH)
- Target product profile for proposed indication
- Gantt chart of development timeline, including information on all areas noted below
- Proposed communication plan for periodic development program updates to the FDA, including timelines and content

**Clinical Activity and Data Analysis:**

- Existing and planned clinical sites and accrual data
- Efficacy
  - Status of all clinical studies and topline summary results
  - Preliminary evidence of proof of concept
  - Planned or completed clinical trials intended to support efficacy, including:
    - Overall study design, the population to be studied, trial size, proposed indications, endpoints, power, plans for interim analyses, plans for resizing of trials, Type I error control, and expected initiation/completion dates
    - Validity of the outcomes and endpoints. If using drug development tools, such as a patient reported outcomes or biomarkers, plans for the development and validation of the instrument, if appropriate.
- Safety
  - Potential safety issues from nonclinical studies/early clinical trials
  - Liver, kidney, cardiac, immune suppression, carcinogenicity, genotoxicity, and immunogenicity safety profile
  - Clinical trials safety monitoring plan for safety signals identified in nonclinical studies and early clinical trials, and for post-market drug safety and surveillance (pharmacovigilance)
    - Proposed size of safety population
    - Plan or need for long-term safety studies

- Pre-approval
- Post-approval
- Plans to mitigate/minimize risk, proposed Risk Evaluation and Mitigation Strategy (REMS)
- Specific Populations
  - Dose, study design, efficacy endpoints, size and composition of population, additional safety trials, for populations such as:
    - Geriatrics
    - Pediatrics
    - Hepatically/Renally Impaired
  - Proposed pediatric development plan with outlines/synopses of additional studies.

#### **Clinical Pharmacology and Pharmacokinetics:**

- Justification for all dose selections, including number of doses, dose intervals, etc
- Clinical pharmacology, pharmacodynamics, and pharmacokinetics studies: completed, ongoing, planned, and requests for deferral, such as:
  - Immunogenicity
  - Dosing
    - Single ascending dose
    - Multiple ascending dose
    - Dose response study
  - Food-effect
  - Drug-drug interactions (DDI)
  - Thorough QT/QTc
  - Organ impairment
  - Pharmacogenomics
  - Plans for an in vivo bridging trial of the formulation studied in the clinical development program to the to-be-marketed formulation
  - Plans for conducting population pharmacokinetics, exposure-response modeling/simulation analyses
  - Plans to describe dose modifications in labeling based on DDI, age, organ impairment, etc.

#### **Nonclinical Pharmacology, Pharmacokinetics, and Toxicology**

- Nonclinical studies completed, ongoing, and planned, including, the number and sex of animals per dose, doses, route of administration, toxicities, duration of study and study results. For studies planned timelines for initiation and submission of study reports. Examples of such studies include:

- Subacute and chronic toxicology
- Gene toxicology
- Reproductive toxicology
- Carcinogenicity studies
- Animal models of disease and PK parameters associated with efficacy

- Evidence of mechanism of action
- Safety pharmacology, where appropriate
- Disease specific animal models

#### **Chemistry, Manufacturing, and Controls:**

- Drug product:
  - Dosage form
  - Formulation description
  - Administration instructions, delivery systems (e.g. vials, pre-filled syringes, etc.) proposed draft packaging, and disposal instructions
  - Critical quality attributes
  - Control and stability strategies
  - Proposed shelf life and required stability studies
- Drug substance:
  - Characterization
  - Critical quality attributes
  - Control and stability strategies
  - Proposed shelf life or retest period and required stability studies
- Proposed commercial processes:
  - Manufacturing process, in process controls, scale-up plans
  - Comparison of proposed commercial manufacturing processes to clinical manufacturing processes
  - Physico-chemical comparability of lots used in clinical studies and commercial lots or a plan to establish analytical comparability
  - Current manufacturing site(s) and proposed commercial site(s), if different, registration numbers, readiness, and manufacturing timelines
  - Current release and stability testing site(s) and proposed commercial testing site(s), if different
  - Anticipated market demand at launch
- Proposed validation approaches:
  - Drug substance and drug product manufacturing process
  - Microbial control and sterility assurance
  - Viral clearance
  - Analytical methods

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/s/  
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ANN T FARRELL  
05/12/2014



IND 100043

**MEETING MINUTES**

Bristol-Myers Squibb  
Attention: Kathleen O'Donnell  
Director, Global Regulatory Sciences – US Liaison  
P.O. Box 4000  
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Investigational New Drug Application (IND) file for Elotuzumab.

We also refer to the telecon between representatives of your firm and the FDA on October 17, 2012. (b) (4)

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Albert Deisseroth, M.D., Ph.D.,  
Clinical Team Leader  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

Meeting Minutes  
Pre-Phase 3 Meeting

### MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-Phase 3

**Meeting Date and Time:** October 17, 2012, 2:00 PM – 3:00 PM ET  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1415  
Silver Spring, Maryland 20903

**Application Number:** IND 100043  
**Product Name:** Elotuzumab  
**Indication:** Elotuzumab is indicated for the treatment of relapsed/refractory Multiple Myeloma (b) (4)

**Sponsor/Applicant Name:** Bristol-Myers Squibb Company  
**Meeting Chair:** Albert Deisseroth  
**Meeting Recorder:** Jessica Boehmer

#### FDA ATTENDEES

Division of Hematology Products (DHP)

Edvardas Kaminskas, M.D., Deputy Director  
Albert Deisseroth, M.D., Ph.D., Clinical Team Leader  
Thomas Herndon, M.D., Clinical Reviewer  
Brenda Gehrke, Ph.D., Pharmacology/Toxicology Reviewer  
Matthew Wang, Pharmacy Student  
Jessica Boehmer, M.B.A., Regulatory Project Manager

Office of Clinical Pharmacology (OCP)

Bahru Habtemariam, Pharm.D., Clinical Pharmacologist  
Rachelle Lubin, Pharm.D., Clinical Pharmacologist

Office of Biostatistics, Division of Biometrics

Mark D. Rothmann, Ph.D., Statistical Team Leader  
Chia-Wen Ko, Ph.D., Statistician

Office of Biotechnology Products (OBP) /Division of Monoclonal Antibodies (DMA)

Patrick Swann, Ph.D., Chief, Regulatory Science & Policy Branch  
Ram Sihag, Ph.D., Biologist

Meeting Minutes  
Pre-Phase 3 Meeting

## SPONSOR ATTENDEES

Jonathan Leith, Ph.D., Vice President, Global Development Lead – Elotuzumab  
Erick Bleickardt, M.D., Group Director, Oncology, Global Clinical Research  
David Shapiro, M.D., Ph.D., Vice President, Oncology, Global Clinical Research  
Jessica Katz, M.D., Ph.D., F.A.C.P., Associate Medical Director, Oncology, Global Clinical Research  
Pralay Mukhopadhyay, Ph.D., Associate Director, Oncology, Global Biometric Sciences  
Manish Gupta, Ph.D., Associate Director, Oncology, Discovery Medicine and Clinical Pharmacology  
Kathleen O'Donnell, Director, U.S. Regulatory Sciences  
Ann Cross, Ph.D., Executive Director, Oncology, Global Biometric Sciences  
Mark Moyer, M.S., Vice President, Oncology, Global Regulatory Sciences  
Penelope Sinanian, M.P.H., Global Regulatory Manager  
Lisa Wax, Director, Global Regulatory Affairs, Abbott  
Jeff Petty, Manager, Global Pharmaceutical Regulatory Affairs, Abbott

### 1.0 BACKGROUND

The purpose of this meeting is to discuss the design and conduct of the proposed Phase 3 clinical study (b) (4).

Elotuzumab (BMS-901608) is a humanized monoclonal immunoglobulin G1 (IgG1) antibody product directed to human CS1, a cell surface glycoprotein with homology to the CD2 family of cell surface proteins and which is highly expressed in MM cells. The expression of CS1 is restricted to malignant myeloma cells and subsets of normal leukocytes in humans (natural killer [NK], natural killer T-cells [NKT], a subset of CD8+ T cells, and plasma cells). Elotuzumab has been shown to kill MM cell lines and primary myeloma cells in vitro in the presence of peripheral blood mononuclear cells (PBMCs) or purified NK cells.

The initial IND for elotuzumab, IND 100043, was submitted July 11, 2006. Elotuzumab is not approved in any country for any indication.

Three meetings took place with the FDA:

- An End-of-Phase 1 Meeting on July 12, 2010 to discuss study CA204004
- A Type C CMC Meeting on January 24 2011 to discuss the manufacturing program for registration of elotuzumab.
- An End-of-Phase 2 Meeting on February 15, 2011 to discuss study CA204006

Elotuzumab was granted orphan drug status in the US on September 1, 2011.

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/s/  
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ALBERT B DEISSEROTH  
10/18/2012



IND 100043

**MEETING MINUTES**

Bristol Myers Squibb, Company  
Attention: Marie-Laure Papi, Pharm. D.  
Director-Oncology, Global Regulatory Sciences  
5 Research Parkway  
Wallingford, CT 06492

Dear Ms. Papi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “Humanized Monoclonal Antibody (huLuc63) to CS1.”

We also refer to the meeting held on February 15, 2011, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4248.

Sincerely,

*{See appended electronic signature page}*

Vaishali Jarral, M.S., M.B.A.  
Regulatory Project Manger  
Division of Biologic Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure – Meeting Minutes, Additional DBOP CDISC Guidance and OODP’s End-of-Phase 2 General Advice for Planned Marketing Applications

## MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 15, 2011  
TIME: 1:00 PM-2:00 PM EDT  
APPLICATION: IND 100043  
SPONSOR: Bristol Myers Squibb [BMS]/Abbott Laboratories  
[BMS/Abbott]  
DRUG NAME: Elotuzumab (BMS-901608), humanized anti-CS1  
Monoclonal IgG1 antibody  
TYPE OF MEETING: End of Phase 2, Type B Meeting  
MEETING CHAIR: Suzanne Demko  
MEETING RECORDER: Vaishali Jarral  
SUBJECT: To discuss and obtain FDA feedback on the Phase 3  
(b) (4) for elotuzumab in  
patients with multiple myeloma eligible for Stem Cell  
Transplant (SCT).

### LIST OF FDA ATTENDEES

|                   |                                             |
|-------------------|---------------------------------------------|
| Joseph Gootenberg | Deputy Director, DBOP/OODP                  |
| Suzanne Demko     | Clinical Team Leader, DBOP/OODP             |
| Thomas Herndon    | Clinical Reviewer, DBOP/OODP                |
| Stacey Ricci      | Pharmacology/Toxicology Reviewer, DBOP/OODP |
| Vaishali Jarral   | Regulatory Project Manager, DBOP/OODP       |

#### **Office of Pharmaceutical Sciences Office of Biotechnology Products Division of Monoclonal Antibodies**

|                        |                     |
|------------------------|---------------------|
| Ram Sihag              | Quality Reviewer    |
| Ruth Cordoba-Rodriguez | Quality Team Leader |

#### **Office of Clinical Pharmacology**

|                       |                              |
|-----------------------|------------------------------|
| Division V            |                              |
| Hong Zhao             | Team Leader                  |
| Li Zhang              | Pharmacometrics reviewer     |
| Garnett, Christine;   | Team Leader, Pharmacometrics |
| Grimstein, Christian; | Genomics Reviewer            |

#### **Office of Biostatistics**

|                             |             |
|-----------------------------|-------------|
| Division of Biostatistics V |             |
| Yuan Li Shen                | Reviewer    |
| He Kun                      | Team Leader |

**LIST OF SPONSOR ATENDEES:**

**Bristol-Myers Squibb**

|                            |                                                                     |
|----------------------------|---------------------------------------------------------------------|
| Jonathan Leith, M.D.       | Vice President, Global Development Lead - Elotuzumab                |
| Glenn Kroog, M.D., Ph.D.   | Director, Oncology, Global Clinical Research                        |
| Marie-Laure Papi, Pharm.D. | Director, Global Regulatory Science                                 |
| David Shapiro, M.D., Ph.D. | Vice President, Oncology, Global Clinical Research                  |
| Justin Kopit, Ph.D.        | Associate Director, Oncology, Global Clinical<br>Development        |
| Ashley Pereira, Pharm.D    | Director, US Regulatory Sciences                                    |
| Joseph Lamendola, Ph.D.    | Vice President, US Regulatory Sciences and Regulatory<br>Policy     |
| Bindu Murthy, Pharm.D      | Associate Director, Discovery Medicine and Clinical<br>Pharmacology |
| Margo Herron               | Director, US Regulatory Policy                                      |
| Charlene Craig             | Associate Director, CMC Regulatory Sciences                         |

**Abbott Laboratories**

|                       |                                                           |
|-----------------------|-----------------------------------------------------------|
| Anil Singhal, Ph.D.   | Program Director, Clinical Research                       |
| David Ross, Pharm. D. | Senior Director, Global Pharmaceutical Regulatory Affairs |
| Jeff Petty            | Manager, Global Pharmaceutical Regulatory Affairs         |

**MEETING OBJECTIVE:**

The purpose of this meeting is for Bristol-Myers Squibb (BMS)/Abbott to obtain FDA feedback on the clinical development of elotuzumab (BMS-901608) for the (b) (4) treatment of patients with multiple myeloma (MM). The scope of clinical questions for discussion on the study (b) (4) CA204006, includes: the target population, the comparator, the selected dose and schedule, the endpoints and analyses, the clinical pharmacology plan, and support for approval.

**BACKGROUND**

On November 22, 2010, Bristol-Myers Squibb/Abbott requested a Type B End of Phase 2 meeting to discuss the clinical development of elotuzumab (BMS-901608) for the first line treatment of patients with multiple myeloma (MM). The meeting briefing packages were received electronically on January 7, 2011.

History

This IND was originally sponsored by Facet Biotech Corporation, submitted on July 11, 2006 and was transferred to BMS effective July 1, 2010. BMS and Facet/Abbott have entered an agreement to co-develop elotuzumab. Previous interactions with Facet Biotech include pre-IND meetings held on October 27, 2005 and April 20, 2006.

Facet Biotech/Abbott and BMS also met with FDA in a Type B EOP1/PP3 meeting held on July 12, 2010 to discuss the clinical program of elotuzumab specifically to seek FDA's feedback for the study intended to support a regulatory filing, Study CA204004, of elotuzumab with and without Lenalidomide and low dose dexamethasone in patients with relapsed MM who have received 1 to (b) (4) prior therapies. (b) (4) meeting to seek FDA's feedback for an additional trial (b) (4) CA204006 for the treatment of (b) (4) MM with elotuzumab in combination with and without lenalidomide and low dose dexamethasone in subjects not eligible for hematopoietic stem cell transplant (SCT).

### Proposed Registration Plan

The Sponsor's proposed registration plan for elotuzumab in MM consists of one trial in (b) (4) (b) (4) in patients with either relapsed/refractory MM (CA204004) (previously discussed with FDA at an End of Phase 1 meeting dated 12-Jul-2010) and one in patients with previously untreated MM who are not candidates for SCT (CA204006). The initial BLA (the sponsor is planning to submit the initial BLA in the fourth quarter of 2014) will be for relapsed/refractory MM and will be based on Study CA204004. (b) (4)

(b) (4) The sponsor intends to seek Orphan Designation for MM in 2011.

### Chemistry, Manufacturing and Controls

Elotuzumab is a humanized monoclonal IgG1 antibody directed to human CS1, a cell surface glycoprotein with homology to the CD2 family of cell surface proteins. Elotuzumab consists of the complementary determining regions (CDR) of the mouse antibody MuLuc63 grafted onto human IgG1 heavy and kappa light chain frameworks.

CS1 is expressed on MM cells and on NK cells, NK target cells, a subset of CD8+ cells, and plasma cells. The proposed mechanism of action of elotuzumab involves natural killer (NK) cell-mediated antibody dependent cellular cytotoxicity (ADCC). To discuss the pharmaceutical development plan in support of elotuzumab registration BMS/Abbott has also submitted a CMC End of Phase 2 Meeting request which was held on January 25, 2011.

### Nonclinical

Because of limitations in species-specific cross-reactivity and lack of a relevant animal species in which to conduct toxicological studies, the nonclinical safety assessment of elotuzumab consists primarily of in vitro safety and in vivo biological activity assessments to address its selectivity and potential toxicities. BMS/Abbott refers to the End of Phase 1 Meeting dated 12-Jul-2010 where FDA agreed that the limited nonclinical package was sufficient to support Biologics License Application registration for elotuzumab.

### Clinical Pharmacology

The clinical pharmacology plan was designed to characterize the PK, immunogenicity, and cardiovascular (CV) safety of elotuzumab. BMS/Abbott states that the data obtained from the

Phase 1 monotherapy (HuLuc63-1701) and combination therapy trials (HuLuc63-1702 and HuLuc63-1703 Phase 1 and 2 portions) and the sparse PK data that will be collected in Studies CA204004 and CA204006 are considered adequate to characterize the PK of elotuzumab. The PK of elotuzumab will be characterized using noncompartmental PK analysis as well as PPK analysis. Using the PPK model, the covariate effects of age, gender, body weight, concomitant medications, and GFR on the PK of elotuzumab will be evaluated.

The proposed dose selection of a starting dose of 10 mg/kg IV on Days 1, 8, 15, and 22 of a 28 day cycle for Cycles 1 and 2, and subsequent administration of elotuzumab at 10 mg/kg IV on Days 1 and 15 for Cycles 3 to 18, and 20 mg/kg on Day 1 for Cycle 19 and beyond appears acceptable. This is based on preliminary safety data from 35 subjects in HuLuc 63-1701 and 119 subjects treated in HuLuc63-1702, and HuLuc63-1703. Data included in the meeting packet show at least 95% saturation of CS1 target sites on bone marrow plasma cells at the 10 mg/kg dose. The decision to decrease the frequency of administration of elotuzumab beginning in Cycle 19 is based on published data showing that in relapsed MM the maximum depth of response to lenalidomide and low dose dexamethasone is achieved by Cycle 18. The sponsor asserts that simulations of predicted steady-state exposure based on population PK modeling suggest that a dose higher than 10 mg/kg will be needed to support switching from a biweekly to a monthly dosing regimen after Cycle 18. Data included in the meeting packet show that a dose of 20 mg/kg every 4 weeks will maintain elotuzumab trough levels above 70 mcg/ml (the minimum trough concentration at which a maximum activity was seen in preclinical studies).

In addition, the meeting package indicates that the effects of elotuzumab on ECG parameters will be also evaluated in the Phase 3 relapsed/refractory MM study (CA204004). BMS/Abbott is proposing that serial ECGs in triplicate be collected and time-matched PK samples will be drawn within the dosing interval following both single dose and multiple dose elotuzumab administration (in combination with lenalidomide and dexamethasone) in order to cover the full systemic exposure range. ECGs will be centrally read and evaluated for heart rate, abnormal wave rhythms or morphology and interval lengths for PR, QRS, QT and QTc.

### Clinical

To date, elotuzumab has been evaluated in 3 clinical studies, HuLuc63-1701, HuLuc63-1702, and HuLuc63-1703, (see summary table 2 below). The sponsor has provided data for a total of 154 patients with advanced MM treated in these studies. The three studies had an initial, sequential dose-escalation, dose-finding component (Phase 1) and a fixed dose, activity-estimating (Phase 2) component. Protocol HuLuc63-1701 is closed to accrual and enrolled 35 patients with advanced MM. Protocol HuLuc63-1702 has completed the dose-finding portion of the study of elotuzumab in combination with bortezomib and enrollment in the dose-expansion (Phase 2) component is ongoing; the study has enrolled 28 patients with MM who received elotuzumab in combination with bortezomib. The Phase 2 portion of study HuLu63-1703 will enroll 103 patients with relapsed/refractory MM who have received 1-<sup>(b)</sup><sub>(4)</sub> prior therapies of elotuzumab administered in combination with lenalidomide and low-dose (40 mg weekly) dexamethasone.

**Table 2: Completed, Ongoing, and Planned Elotuzumab Studies**

| Study No<br>(Phase)         | Brief Study Title                                                                                                                                                                                                       | Study Status | Number of Subjects |          |                 |
|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------------|----------|-----------------|
|                             |                                                                                                                                                                                                                         |              | Planned            | Enrolled | Treated         |
| HuLuc63-1701<br>(Phase 1)   | Dose escalation study of elotuzumab in advanced multiple myeloma<br>(Initiated: September 2006)                                                                                                                         | Complete     | 42                 | 35       | 34              |
| HuLuc63-1702<br>(Phase 1)   | Dose escalation study of elotuzumab and bortezomib in multiple myeloma following one to three prior therapies<br>(Initiated: May 2008)                                                                                  | Ongoing      | 49                 | 28       | 28 <sup>a</sup> |
| HuLuc63-1703<br>(Phase 1/2) | Dose escalation study of elotuzumab with lenalidomide and dexamethasone in relapsed multiple myeloma<br>(Initiated: July 2008)                                                                                          | Ongoing      | 33                 | 29       | 28 <sup>a</sup> |
|                             |                                                                                                                                                                                                                         | Ongoing      | 70                 | 63       | 63 <sup>a</sup> |
| CA204004<br>(Phase 3)       | A Phase 3, randomized, open label trial of lenalidomide/dexamethasone with or without elotuzumab in relapsed or refractory multiple myeloma                                                                             | Planned      | 640                | -        | -               |
| CA204006<br>(Phase 3)       | A Phase 3, randomized, open label trial of lenalidomide/dexamethasone with or without elotuzumab in subjects with newly diagnosed, untreated, symptomatic, measurable myeloma ineligible for high-dose therapy plus SCT | Planned      | 750                | -        | -               |

Source: Elotuzumab IB ([Appendix 1](#))

<sup>a</sup> Treated as of 07-Jul-2010 for HuLuc63-1702 and Phase 1 of HuLuc63-1703 and as of 03-Sep-2010 for Phase 2 of HuLuc63-1703.

BMS/Abbott's current plan for elotuzumab clinical development is to conduct 2 registrational studies, CA204004 and CA204006, which are scheduled to begin accruing patients in March 2011. As indicated above, the feedback from FDA for Study CA204004 was obtained at an End of Phase 1 Meeting dated 12-Jul-2010 and now the sponsor is seeking feedback from FDA for Study CA204006 for the treatment of (b)(4) MM with elotuzumab with or without lenalidomide and low dose dexamethasone in patients not eligible for SCT.

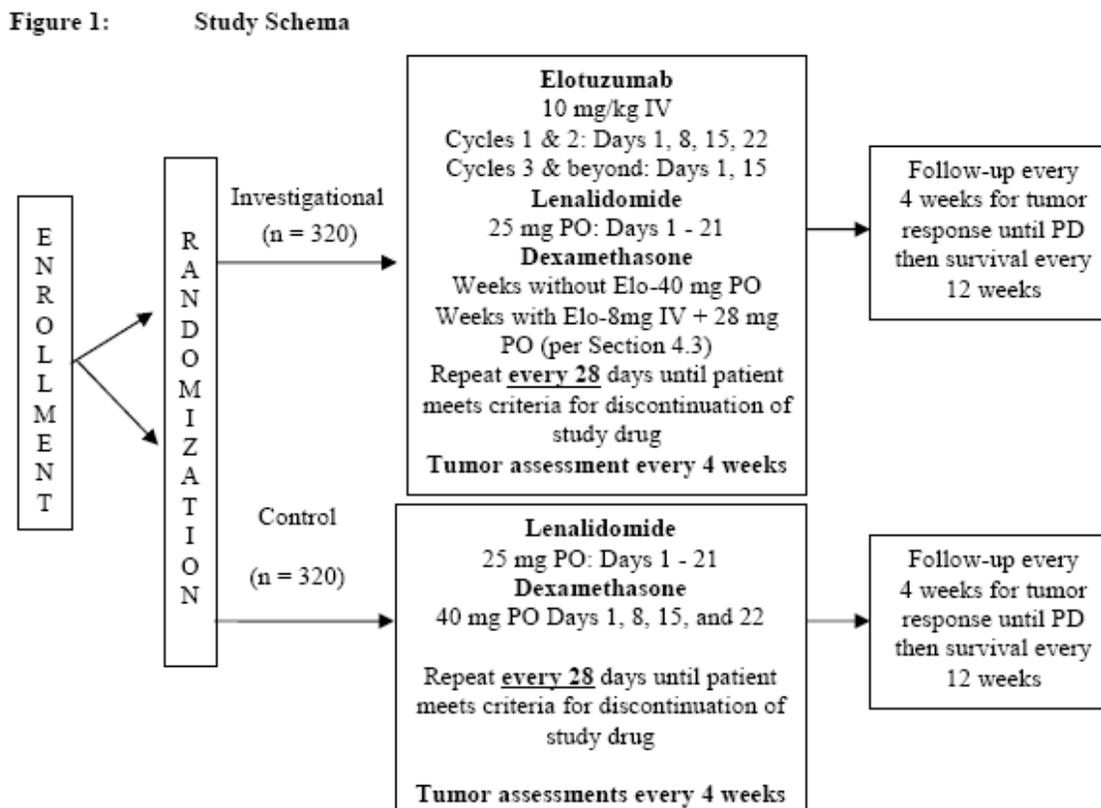
**Study CA204004** is a multicenter, open label, randomized (1:1), trial of lenalidomide (25mg) plus low-dose dexamethasone (40mg) ± elotuzumab (10 mg/kg) that is planned to enroll 640 patients with relapsed or refractory MM who have received 1 to (b)(4) prior therapies.

Randomization will be stratified by:

- $\beta$ 2 microglobulin (< 3.5 mg/L vs  $\geq$  3.5 mg/L)
- Number of prior lines of therapy (1 vs. 2 or more)

- Prior immunomodulatory drugs (none vs. prior thalidomide only vs other)

Subjects will receive lenalidomide and low dose dexamethasone with or without elotuzumab in 28-day cycles until disease progression, unacceptable toxicity, or until the subject meets other criteria for discontinuation of study drug outlined in protocol, per the schema below:



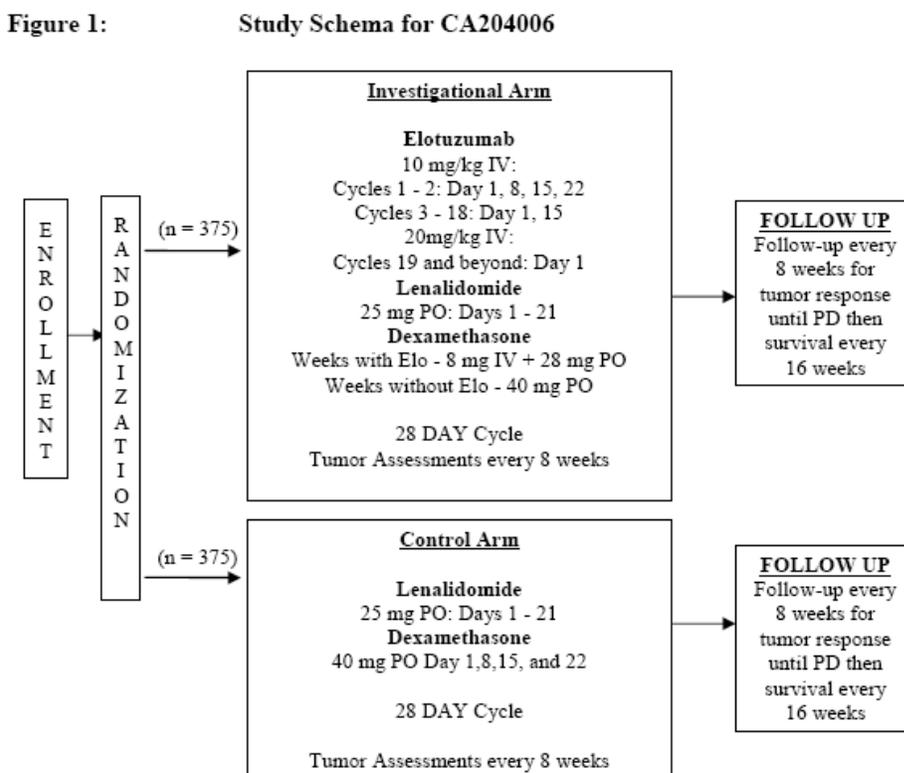
BMS/Abbott are proposing that an independent Data Monitoring Committee (DMC) will review the safety of the trial on a routine basis, including a pre-planned safety interim analysis after 120 subjects have been treated and followed for at least 16 weeks. An additional pre-planned interim analysis for safety and efficacy will occur after approximately 239 progression events.

The primary objective in this study will be to compare progression free survival (PFS) between treatment groups using a stratified log rank test and a one-sided 2.5% type I error rate. The primary endpoint of PFS will be based on the IRC assessment.

The hazard ratio of the experimental to control arm and corresponding two-sided 95% confidence interval will be calculated using a stratified Cox proportional hazards model with treatment arm as the sole covariate. The Kaplan-Meier product limit method will be used to display the PFS curves and to calculate the median PFS and corresponding two-sided 95% confidence interval for each treatment arm.

Key secondary endpoints include objective response (partial response or better) rate and overall survival, for which a hierarchical testing procedure will be used so that the overall experiment-wise  $\alpha$ -level is 2.5%.

**Study CA204006** is a, randomized (1:1), open-label, multicenter trial (N=750) that will investigate lenalidomide and low dose dexamethasone with and without elotuzumab in patients with newly diagnosed, untreated, symptomatic, measurable MM who are ineligible for high-dose therapy plus SCT because of age ( $\geq 65$  years) or coexisting conditions. All subjects will receive lenalidomide and low dose dexamethasone until progression; subjects in the experimental arm will also receive elotuzumab until progression. The general design of the study is based on the ongoing MM-020 Phase 3 study (lenalidomide and low dose dexamethasone for 18 cycles vs. lenalidomide and low dose dexamethasone until progression vs. melphalan, prednisone, and thalidomide for 12 cycles). Figure 1 of the meeting package shows the following diagram of the design and dosing scheme for study CA204006.



Source: CA204006 Draft Protocol ([Appendix 2](#))

PFS will be the primary endpoint in this study. PFS will be compared between arms at the interim and final looks using a stratified log-rank test. The stratification factors are the same as those used in the randomization. Approximately 750 subjects will be enrolled to obtain a total of 482 progression events. BMS/Abbott states that this number of events will ensure that a HR of 0.74 (i.e., for an increase in median PFS from 25 months to 33.75 months) can be detected with 90% power assuming a one-sided,  $\alpha = 0.025$  level with 1 interim analysis. The sponsor indicates that in view of evolving results with frontline lenalidomide therapy, a reassessment of the sample size could be made.

The secondary endpoints in this study are time in response (time in response is the time from first objective response until the date of progression or death; subjects who do not achieve a response will be considered to have progressed on their date of randomization), overall response rate (ORR), and overall survival (OS). P-values for each of these endpoints will be included in the study report for the submission as supportive evidence. The tests for these endpoints will be considered in a hierarchy. The first endpoint in the hierarchy will be time in response, followed by ORR, and then by OS. ORR will be compared between arms using a Cochran-Mantel Haenszel test and both time in response and OS will be compared via stratified log-rank tests. All tests will be stratified by the same factors used in the PFS comparison. No labeling claims will be made about an endpoint unless it and endpoints ahead of it in the hierarchy are significant at the one-sided,  $\alpha = 0.025$  level.

OS, the final endpoint in the hierarchy, will be mature after 282 deaths have been observed. This is projected to occur approximately 9 years after the initiation of the study, or approximately 4 years after the final analysis of PFS. Two hundred and eighty two deaths ensure 70% power for a HR of 0.74.

### Interim Analysis

BMS/Abbott is advocating the use of an interim analysis of PFS as they believe that otherwise the study will take approximately (b) (4) years to reach the total number of events and that there should already be PFS data on lenalidomide and dexamethasone in combination with elotuzumab from study CA204004. The Sponsor asserts that tumor assessments in MM are robust because they are primarily based on serum and urine tests (laboratory measurement of M-protein conducted by an independent review committee blinded to treatment assignment) and are therefore relatively objective. In addition, BMS/Abbott is proposing that a Data Monitoring Committee (DMC) will monitor study CA204006 and will oversee the safety of the enrolled subjects with periodic pre-scheduled safety reviews (b) (4). The DMC will conduct an interim analysis for safety and efficacy after approximately 241 progression events (50% information level, (b) (4)) have occurred. O'Brien-Fleming  $\alpha$  and  $\beta$  spending functions will be used to determine the stopping boundaries for PFS. If 241 events are observed at the interim analysis, the study will be stopped for efficacy if p-value (b) (4) or will be stopped for futility if the p-value (b) (4). An interim analysis for OS was planned at the time of the final analysis for PFS. (b) (4)

## DISCUSSION

### Sponsor Submitted Questions and FDA Response:

1. **Sponsor Question #1:** The Phase 3 study CA204006 will enroll patients with previously untreated multiple myelomas who are not candidates for SCT because of age or co-existing conditions. (b) (4)

(b) (4)

**FDA Response:** Yes.

(b) (4)

**Discussion:** BMS/Abbott acknowledged FDA's response and there was no discussion at the meeting.

2. **Sponsor Question #2:** Does FDA agree that the lenalidomide plus low-dose dexamethasone regimen in Study CA204006 is a suitable comparator in multiple myeloma patients who have received no prior therapy and are not eligible for SCT?

**FDA Response:** Yes, the lenalidomide plus low-dose dexamethasone regimen in Study CA204006 is a suitable comparator for a trial conducted in multiple myeloma patients who have received no prior therapy and are not eligible for SCT.

**Discussion:** BMS/Abbott acknowledged FDA's response and there was no discussion at the meeting.

3. **Sponsor Question #3:** For the Phase 3 Study CA204006, does FDA agree with the primary efficacy endpoint of PFS and the proposed hierarchy and analyses for the primary and secondary endpoints as described in the attached Statistical Analysis Plan (SAP; Appendix 3)? Does FDA agree with the proposed sensitivity analyses?

**FDA Response:** FDA agrees that the primary efficacy endpoint of PFS is consistent with the International Myeloma Working Group uniform response criteria and is an appropriate endpoint. However, FDA does not agree with the proposed hierarchy for analyses of the secondary endpoints because the 'time in response' endpoint is not an acceptable regulatory efficacy endpoint and it is not clear how the results can be interpreted based on the definition. The proposed primary and sensitivity analyses for PFS appear to be acceptable.

***BMS/Abbott response dated February 13, 2011:** Time in response measures the duration of objective response for all patients. The difference between the time in response and duration of response is that the former is based on all randomized subjects while the latter includes only subjects whose best response was PR or better. Non-responders are considered to have "progressed" at randomization for time in response and therefore to have had no "time in response."*

*The sponsor proposes to change Time in Response to Duration of Response if deemed more appropriate by the FDA.*

**Discussion during the meeting:** FDA stated that both Time in Response and Duration of Response are not acceptable for hierarchical analysis. Duration of Response is considered descriptive and may be included in the label if appropriate.

4. **Sponsor Question #4:** Does the FDA agree with inclusion of an interim analysis for early stopping for efficacy or futility in this frontline study in view of the additional data that will be available from the study in relapsed/refractory MM?

**FDA Response:** No, FDA has the following comments for the proposed interim analysis for PFS and OS:

- a. FDA strongly discourages BMS/Abbott from seeking approval based on an interim analysis of PFS, since the treatment effect of PFS as determined at interim analysis with immature data tends to be subject to overestimation, is not robust, and is rarely reproducible when more mature data are available. Also, there may be inadequate characterization of safety in support of a BLA if the trial is stopped early.
- b. BMS/Abbott indicates that the interim analysis for PFS will be performed after approximately 241 progression events have been observed among the (b) (4) randomized subjects. FDA recommends that the interim analysis to be performed at 241 PFS events observed based on all subjects. In addition, all patients should have been enrolled before the interim analyses was performed
- c. BMS/Abbott indicates that in view of evolving results with frontline lenalidomide therapy, a reassessment of the sample size could be made. Please describe in detail the nature of such reassessment in the statistical analysis plan (SAP).

***BMS/Abbott response dated February 13, 2011: The sponsor wishes to retain an interim***

(b) (4)

**Discussion during the meeting:** FDA continues to strongly discourage interim analysis of PFS. However, FDA would consider interim results if the data are compelling, robust and clinically meaningful.

5. **Sponsor Question #5:** Does FDA agree with the proposed Data Monitoring Committee (DMC) monitoring plan outlined in this submission?

**FDA Response:** Yes, FDA agrees that, in general, the proposed Data Monitoring Committee monitoring plan is acceptable. However, please refer to FDA's responses to question #4 for comments on the interim analysis.

**Discussion:** BMS/Abbott acknowledged FDA's response and there was no discussion at the meeting.

6. **Sponsor Question #6:** Does FDA agree with the CA204006 draft independent review committee (IRC) charter (Appendix 15)?

**FDA Response:** Yes, the CA204006 draft independent review committee charter appears acceptable.

**Discussion:** BMS/Abbott acknowledged FDA's response and there was no discussion at the meeting.

7. **Sponsor Question #7:** Does FDA agree with the proposed dose selection and elotuzumab schedule for CA204006 based on Phase 1/2 data from Study HuLuc63-1703 as described in Section 7.2.2.4 and modeling data?

**FDA Response:** Yes, the proposed elotuzumab dose selection and schedule appear acceptable.

**Discussion:** BMS/Abbott acknowledged FDA's response and there was no discussion at the meeting.

8. **Sponsor Question #8:** Does FDA agree with the proposed clinical pharmacology plan, which includes the evaluation of the pharmacokinetics, immunogenicity, and the cardiovascular safety of elotuzumab? Does the FDA agree with the proposed population pharmacokinetic (PPK) approach and that it is sufficient to evaluate the effect of age, gender, body weight, concomitant chemotherapy, and glomerular filtration rate on the pharmacokinetics of elotuzumab?

**FDA Response:** In general, FDA agrees with the proposed clinical pharmacology plan. However, FDA has the following comments:

- a. Please submit the protocol for the Phase 1 PK/safety trial in patients with severe renal impairment for FDA review.

***BMS/Abbott response dated February 13, 2011:*** BMS/Abbott agrees with FDA and will submit a protocol for a Phase 1 PK/Safety trial in patients with severe renal impairment formally to the IND for FDA review.

**Discussion during the meeting:** FDA acknowledged BMS/Abbott's response and there was no discussion at the meeting.

- b. FDA has concern regarding the potential for elotuzumab induction of cytokines such as IL-6, resulting in effects on cytochrome P-450 metabolic enzyme activities. Please provide a plan to address this issue for FDA review.

***BMS/Abbott response dated February 13, 2011:*** Results of the clinical biomarker evaluations from the HuLuc63-1701 study have shown increases in inducible protein (IP)-10, tumor necrosis factor (TNF)- $\alpha$  and monocyte chemoattractant protein (MCP) 1 (presented in Appendix 14 of the briefing book). These increases generally occurred after the first dose, and were attenuated after subsequent doses. The increase was typically of lesser magnitude for subjects with the 10 and 20 mg/kg treatments as compared to subjects who received lower dose treatments. IL-6 showed a similar pattern to what was observed for IP-10, TNF- $\alpha$  and MCP-1. These alterations in IL-6 were considered transient and occurred to a lesser degree at the higher doses of 10 and 20 mg/kg, which are the doses to be evaluated in the Phase 3 program. Therefore these alterations are not expected to have effects on the cytochrome (CYP) 450 system.

**Discussion during the meeting:** FDA requested that BMS/Abbott provide data and justification to support their conclusion. This issue should be addressed during drug development. BMS/Abbott acknowledged and will provide such data to the IND.

- c. FDA recommends BMS/Abbott explore exposure-response relationships of elotuzumab in the proposed Phase 3 trials. Response endpoints should include the clinical efficacy endpoint (PFS) and toxicity outcome measures as well as the relevant biomarker endpoints in the protocol.

***BMS/Abbott response dated February 13, 2011:*** The Sponsor agrees with FDA recommendation and will perform exposure-response analysis using efficacy and safety endpoints as suggested. Exposure-response analysis using biomarker endpoints will only be performed if biomarkers are shown to be predictive of clinical response.

**Discussion during the meeting:** FDA acknowledged BMS/Abbott's response and there was no discussion at the meeting.

- d. Assess the influence of baseline soluble CS1 serum levels on elotuzumab response, given the ability of elotuzumab to bind to circulating CS1.
- e. Variations in genes relevant to elotuzumab mechanism of action (e.g., Fc-gamma receptor) have been described. FDA recommends collection of non-tumor DNA (e.g., buccal) from all enrolled patients for future pharmacogenomic analyses.
- f. Consider collection of tumor DNA from all enrolled patients for exploratory analyses.

***BMS/Abbott response dated February 13, 2011: BMS/Abbott acknowledges FDA responses 8d, e and f and will consider the collection of data as recommended.***

**Discussion during the meeting for 8d, e and f:** FDA acknowledged BMS/Abbott's response and there was no discussion at the meeting.

9. **Sponsor Question #9:** Does FDA agree with the design of the proposed ECG substudy to the Phase 3 relapsed/refractory multiple myeloma study (CA204004)?

**FDA Response:** Dedicated QT studies are not required for monoclonal antibodies. FDA recommends collecting baseline and on-therapy ECGs after multiple dosing in all subjects in all clinical trials including the proposed study CA204004 on elotuzumab or active comparator to exclude large ECG effects. BMS/Abbott should submit an integrated cardiac safety analysis of all subjects in clinical studies. This should include categorical analyses as follows:

- a. Number and percentage of individuals with:
  - 1) Absolute QT/QTc values > 450 ms, >480 ms, and >500 ms; as well as the number and percentage of individuals with change from baseline > 30 ms and > 60 ms.
  - 2) PR interval changes from baseline  $\geq$  25% and absolute value > 200 ms.
  - 3) QRS changes from baseline  $\geq$  25% and absolute value > 110 ms.
- b. Number and percentage of individuals with abnormal ECG findings.
- c. Number and percentage of individuals with AEs that could be associated with prolongation of cardiac repolarization or proarrhythmia, e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death.

***BMS/Abbott response dated February 13, 2011: Rather than collecting ECG data from all elotuzumab studies, the Sponsor proposes to complete intensive central ECG's with triplicate reports from the CA204004 substudy in 50 subjects in order to ensure that there are at least 40 subjects who were treated with the full study dose of elotuzumab for at least 2 cycles and who completed ECGs assessment at all prespecified timepoints. The final substudy report will include the categorical analyses recommended by the FDA. In addition, BMS/Abbott will collect and submit ECG AEs on all other subjects as captured in CRFs from the***

*two phase III trials CA204004 and CA204006. These data will be submitted as an integrated safety analysis from all studies as recommended by FDA.*

**Discussion during the meeting:** FDA stated that the proposed QT evaluation plan is acceptable.

10. **Sponsor Question #10:** Does FDA agree that demonstration of clinically relevant superiority in the PFS analysis (at the interim or final time point) and an acceptable benefit/risk profile for elotuzumab/lenalidomide/dexamethasone vs. lenalidomide/dexamethasone in a frontline multiple myeloma population ineligible for SCT will be adequate to support full approval of elotuzumab in this population?

**FDA Response:** In general, the criteria in Question #10 in addition to Study CA204004 appear adequate to support a submission for regular approval of elotuzumab in the intended population. However, this will be a review issue at the time of submission of the BLA. Please see FDA Response to Sponsor Question #4 regarding interim PFS analysis.

**Discussion:** BMS/Abbott acknowledged FDA's response and there was no discussion at the meeting.

#### **ADDITIONAL COMMENT**

BMS/Abbott notified FDA that the Study CA204004 will be initiated at the end of March 2011 and that Study CA204006 will be initiated in May 2011.

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/s/  
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VAISHALI JARRAL  
02/15/2011



IND 100043

**MEETING MINUTES**

Bristol Myers Squibb, Company  
Attention: David Peck  
Associate Director-CMC, Global Regulatory Sciences  
P.O. Box 5400  
Princeton, NJ 08543-5400

Dear Mr. Peck:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “Humanized Monoclonal Antibody (huLuc63, PDL BioPharma) to CS1.”

We also refer to the meeting held on January 25, 2011, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4248.

Sincerely,

*{See appended electronic signature page}*

Vaishali Jarral, M.S., M.B.A.  
Regulatory Project Manger  
Division of Biologic Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure - Teleconference Minutes, Additional DBOP CDISC Guidance and OODP’s End-of-Phase 2 General Advice for Planned Marketing Applications

## MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 25, 2011  
TIME: 2:00 PM-3:00 PM EDT  
APPLICATION: IND 100043  
SPONSOR: Bristol Myers Squibb [BMS]  
DRUG NAME: Elotuzumab (BMS-901608), humanized anti-CS1  
Monoclonal IgG1 antibody  
TYPE OF MEETING: End of Phase 2 CMC, Type B Meeting  
MEETING CHAIR: Patricia Keegan  
MEETING RECORDER: Vaishali Jarral  
SUBJECT: To discuss and obtain FDA feedback on the manufacturing and development program for registration of elotuzumab in multiple myeloma.

### LIST OF FDA ATTENDEES

|                 |                                               |
|-----------------|-----------------------------------------------|
| Patricia Keegan | Director, DBOP/OODP                           |
| Suzanne Demko   | Clinical Reviewer/Team Leader, DBOP/OODP      |
| Thomas Herndon  | Clinical Reviewer, DBOP/OODP                  |
| Anne M. Pilaro  | Pharmacology/Toxicology Supervisor, DBOP/OODP |
| Stacey Ricci    | Pharmacology/Toxicology Reviewer, DBOP/OODP   |
| Vaishali Jarral | Regulatory Project Manager, DBOP/OODP         |

### Office of Pharmaceutical Sciences Office of Biotechnology Products Division of Monoclonal Antibodies

|                        |                    |
|------------------------|--------------------|
| Ram Sihag              | Quality Reviewer   |
| Ruth Cordoba-Rodriguez | Quality Supervisor |

### Office of Clinical Pharmacology

|            |             |
|------------|-------------|
| Division V |             |
| Jian Wang  | Reviewer    |
| Hong Zhao  | Team Leader |

### LIST OF SPONSOR ATENDEES

#### Bristol-Myers Squibb Participants

|                |                                                     |
|----------------|-----------------------------------------------------|
| Claudia Arana  | Group Leader, AR&D                                  |
| Charlene Craig | Associate Director, Global Regulatory Sciences, CMC |
| Michael Grace  | Executive Director, BPPD                            |
| Phillip Ng     | Senior Scientist, BPPD                              |
| Abhinav Shulka | Associate Director, Manufacturing Sciences          |
| Sean Tonzi     | Group Leader, Biologics Analytical Dev. and Testing |
| David Berman   | Group Director, Global Clinical Research            |
| Bindu Murthy   | Associate Director, Clinical Pharmacology           |

**Abbott Company Participants**

|              |                                          |
|--------------|------------------------------------------|
| Bob Duffy    | Senior Scientist, Process Development    |
| Jeff Petty   | Manager, Regulatory Affairs              |
| Tom Robinson | Senior Scientist, Analytical Development |
| Amy Varga    | Director, CMC Program Management         |
| Amit Varma   | Associate Director, Process Development  |

**MEETING OBJECTIVE:**

The purpose of this meeting is for Bristol-Myers Squibb (BMS) to seek feedback from the FDA on the following:

1. The BMS's comparability plan and data for drug substance manufactured at BMS-Syracuse [REDACTED] (b) (4) compared to drug substance manufactured at [REDACTED] (b) (4)
2. The drug substance/drug product testing (including the potency assay);
3. The drug substance and drug product long term stability study plans and drug substance process validation plan; and
4. A comparability plan for an alternate drug product manufacturing site.

**BACKGROUND**

On October 29, 2010, Bristol-Myers Squibb (BMS) requested a Type B End of Phase 2 CMC meeting to discuss with FDA on a number of CMC related issues for the use of elotuzumab in the treatment of patients with [REDACTED] (b) (4) multiple myeloma. The meeting briefing packages were received on December 17, 2010.

This IND was previously sponsored by Facet Biotech Corporation and was transferred to BMS effective July 1, 2010. Previous interactions with Facet Biotech on the development program included pre-IND meetings held on September 14, 2005 and March 17, 2006 and EOP1/Pre-Phase 3 meeting on July 12, 2010 with both Facet Biotech and BMS to discuss the Phase 3 clinical program of elotuzumab. The original IND was submitted on July 11, 2006.

Elotuzumab is a humanized monoclonal IgG1 antibody directed to human CS1, a cell surface glycoprotein with homology to the CD2 family of cell surface proteins. CS1 is expressed on malignant myeloma cells and on NK cells, NK target cells, a subset of CD8+ cells, and plasma cells. The proposed mechanism of action of elotuzumab involves natural killer (NK) cell-mediated antibody dependent cellular cytotoxicity (ADCC).

[REDACTED] (b) (4)

(b) (4)

(b) (4) The purpose of that submission was to describe changes made to the manufacture of drug substance (DS) and drug product (DP) for elotuzumab. In response to this submission from BMS, the agency had issued an Advice and Information request letter, recommending BMS to request an End of Phase 2 meeting to discuss the adequacy of the CMC information for elotuzumab.

(b) (4)

As indicated above, the proposed mechanism of action of elotuzumab is ADCC. BMS indicated in the briefing package that even though the classic ADCC assay is widely used to measure the ADCC activity of many therapeutic antibodies, this approach is not suitable for product release and stability testing. Instead BMS is proposing to develop an approach that uses (b) (4) (b) (4), (b) (4). BMS is proposing that the (b) (4)

(b) (4)

**Figure 2.3.F02: ADCC Results**

(b) (4)

(b) (4)

**Table 2.6.T01: Proposed Methods for Elotuzumab Drug Substance and Drug Product Release and Stability Testing**

(b) (4)



## **DISCUSSION**

### **Sponsor Submitted Questions and FDA Response:**

1. **Question #1:** Does the FDA agree that the data package provided is sufficient to demonstrate analytical comparability in order to introduce drug substance made from BMS-SYR into phase 3 clinical studies?

**Discussion during the Meeting:** Regarding comment 1a and 1b- BMS informed FDA that an IND amendment with comparability data for the drug substance manufactured at BMS-SYR facility will be submitted to the IND by February, 2011 and that BMS expects to initiate Phase 3 studies in March, 2011. The data will include tabulated side by side accelerated and stressed stability data for drug substance lots manufactured at (b) (4) and BMS-SYR facility. FDA stated that this approach was acceptable.

Regarding comment 1c- BMS agreed that the specifications for release and stability assays will be updated to reflect FDA's recommendations as communicated in the Advice letter dated July 29, 2010 for new drug substance lots currently planned to be manufactured in second half of 2011. FDA acknowledged this information.

Regarding comment 1d- FDA requested all available data on (b) (4) levels for the drug substance manufactured at BMS-SYR. These data will be compared to the historical (b) (4) data from drug substance lots manufactured at (b) (4). The (b) (4) data should be submitted to the IND in the February, 2011 amendment. The need for additional PK studies will depend on the outcome of CMC data review.

2. **Question #2:** Does FDA agree with the approach for demonstrating that drug product manufactured from BMS-New Brunswick is comparable to drug product manufactured at BMS-Manati?

**FDA Response:** Based on the information in the meeting package the approach appears to be reasonable. Comparability studies should conform to the principles outlined in ICH Q5E. Please note that the number of lots required for a comparability analysis can depend

on the type and magnitude of any differences observed. Therefore, data from one lot of drug product manufactured at BMS-New Brunswick may not be sufficient to support comparability.

**Discussion:** BMS agreed with FDA's response and there was no discussion at the meeting.

3. **Question #3:** Does the FDA agree that the [REDACTED] (b) (4) [REDACTED] are sufficient to measure biological activity for commercial product?

**FDA Response:** No. There is not sufficient information in the package to determine the suitability of the [REDACTED] (b) (4) [REDACTED] to be representative of the proposed mechanism of action of elotuzumab. By pivotal studies, a cell-based potency assay (with acceptance criteria) that reflects the primary presumed *in-vivo* mechanism of action of elotuzumab should be implemented. FDA notes that the sponsor is developing ADCC cell-based assays. The agency recommends optimizing those assays for assay validation for drug substance and drug product release. Non cell-based potency assays might be acceptable for commercial product if it can be demonstrated that the activity measured by those assays is comparable or better than ADCC cell-based assays including their stability indicating properties. Suitability of the proposed [REDACTED] (b) (4) [REDACTED] assays as potency assays will be a review issue.

**Discussion during the Meeting:** BMS proposed to implement a cell-based assay during Phase 3 trials. Following qualification, the assay will be used as an additional release and stability potency assay at an appropriate point during the Phase 3 studies. FDA stated that this proposal was acceptable.

4. **Question #4:** Does FDA have any comments on the approach for the drug substance and drug product registrational stability studies?

**FDA Response:** Based on the information in the meeting package the approach appears to be reasonable. Stability studies should conform to the principles outlined in ICH Q1a and ICH Q5c.

**Discussion:** BMS agreed with FDA's response and there was no discussion at the meeting.

5. **Question #5:** Does FDA have any comments on the drug substance process validation plans?

**FDA Response:** There is insufficient information provided in the package to provide specific comments on the drug substance validation plans. For drug substance process validation, please refer to the FDA draft guidance link below:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

**Discussion:** BMS agreed with FDA's response and there was no discussion at the meeting.

6. **Question #6:** Does FDA agree with the proposed set of methods to be used for release and stability testing and subsequent use for establishing acceptance criteria for BLA specifications?

**FDA Response:** No. Although the proposed release and stability specifications may be appropriate for clinical phase, the Division cannot agree to release and stability specifications for licensure at this time. The acceptability of commercial specification is a BLA review issue. In addition, FDA recommends referring to the Agency advice letter communicated on 29 July 2010 for implementing specification by pivotal phase.

**Discussion:** BMS agreed with FDA's response and there was no discussion at the meeting.

**ADDITIONAL COMMENT:**

Clinical Pharmacology

7. Depending on the CMC comparability results, a pharmacokinetic (PK) comparability assessment (b) (4)

**Discussion:** BMS agreed with FDA's response and there was no discussion at the meeting.

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/s/  
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VAISHALI JARRAL  
01/28/2011



IND 100043

**MEETING MINUTES**

Bristol-Myers Squibb Company  
Attention: Catherine Burgess, Ph.D.  
Associate Director-Oncology  
Global Regulatory Science  
5 Research Parkway  
Wallingford, CT 06492

Dear Dr. Burgess:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Elotuzumab (HuLuc63), humanized monoclonal antibody to CS1."

We also refer to the teleconference held on July 12, 2010, between representatives of your firm and the FDA. A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4248.

Sincerely,

*{See appended electronic signature page}*

Vaishali Jarral, M.S, M.B.A  
Regulatory Project Manager  
Division of Biologic Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosures –

- (1) Meeting Minutes
- (2) OODP's advice for EOP2 meetings
- (3) Facet Biotech/BMS Slides presentation.

## MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 12, 2010  
TIME: 2:00 PM-3:00 PM EDT  
APPLICATION: IND 100043  
SPONSOR: Facet Biotech Corporation [Facet Biotech] and Bristol Myers Squibb [BMS] (Current sponsor)  
DRUG NAME: Elotuzumab (BMS-901608), humanized anti-CS1 Monoclonal IgG1 antibody  
TYPE OF MEETING: End of Phase 1/ pre Phase 3  
MEETING CHAIR: Patricia Keegan  
MEETING RECORDER: Vaishali Jarral  
SUBJECT: To discuss and obtain FDA feedback on the clinical and nonclinical development program for registration of elotuzumab in multiple myeloma.

### LIST OF FDA ATTENDEES

|                 |                                               |
|-----------------|-----------------------------------------------|
| Patricia Keegan | Director, DBOP/OODP                           |
| Suzanne Demko   | Clinical Reviewer/Team Leader, DBOP/OODP      |
| Thomas Herndon  | Clinical Reviewer, DBOP/OODP                  |
| Anne M. Pilaro  | Pharmacology/Toxicology Supervisor, DBOP/OODP |
| Stacey Ricci    | Pharmacology/Toxicology Reviewer, DBOP/OODP   |
| Vaishali Jarral | Regulatory Project Manager, DBOP/OODP         |

### Office of Clinical Pharmacology

Division V  
Jian Wang  
Hong Zhao, Team Leader

### Office of Biostatistics

Division of Biostatistics V  
Yuan Li Shen  
He Kun, Team Leader

### LIST OF SPONSOR ATTENDEES

#### Bristol Myers Squibb Attendees

Elyse Stock, M.D., Vice President, Global Development Lead - Elotuzumab  
David Berman, M.D., Ph.D. Group Director, Oncology, Global Clinical Research  
Ute Dugan, M.D., Ph.D. Executive Director, Oncology, Global Clinical Research  
Justin Kopit, Ph.D., Associate Director, Oncology, Global Biometric Sciences  
Aparna Anderson, Ph.D., Director, Global Biometric Sciences  
Bindu Murthy, Associate Director, Clinical Pharmacology  
Catherine Burgess, Ph.D., Associate Director, Global Regulatory Science  
Marie-Laure Papi, Pharm.D., Director, Global Regulatory Science

### **Facet Biotech Attendees**

Anil Singhal, M.D., Clinical

Danny Afar, Ph.D., Elotuzumab Program Team Leader

Jeff Petty, Senior Manager, Regulatory Affairs

Lisa Bell, Ph.D., Senior Director, Regulatory Affairs and Drug Safety

Han Ding, Ph.D., Clinical Pharmacology

### **Abbott Attendees**

David Ross, Pharm.D., Senior Director, Regulatory Affairs

Sari Enschede, M.D., Oncology Development

## **MEETING OBJECTIVE**

The objective of the meeting is for Facet Biotech and Bristol Myers Squibb to discuss with FDA the proposed registration study (CA204004) for the treatment of patients with relapsed/refractory multiple myeloma and additional contents of the BLA package to obtain FDA feedback on the clinical and nonclinical development program for registration of elotuzumab in multiple myeloma. Bristol Myers Squibb will request a separate CMC meeting with the Office of Biotechnology Products and the Office of Clinical Pharmacology.

## **BACKGROUND**

On April 16, 2010, Facet Biotech Corporation requested a Type B End of Phase 1/pre- Phase 3 meeting to discuss their clinical development program to support a BLA for the use of elotuzumab in the treatment of patients with (b) (4) multiple myeloma. The meeting briefing packages were received on June 14, 2010 (SDN 0104). Previous interactions with Facet Biotech on the development program include pre-IND meetings held on September 14, 2005 and March 17, 2006. The IND was submitted on July 11, 2006.

Elotuzumab is a humanized monoclonal IgG1 antibody directed to human CS1, a cell surface glycoprotein with homology to the CD2 family of cell surface proteins. CS1 is expressed on malignant myeloma cells and on NK cells, NK target cells, a subset of CD8+ cells, and plasma cells. The proposed mechanism of action of elotuzumab involves natural killer (NK) cell-mediated antibody dependent cellular cytotoxicity.

### Pre-clinical

Facet states that non-clinical studies have demonstrated that elotuzumab recognizes human CS1 protein and does not bind to CS1 from other species, including the chimpanzee, cynomolgus monkey, dog, mini-pig, mouse, rat, rabbit, and rhesus monkey. In the current meeting package, Facet Biotech refers to the pre-IND meetings held on September 14, 2005 and March 17, 2006, in which FDA to note discussions with the FDA regarding the use of *in vitro* and *in vivo* studies to identify a safe starting dose and support initiation of clinical studies due to the lack of cross-reactivity with relevant animal models. Facet and BMS propose to limit the nonclinical toxicology package to support registration to the *in vitro* safety and *in vivo* biological activity studies already conducted. No additional nonclinical toxicology studies in animals are planned.

### Chemistry, Manufacturing and Controls

Facet Biotech/BMS will request a separate meeting with the Office of Biotechnology Products and the Office of Clinical Pharmacology to discuss the manufacturing of elotuzumab. The meeting request will be submitted with a request for a CMC meeting during the second half of 2010.

### Clinical Pharmacology

Facet Biotech/BMS is developing a comprehensive clinical pharmacology plan for elotuzumab which will be submitted to FDA for review and comment the latter part of 2010.

### Clinical Development Program

As of April 8, 2010, the safety and activity of elotuzumab have been studied in 112 patients enrolled in one of three studies, either as monotherapy or in conjunction with other agents. The three studies had an initial, sequential dose-escalation, dose-finding component (Phase 1) and a fixed dose, activity-estimating (Phase 2) component. Across these three studies, 66 patients have been treated at the proposed dose and schedule of elotuzumab to be studied in CA204004 (20 mg). The phase 1-2 studies were Protocol HuLuc63-1701, which is closed to accrual and enrolled 34 patients with advanced multiple myeloma. Protocol HuLuc63-1702 has completed the dose-finding portion of the study of elotuzumab in combination with bortezomib and enrollment in the dose-expansion (Phase 2) component is ongoing; as of April 2010, the study has enrolled 28 patients with multiple myeloma who received elotuzumab in combination with bortezomib. Protocol HuLuc63-1703, has also completed the dose-finding portion for elotuzumab administered in combination with lenalidomide and low-dose (40 mg weekly) dexamethasone. Phase 2 portion of study HuLu63-1703 will enroll 60 patients with relapsed/refractory multiple myeloma who have received 1-<sup>(b)</sup><sub>(4)</sub> prior therapies.

The clinical development plan will include one major efficacy study, a multicenter, randomized clinical trial evaluating the combination of elotuzumab with lenalidomide and low-dose dexamethasone in patients with relapsed or refractory myeloma (Protocol CA204004) to support an initial BLA filing <sup>(b)</sup><sub>(4)</sub>



Protocol CA204004 is a multicenter, open label, randomized (1:1), trial of lenalidomide plus low-dose dexamethasone alone or in combination with elotuzumab that is planned to enroll 640 patients with relapsed or refractory multiple myeloma who have received 1 to 4 prior therapies. Stratification factors include  $\beta$ 2 microglobulin (<2.5 mg/L vs.  $\geq$  2.5 mg/L), number of prior lines of therapy (1 vs. 2 or more), and prior immune-modulatory drugs (none vs. prior thalidomide only vs. other). The primary efficacy endpoint of the study is progression-free survival (PFS) based upon European Group for Blood and Marrow Transplant (EBMT) criteria and determined by an independent review committee. At least 477 progression events will be needed to ensure a one-sided alpha of 0.025 with 90% power to detect a 3.9 month median PFS difference (11.1 vs. 15 months, corresponding to a HR=0.74) between treatment arms. An interim analysis is planned when 239 events have occurred for both efficacy and futility based on O'Brien-Fleming  $\alpha$  and  $\beta$  spending function with non-binding futility boundary. The study will be stopped for efficacy if

$p \leq 0.0015$  and for futility if  $p > 0.3947$ . The nominal significance level for the final analysis of PFS is 1-sided  $\alpha = 0.0245$ . At the time of the final PFS analysis, an interim analysis for OS will be performed. The final analysis for OS will be performed when 425 deaths are achieved. The number of deaths is needed to ensure a one-sided 0.025 with 80% power to detect a difference of 29.6 months vs. 38.9 months median OS time (corresponding to a HR=0.76). The nominal significance level for the interim and final analysis of OS will depend on the number of deaths observed at the interim analysis of OS. Both the interim and final analyses will utilize a one-sided, stratified log-rank test as the primary analysis. The analysis will be based upon the primary definition of PFS (PFS1) which is time from randomization to the first documented tumor progression or death from any cause. Censoring rules for PFS1 include:

- Patients who neither progress nor die will be censored on the date of their last adequate tumor assessment (defined as both serum and urine monoclonal paraprotein results analyzed at the central laboratory)
- Patients who do not have a baseline adequate tumor assessment or an on-study disease assessment and who are not known to have died will be censored on the date of randomization.

Tumor response and overall survival are secondary endpoints. A hierarchical testing procedure is proposed in the order of PFS, ORR and OS.

Based on the proposed elotuzumab development program, the safety database at the time the BLA is filed will consist of the following number of patients:

Enrollment through April 8, 2010

- 34 subjects treated with elotuzumab monotherapy (Protocol HuLuc63-1701)
- 28 subjects treated with elotuzumab + bortezomib (Protocol HuLuc63-1702)
- 28 subjects treated with elotuzumab + lenalidomide/low-dose dexamethasone (Protocol HuLuc63-1703)

Planned enrollment between April 8, 2010 and submission of the BLA

- 60 subjects treated in Phase 2 study with elotuzumab + lenalidomide/low-dose dexamethasone (HuLuc63-1703)
- ~320 subjects treated with lenalidomide/low-dose dexamethasone  $\pm$  elotuzumab in CA204004 (Proposed study to support registration)
- ~245 subjects (at CA204004 interim analysis) (b) (4)

Facet Biotech proposes to initiate study CA204004 based on the available safety data in 112 patients, including at least 60 patients enrolled in the Phase 2 portion of Protocol HuLuc63-1703. Although Protocol CA204004, as currently written, will be intended to establish safety and efficacy with the 20 mg/kg elotuzumab dose (in combination with lenalidomide and low-dose dexamethasone), the study may be revised based on additional data from the ongoing study, HuLuc63-1703.

## DISCUSSION

### Sponsor Submitted Questions and FDA Response

1. Sponsor Question # 1: Does FDA agree that there are sufficient data to support initiation of the proposed Phase 3 study (CA204004) of elotuzumab/Ld in subjects with relapsed multiple myelomas who have received 1 to <sup>(b)</sup><sub>(4)</sub> prior therapies?

**FDA Response:** Yes, based on the activity data provided for 22 patients with multiple myeloma who received the 20 mg/kg dose and were enrolled in the phase 2 portion of study HuLuc73-1703, as well as the safety data provided for 112 patients across all studies there appears to be sufficient safety data to support initiation of the proposed Phase 3 study. The exploration of the dose-response relationship is very limited and there is insufficient data to conclude that elotuzumab at the 20 mg/kg dose is optimal for efficacy.

**Discussion during the meeting:** FDA advised Facet Biotech Corporation and Bristol Myers Squibb (BMS) that the difference in effective exposure, as measured by saturation, for an antibody at the 10 and 20 mg/kg doses would be negligible, so the lower dose level was recommended. However, the Facet and BMS provided additional Phase 2 clinical data to demonstrate the dose-response relationships and justify the inclusion of the 20 mg/kg dose. Facet Biotech and BMS further noted that there is an ongoing randomized Phase 2 study to investigate the efficacy and safety of the 10 and 20 mg/kg doses. FDA pointed out that for a biologic a dose that is 10 times different may not make a difference in saturation and recommended inclusion of 5 mg/kg as the dose for the trial. The sponsor explained that a 5 mg/kg dose was not explored further in Phase <sup>(b)</sup><sub>(4)</sub>

FDA stated that Facet Biotech or BMS provide the saturation data in their protocol to support the selected dose(s).

2. Sponsor Question # 2: Does FDA agree that the population for this Phase 3 study is adequate to support an indication for the treatment of multiple myeloma subjects who have received at least one prior therapy?

**FDA Response:** Yes, the proposed study population of patients with previously treated multiple myeloma is acceptable.

**Discussion during the Meeting:** Facet Biotech and BMS accepted this response.

3. Sponsor Question # 3: Does FDA agree that lenalidomide plus low-dose dexamethasone is an adequate comparator in the proposed study?

**FDA Response:** Yes, lenalidomide and low-dose dexamethasone is an adequate comparator in the proposed study.

**Discussion during the Meeting:** Facet Biotech and BMS accepted this response.

4. Sponsor Question # 4: Does FDA agree with the proposed premedication regimen for subjects receiving elotuzumab?

**FDA Response:** In general, FDA recommends that administration of prophylactic medications for infusion reactions be studied in a manner that will provide data to determine if pre-treatment prophylactic medications are an effective strategy to prevent severe infusion reactions. Facet Biotech has not provided adequate justification in the meeting package for the routine use of prophylactic medications in the proposed trials. Provide an analysis of the incidence and severity of infusion reactions attributed to elotuzumab when given with or without prophylactic medications, or submit a proposal for a trial designed to demonstrate that prophylactic medications confer a benefit (reduction in infusion reactions). Prophylactic medications used as a component of the treatment plan in a clinical trial to support registration of a new agent should be described in the Dosage and Administration section of product labeling.

**Discussion during the meeting:** FDA noted that the meeting package did not have sufficient information to determine if routine administration of prophylactic medications in the proposed trials was justified; i.e., no data were presented demonstrating that the use of premedication reduced the incidence or severity of infusion reactions. Facet Biotech and BMS provided additional data (slides attached) indicating that the incidence and severity of infusion-related adverse events (AEs) was reduced in patients who received premedications as compared to those who did not receive consistent premedications. Facet Biotech and BMS provided additional data regarding the proposed steroid premedication regimen in Phase 2 and updated Phase 3 trials. It is Facet Biotech's and BMS' contention that the additional data provide justification for the proposed premedication regimen because the regimen results in a reduction in serious infusion-related AEs. Facet Biotech and BMS further noted that the premedication plan will be studied in phase 2 before initiating its use in phase 3. FDA stated that the data provided during the meeting should be formally submitted in justification of the proposed premedication regimen.

5. Sponsor Question # 5: Does FDA agree with the definition of primary efficacy analysis for PFS?

FDA Response: No, FDA recommends incorporating the following two rules for determining PFS events according to the guidance: Clinical Trial Endpoint for the Approval of Cancer Drugs and Biologic--  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf> :

- a. Censor patients who took initiated new anti-myeloma therapy on the date of the last adequate tumor assessment time prior to initiation of new anti-myeloma therapy;
- b. Censor patients who had events which occurred  $\geq 2$  assessment periods from the last adequate tumor assessment at the last adequate tumor assessment time.

**Discussion during the meeting:** Facet Biotech and BMS stated that they have reviewed the Guidance provided via the link above, but raised concerns regarding the proposed censoring rules. FDA reminded Facet Biotech and BMS to review the Guidance regarding censoring and that the Guidance's censoring rules should be employed for the primary analysis. FDA also informed Facet Biotech and BMS that the intent-to-treat analysis can be retained as a supportive or sensitivity analysis. Facet Biotech and BMS accepted the FDA's proposal.

6. Sponsor Question # 6: Does FDA agree with the proposed sensitivity analyses?

**FDA Response:** Missing data/assessments of progression should be kept at a minimum. A substantial amount of missing data or events could undermine confidence in the PFS results of the trial and may prevent a labeling claim on PFS.

Please treat the original primary efficacy analysis (PFS1) as a sensitivity analysis.

FDA also recommends that additional sensitivity analyses that assess the impact of loss to follow-up be considered. For example, a worst comparison case analysis by treating lost-to-follow-ups as censored on the control arm and as events on the experimental arm may be performed to assess the robustness of the result of the primary analysis of PFS.

Please also perform a sensitivity analysis for patients who did not have progression or death to be censored at the last tumor assessment date for the primary analysis, regardless whether the visit has sufficient information to rule out progression.

**Discussion during the meeting:** Facet Biotech and BMS agreed to perform a sensitivity analysis for patients who did not have progression or death to be censored at the last tumor assessment date for the primary analysis. Facet Biotech and BMS stated that they would incorporate the sensitivity analysis in the SAP to address the FDA concerns.

The discussion regarding PFS1 is captured under questions 5.

7. Sponsor Question # 7: Does FDA agree with the proposed analyses for the secondary endpoints, including the proposed hierarchy intended to support labeling claims, as described in the attached SAP?

**FDA Response:** FDA strongly recommends that the hierarchical testing procedure be revised in the order, such that comparison of overall survival is tested first, before comparison of overall response rates.

**Discussion during the meeting:** FDA recommended that Facet Biotech and BMS analyze overall survival (OS) at the time of the final PFS analysis. Facet Biotech and

BMS were concerned that the OS data would not be mature until 3 years after the PFS data was available. Facet Biotech and BMS also noted that the overall response rate (ORR) data would be available at the time of the final analysis of PFS and indicated that this was clinically meaningful data for physicians because it is useful for demonstrating consistency across endpoints. FDA stated that the survival data is important for understanding both safety and efficacy relative to the PFS results. FDA reminded Facet Biotech and BMS that acceptability of an approval based on PFS is contingent upon submission of preliminary survival data indicating no decrement in survival for patients treated with elotuzumab. Facet Biotech and BMS then proposed to amend the DMC charter to allow FDA to review the interim or preliminary survival data at the time of the final analysis of PFS while maintaining the treatment blind for Applicant (Facet Biotech or BMS). With this new information, FDA agreed with this approach and Facet Biotech's and BMS' original proposed hierarchy for secondary endpoint analyses (response rate followed by overall survival).

8. Sponsor Question # 8: Does FDA agree that demonstration of clinically relevant superiority in the PFS analysis (at the interim or final time point) and an acceptable benefit/risk profile for elotuzumab/lenalidomide/dexamethasone vs. lenalidomide/dexamethasone in a multiple myeloma population that has received at least one prior regimen will be adequate for full approval of elotuzumab in this population?

**FDA Response:** FDA strongly discourages Facet/BMS from seeking approval based on an interim analysis of PFS, since the treatment effect of PFS as determined at interim analysis with immature data tends to be subject to overestimation, is not robust, and is rarely reproducible when more mature data are available. Also, there may be inadequate characterization of safety in support of a BLA if the trial is stopped early.

In general, two trials are required to support licensure. FDA would accept a single study to support licensure if the results are highly statistically significant. The results of the single trial must be sufficiently robust, internally consistent and so compelling that it would be unethical to repeat the study. 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>.

**Discussion during the meeting:** Facet Biotech and BMS presented data regarding the use of interim analyses to support approval of multiple myeloma compounds in the US and EU. FDA stated that interim analyses often overestimate treatment effect and further discouraged seeking approval based on an interim analysis of PFS. FDA also commented that in order to support licensure a single trial requires results that are highly statistically significant, internally consistent, and robust. Facet Biotech and BMS inquired whether this requirement was specific to multiple myeloma. FDA responded that these requirements are applicable across tumor populations. FDA noted that their original response to this question would stand and that any decisions made will be based on the strength of the data submitted. There was additional discussion regarding the size of the safety data base at the time of the interim analysis of PFS. Facet Biotech and BMS noted that they expect to have a safety data base of 320 patients at this time point.

9. Sponsor Question # 9: Does FDA agree that the size of the safety database at the time of BLA submission will be sufficient to support a BLA application for elotuzumab in the relapsed multiple myeloma population?

**FDA Response:** Yes. In general to support an application for registration, FDA requires a safety data base of at least 300 subjects exposed to the investigational agent at the dose and schedule intended for labeling. However, whether the data are sufficient to support the approval of an application will be determined during the review of the BLA.

**Discussion during the Meeting:** Facet Biotech and BMS accepted this response.

10. Sponsor Question # 10: Does FDA agree that the proposed nonclinical toxicology package is sufficient to support registration of elotuzumab?

FDA Response: Yes.

**Discussion during the Meeting:** Facet Biotech and BMS accepted this response.

#### **Additional FDA Statistical Comments**

11. As indicted in section 8.2.2.4, a summary of time between dates of documented progression according to both the IRC and the investigator will be provided. Please summarize such data based on the actual value, not the absolute value, so the results of which assessment performed earlier or later can be seen by treatment arm.

**Discussion during the Meeting:** Facet Biotech and BMS accepted this comment.

#### **Additional FDA Clinical Comments**

12. FDA recommends that the randomization methods in Protocol CA204004 be revised to include stratification by type of prior treatments received in addition to the proposed methods of stratification ( $\beta$ 2 microglobulin level, number of prior lines of therapy, and prior immunomodulator therapy).

**Discussion during the meeting:** Facet Biotech and BMS requested clarification about the ‘type of prior treatments’ specified by FDA. FDA stated that a stratification factor based on the drug class(es) for treatments received by patients rather than the number of treatments received was preferred. Facet Biotech and BMS expressed concern that their current design for study CA204004 uses 12 strata and inclusion of an additional stratification factor would result in too many strata. Facet Biotech and BMS also noted that number of prior therapies has prognostic value in this disease. The Sponsor proposed to include subgroup analyses based on “type of prior treatments”, instead of including it as a stratification factor and FDA agreed.

13. FDA recommends that additional information on the role of Study (b)(4) in the overall development program be provided.

**Discussion during the meeting:** FDA inquired whether study (b)(4) will be included in the initial BLA or whether the initial approval would be based solely on Study CA204004. The Sponsor confirmed that the initial BLA will be based solely on Study CA204004; (b)(4)

## **OODP's End-of-Phase 2 General Advice for Planned Marketing Applications**

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at [www.fda.gov/RegulatoryInformation/Guidances/default.htm](http://www.fda.gov/RegulatoryInformation/Guidances/default.htm)) that contain important information necessary for preparing a complete, quality application.

The following comments, based on our experience with other applications, are intended to help you plan and prepare for submitting a quality application. This list is not inclusive of all issues you need to consider in preparing an application, but highlights areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

The 'Study Data Specifications' includes points to be considered for electronic submission, but it is not guidance. We are aware that the statement 'It is not necessary to provide analysis datasets and programs that will enable the reviewer to directly reproduce reported results using agency hardware and software.' in the document, which leads to the absence of analysis datasets and programs in some of the recently submission to FDA. Currently, there is an internal effort in CDER on revising the 'Study Data Specifications', and the effort is specifically focused on the need of including analysis dataset and programs in electronic submission. Providing analysis dataset and programs is necessary in improving the efficiency of review process, which is critical with the 21<sup>st</sup> central review timeline. Besides evaluating efficacy and safety claims, reviewers will also verify important descriptive statistics used in describing the clinical studies. Therefore, we need to know the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label or package insert.

### **Clinical:**

- 1) Submit copies of the original versions of all protocols, statistical analysis plans, DSMB and adjudication committee charters, and all amendments.
- 2) Submit copies of minutes of all DSMB, and adjudication committee meetings.
- 3) If investigator instructions were produced in addition to the protocol and investigator brochure, submit copies of all such instructions.
- 4) Submit copies (in SAS transport format) of randomization lists and, if used, IVRS datasets.
- 5) Submit copies (in SAS transport format) of all datasets used to track adjudications.
- 6) Clinical study report(s) should follow the ICH E3 Structure and Content of Clinical Study Reports guidance ([www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf)).
- 7) For each of the completed Phase 3 clinical trials, submit a table with the following columns:
  - a) Site number
  - b) Principle investigator

- c) Location: City State, Country
  - d) Number of subjects screened
  - e) Number of subjects randomized
  - f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites
  - g) Number of protocol violations (Major, minor, definition)
- 8) Prepare integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:
- a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document  
([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf))
  - b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications  
([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf))
- 9) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment  
([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf)).
- 10) Safety Analysis Plan. In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. At a minimum the Safety Analysis Plan should address the following components:
- a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment,  
([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf)).
  - b) Safety endpoints for Adverse Events of Special Interest (AERI)
  - c) Definition of Treatment Emergent Adverse Event (TEAE)
  - d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter))
  - e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
  - f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
  - g) When unanticipated safety issues are identified the QSAP may be amended.
- 11) Provide detailed information, including a narrative, for all patients terminating study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision.
- 12) Narrative summaries should contain the following components:
- a) subject age and gender
  - b) signs and symptoms related to the adverse event being discussed

- c) an assessment of the relationship of exposure duration to the development of the adverse event
  - d) pertinent medical history
  - e) concomitant medications with start dates relative to the adverse event
  - f) pertinent physical exam findings
  - g) pertinent test results (for example: lab data, ECG data, biopsy data)
  - h) discussion of the diagnosis as supported by available clinical data
  - i) a list of the differential diagnoses, for events without a definitive diagnosis
  - j) treatment provided
  - k) re-challenge results (if performed)
  - l) outcomes and follow-up information
  - m) an informed discussion of the case, allowing a better understanding of what the subject experienced.
- 13) Provide complete CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs upon request.
- 14) For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.
- 15) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators ([www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm)).
- 16) Pediatric Studies. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.
- 17) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis.

- 18) In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.
- 19) The NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 ([www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf](http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf)). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:
- a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
  - b) Exposure-Response Relationships – important exposure-response assessments.
  - c) Less common adverse events (between 0.1% and 1%).
  - d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
  - e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
  - f) Marked outliers and dropouts for laboratory abnormalities.
  - g) Analysis of vital signs focused on measures of central tendencies.
  - h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
  - i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
  - j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
  - k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
  - l) Standard analyses and explorations of ECG data.
  - m) Overdose experience.
  - n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
  - o) Explorations for:
    - i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
    - ii) Dose dependency for adverse findings
    - iii) Provide summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
    - iv) Time dependency for adverse finding

- v) Provide data summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
- vi) Drug-demographic interactions
- vii) Drug-disease interactions
- viii) Drug-drug interactions
- p) Dosing considerations for important drug-drug interactions.
- q) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

**Datasets and Programs:**

- 20) The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included. If the SAS programs use any macro programs, please provide all necessary macro programs.
- 21) Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every value proposed to be included in the label.
- 22) The SAS transport files should be created by a procedure which allows the file to be easily read by the JMP software.
- 23) Data Format:
  - a) All datasets should be supplied in **CDISC format**. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis ([www.cdisc.org](http://www.cdisc.org)).
  - i) Study Data Tabulation Model (SDTM) Issues:
    - (1) The current published SDTM and SDTM Implementation Guide (SDTMIG) should be followed carefully. Refer to the SDTMIG section on Conformance (3.2.3)
    - (2) Domains
    - (3) There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at [www.cdisc.org](http://www.cdisc.org) and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.
      - (a) (DV) Protocol deviations
      - (b) (DA) Drug Accountability
      - (c) (PC, PP) Pharmacokinetics
      - (d) (MB, MS) Microbiology
      - (e) (CF) Clinical Findings
    - (4) The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.
      - (a) Tumor information
      - (b) Imaging Data
      - (c) Complex Inclusion/Exclusion Criteria
    - (5) Variables
      - (a) All required variables are to be included.
      - (b) All expected variables should be included in all SDTM datasets.

- (c) Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
  - (d) A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
  - (e) A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
  - (f) Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.
- (6) Specific issues of note:
- (a) SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.
  - (b) Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy should be placed in the SUPQUAL dataset or an ADaM dataset.
  - (c) These issues can be addressed through the request for ADaM datasets
- ii) Analysis Data Model (ADaM) Issues:
- (1) Specify which ADaM datasets you intend to submit.
  - (2) Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
  - (3) Discuss the structure of the datasets with the reviewing division and specify in the QSAP.
  - (4) Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.
  - (5) Indicate which core variables will be replicated across the different datasets, if any.
  - (6) SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.
- iii) General Items:
- (1) Controlled terminology issue:
    - (a) Use a single version of MedDRA for a submission. Does not have to be the most recent version
    - (b) We recommend that the WHO drug dictionary be used for concomitant medications.
    - (c) Refer to the CDISC terminology for lab test names.
    - (d) Issues regarding ranges for laboratory measurements should be addressed.
  - (2) Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.
  - (3) Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.

## **Physician's Labeling:**

### **24) Highlights:**

- a) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
- b) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
- c) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
- d) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
- e) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a)(4) and to [www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm) for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).
- f) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
- g) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”
- h) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
- i) Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
- j) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].
- k) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights.
- l) The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]
- m) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be

left blank at the time of submission and will be edited to the month/year of application or supplement approval.

- n) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

## 25) Table of Contents:

- a) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
- b) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
- c) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
- d) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
- e) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d)(1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (*not 8.2*)
  - 8.4 Pediatric Use (*not 8.3*)
  - 8.5 Geriatric Use (*not 8.4*)
- f) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:
  - “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## 26) Full Prescribing Information (FPI):

- a) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
- b) Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
- c) Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format” ([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf)).
- d) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf>]

- e) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
- f) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
- g) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
- h) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
- i) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
- j) If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
- k) Refer to [www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm) for fictitious examples of labeling in the new format.
- l) Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

**Electronic Common Technical Document (eCTD):**

27) Relating sequences properly allows reviewers to easily navigate the application’s original and supplemental submissions. By relating sequences correctly a reviewer can focus on the data at hand without wondering “what is missing” or “what are the reasons for this disorganized submission?” Delays in your review are also avoided.

- a) First-level submission types should not use related sequence
  - i) First-level submission types are
    - (1) “original-application”
    - (2) "annual-report"
    - (3) "efficacy-supplement"
    - (4) "labeling-supplement"
    - (5) "chemistry-manufacturing-controls-supplement"
    - (6) "other"
- b) Second-level submission types should use a single related sequence

- i) The related sequence should always be a first-level submission type
- ii) Second-level submission types are:
  - (1) "amendment"
  - (2) "resubmission"
- iii) Related Sequences are indicated in the us-regional.xml file:

| <b>Submission Type</b> | <b>Level</b> | <b>Related Sequence</b> |
|------------------------|--------------|-------------------------|
| Original               | Primary      | NO                      |
| Annual Report          | Primary      | NO                      |
| Efficacy Supplement    | Primary      | NO                      |
| Labeling Supplement    | Primary      | NO                      |
| CMC Supplement         | Primary      | NO                      |
| Other                  | Primary      | NO                      |
| Amendment              | Secondary    | YES                     |
| Resubmission           | Secondary    | YES                     |

- c) See Appendix 1 for examples of correct usregional.xml file submission code. Contact [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov) with any questions.

**Other Issues:**

- 28) The application should include a statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application.
- 29) The application should contain a table that list all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).
- 30) Review of an application can be facilitated by including a chronology of prior substantive communications with FDA and copies of official meeting/telecon minutes.

**Figure 1:**

Please note that the HLGT and HLT level terms in this table are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data that is typically found in an adverse event data set.

| Unique Subject Identifier (USUBJID) | Sequence Number (AESEQ) | Study Site Identifier (SITEID) | Unique Subject Identifier | Coding Dictionary Information | Reported Term for AE (Verbatim) | Lower Level Term MedDRA Code | Lower Level Term (LLT)   | Preferred Term High Level Term (HLT) | High Level Group Term (HLGT)  | System Organ Class (SOC)                             | Secondary System Organ Class 2 (SOC2)  | Secondary System Organ Class 3 (SOC3) | Secondary System Organ Class 4 (SOC4) |
|-------------------------------------|-------------------------|--------------------------------|---------------------------|-------------------------------|---------------------------------|------------------------------|--------------------------|--------------------------------------|-------------------------------|------------------------------------------------------|----------------------------------------|---------------------------------------|---------------------------------------|
| 01-701-1015                         | 1                       | 701                            | 1015                      | MedDRA version 8.0            | redness around application site | 10003058                     | Application site redness | Application site redness             | Administration site reactions | General disorders and administration site conditions | Skin and subcutaneous tissue disorders |                                       |                                       |

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

| Application Type/Number | Submission Type/Number | Submitter Name             | Product Name                                                        |
|-------------------------|------------------------|----------------------------|---------------------------------------------------------------------|
| IND-100043              | GI-1                   | BRISTOL MYERS<br>SQUIBB CO | Humanized Monoclonal Antibody<br>(huLuc63, PDL BioPharma) to<br>CS1 |

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VAISHALI JARRAL  
08/12/2010

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



BLA 761035

**LATE-CYCLE MEETING MINUTES**

Bristol-Myers Squibb Company  
Attention: Julie Dixon, PhD  
Group Director, Global Regulatory Safety & Biometrics  
5 Research Parkway  
Wallingford, CT 06492

Dear Dr. Dixon:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for elotuzumab.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 29, 2015.

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 Natasha Kormanik, Regulatory Project Manager at (240) 402-4227.

Sincerely,

*{See appended electronic signature page}*

Albert Deisseroth, MD, PhD  
Clinical Team Leader  
Division of Hematology Products  
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

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** October 29, 2015 from 3:00- 4:00 PM (ET)  
**Meeting Location:** Teleconference

**Application Number:** BLA 761035  
**Product Name:** elotuzumab  
**Applicant Name:** Bristol-Myers Squibb Company

**Meeting Chair:** Albert Deisseroth, MD, PhD  
**Meeting Recorder:** Natasha Kormanik, MSN, RN, OCN®

**FDA ATTENDEES**

Office of Hematology Oncology Products (OHOP)

Richard Pazdur, MD – Director

OHOP/ Division of Hematology Products

Ann Farrell, MD – Director

Edvardas Kaminskas, MD – Deputy Director

Albert Deisseroth, MD, PhD – Clinical Team Leader

Nicole Gormley, MD – Acting Clinical Team Leader/ Reviewer

Ashley Ward, MD – Clinical Reviewer

Theresa Carioti, MPH – Chief, Project Management Staff

Diane Leaman, BS – Safety Regulatory Project Manager

Natasha Kormanik, MSN, RN, OCN® – Regulatory Health Project Manager

OHOP/ Division of Hematology, Oncology, Toxicology

Christopher Sheth, PhD – Team Lead

Michael Manning, PhD – Pharmacologist

Office of Biotechnology Products (OBP)

Jibril Abdus-Samad, PharmD – Labeling Reviewer

OBP/ Division of Biotechnology Review and Research

Sarah Kennett, PhD – Review Chief

Linan Ha, PhD – Team Lead

Office of Process and Facilities/ Division of Microbiology Assessment

Maria Jose Lopez-Barragan, PhD – Reviewer

Natalia Pripuzova, PhD – Reviewer

Office of Clinical Pharmacology

Gene Williams, PhD – Team Leader  
Nitin Mehrotra, MPharm, PhD – Pharmacometrics Team Leader  
Olanrewaju Okusanya, PharmD, MS –Reviewer  
Justin Earp, PhD – Pharmacometrics Reviewer

Office of Biostatistics/ Division of Biometrics V

Lei Nie, PhD –Biostatistics Team Leader  
Chia-Wen Ko, PhD – Biostatistics Reviewer

Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis

Michelle Rutledge, PharmD – Safety Evaluator

OSE/ Division of Pharmacovigilance II

Tracey Salaam, PharmD – Team Leader  
Regina Lee, PharmD – Safety Evaluator

OSE/ Division of Epidemiology I

Carolyn McCloskey, MD, MPH –Epidemiologist

Eastern Research Group

Christopher A. Sese – Independent Assessor  
Marc Goldstein – Independent Assessor

European Medicines Agency

Zahra Hanaizi – Scientific Officer

**APPLICANT ATTENDEES**

Bristol-Myers Squibb Company

Akintunde Bello – Executive Director, Clinical Pharmacology & Pharmacometrics  
Eric Bleickardt, MD – Group Director, Oncology, Global Clinical Research  
R. Todd Bunch – Drug, Safety and Evaluation  
Julie Dixon, PhD – Director, Global Regulatory Sciences – Oncology  
Rajesh Israni – Associate Director, Global Regulatory Sciences- CMC  
Manish Gupta, PhD, FCP – Director, Clinical Pharmacology & Pharmacometrics  
Jonathan Leith, PhD – Vice President, Global Development Lead – Elotuzumab  
George Manos, PhD – Director, Oncology, Global Biometric Sciences  
Mark Moyer, MS – Vice President, Global Regulatory Sciences – Oncology  
Marie-Laure Papi, PharmD – Director, Global Regulatory Sciences – Oncology  
Jan Racenberg, MD – Medical Director, Global Pharmacovigilance & Epidemiology  
David Shapiro, MD, PhD – Vice President, Oncology, Global Clinical Research  
Annie Sturgess, PhD – Executive Director, Global Regulatory Sciences – CMC

Abbvie

Anil Singhal, PhD – Program Director, Clinical Research

Lisa Wax – Director, Global Regulatory Affairs

## 1.0 BACKGROUND

BLA 761035 was submitted on June 29, 2015 for elotuzumab.

Proposed indication(s): Treatment of multiple myeloma in patients who have received one or more prior therapies, in combination with lenalidomide and dexamethasone.

PDUFA goal date: February 29, 2015

FDA issued a Background Package in preparation for this meeting on October 22, 2015.

## 2.0 DISCUSSION

### 1. Introductory Comments

**Discussion:** *Welcome, opening remarks, ground rules, and objectives of the meeting discussed by Agency.*

*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 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.*

### 2. Additional Applicant Data

**Discussion:** *No discussion pertaining to this agenda item.*

### 3. Information Requests

#### Nonclinical

Please provide a risk assessment for the potential for reproductive and developmental toxicity for Empliciti using non-product specific information. Include in your assessment the potential effects of Empliciti binding to NK cells or other SLAMF7-expressing tissues in the developing fetus.

#### CMC

To be provided on October 30, 2015.

***Discussion:*** *The Agency informed the Applicant that the Nonclinical response was acceptable.*

*The Applicant will be responding to the outstanding CMC information requests, including the agreements to adjust the annual stability protocol and potency acceptance criterion. The FDA will communicate follow up information requests on October 30, 2015.*

#### 4. Postmarketing Commitments

##### Draft Clinical Pharmacology PMC

1. To determine if dosing can be optimized in the subgroup of patients who exhibit lower exposures and thus lower PFS with the proposed 10 mg/kg dosing regimen of elotuzumab. The objective is to evaluate if increasing exposures in this subgroup of patients can provide additional PFS benefit.

##### Draft CMC PMCs

1. To re-evaluate elotuzumab drug substance lot release and stability specification acceptance criteria for the cell-based ADCC potency assay and cation exchange chromatography (CEX) assay after 30 lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.
2. To re-evaluate elotuzumab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.
3. To complete the ongoing studies to support the (b) (4) of the elotuzumab master cell bank (MCB). The results of th (b) (4) using multiple cells from the MCB will be provided in the final study report.
4. To validate maximum hold times for the (b) (4) for microbial quality and submit validation report per 21CFR601.12.

5. To perform a repeat microbial retention study for the (b) (4) using a suitable surrogate solution. Alternatively, perform the study using a modified process, a modified formulation (e.g., (b) (4)), or a reduced exposure time for the challenge organism. Provide the summary data, the associated report, and justification for any modifications to the study. If any (b) (4) parameters are changed as a result of the study, update the BLA file accordingly.

***Discussion:*** *The Applicant acknowledged the Clinical Pharmacology draft post marketing commitment and proposed to consider evaluating data from the study 06 to see if similar data exists before proceeding to evaluate further. The Agency will take this into consideration and communicate accordingly to the Applicant.*

*The Agency discussed the draft CMC PMCs and the Applicant acknowledged the proposals.*

5. Major labeling issues

***Discussion:*** *The Applicant requested clarity on the infusion rate and hepatotoxicity.*

*The Agency discussed the rationale of inclusion of hepatotoxicity in the warning and precautions of the label. The Applicant stated they understood the rationale. Additionally, the Agency communicated the intent behind the lower infusion rate to be included in the label. The Applicant requested to have a separate discussion to understand further the Agency's position about required information to support faster infusion rates.*

6. Review Plans

FDA plans to send PMCs to Applicant by November 6, 2015.

***Discussion:*** *No further discussion pertaining to this agenda item.*

7. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/  
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ALBERT B DEISSEROTH  
11/03/2015



BLA 761035

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Bristol-Myers Squibb Company  
Attention: Julie Dixon, PhD  
Group Director, Global Regulatory Safety & Biometrics  
5 Research Parkway  
Wallingford, CT 06492

Dear Dr. Dixon:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for elotuzumab.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 29, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Natasha Kormanik Regulatory Project Manager, at (240) 402-4227.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, MD  
Director  
Division of Hematology Products  
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:** October 29, 2015; 3:00 – 4:00 PM (ET)  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1313  
Silver Spring, MD 20903

**Application Number:** BLA 761035  
**Product Name:** elotuzumab  
**Indication:** Treatment of multiple myeloma in patients who have received one or more prior therapies, in combination with lenalidomide and dexamethasone  
**Sponsor/Applicant Name:** Bristol-Myers Squibb 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.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

#### 2. Substantive Review Issues

There are no substantive review issues at this time.

## **ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

## **REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

## **LCM AGENDA**

### 1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

### 2. Information Requests – 10 minutes

Nonclinical

Please provide a risk assessment for the potential for reproductive and developmental toxicity for Empliciti using non-product specific information. Include in your assessment the potential effects of Empliciti binding to NK cells or other SLAMF7-expressing tissues in the developing fetus.

### 3. Postmarketing Commitments – 30 minutes

Clinical Pharmacology

1. To determine if dosing can be optimized in the subgroup of patients who exhibit lower exposures and thus lower PFS with the proposed 10 mg/kg dosing regimen of elotuzumab. The objective is to evaluate if increasing exposures in this subgroup of patients can provide additional PFS benefit.

CMC

1. To re-evaluate elotuzumab drug substance lot release and stability specification acceptance criteria for the cell-based ADCC potency assay and cation exchange chromatography (CEX) assay after 30 lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.
2. To re-evaluate elotuzumab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process and

tested at the time of release using the commercial specification methods. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

3. To complete the ongoing studies to support the (b) (4) of the elotuzumab master cell bank (MCB). The results of the (b) (4) using multiple cells from the MCB will be provided in the final study report.
4. To validate maximum hold times for the (b) (4) for microbial quality and submit validation report per 21CFR601.12.
5. To perform a repeat microbial retention study for the sterilizing filter using a suitable surrogate solution. Alternatively, perform the study using a modified process, a modified formulation (e.g., (b) (4)), or a reduced exposure time for the challenge organism. Provide the summary data, the associated report, and justification for any modifications to the study. If any filtration parameters are changed as a result of the study, update the BLA file accordingly.

4. Review Plans – 5 minutes

FDA plans to send PMCs to Applicant by November 6, 2015.

5. Wrap-up and Action Items – 5 minutes

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/s/  
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ANN T FARRELL  
10/22/2015